Evolutionary Background Entities at the Cellular and Subcellular Levels in the Human Body §

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Abstract

Since the extensive application of culture-independent approaches to the life sciences in the 1990s, the data on microorganisms in the human body has been increasing in an unprecedented pace, greatly enriching our previous limited knowledge of the microorganisms associated with the human body. In recent years, partial hominal microorganisms such as bacteria, viruses, and fungi have been studied or reviewed separately according to the anatomic sites, such as the skin, oral cavity, gastrointestinal tract, respiratory tract, genitourinary tract, vagina, and amniotic cavity. In recent novel evolution theories, the relationship between animals and their environments has been understood to be the interaction between animals and their environmental evolutionary entities at the same and/or different evolutionary levels; [1-3] and it is hypothesized that evolutionary entities at lower evolutionary levels are the evolutionary background entities of entities at higher evolutionary levels.[1,2] Therefore, understanding the normal existence of evolutionary background entities, including various microorganisms, in our bodies is becoming the first priority for elucidating the ecological and evolutiological relationships between humans and their host-associated evolutionary background entities. Recently, host-associated microentities, or evolutionary background entities (EBEs) such as eukaryotic and prokaryotic mono-cellular entities including bacteria, archaea and fungi, and subcellular entities such as viruses/phages and extracellular vesicles in vertebrate and invertebrate animals have been partially summarized.[4-7] In this paper, I try to briefly review the evolutionary background entities (EBEs) at the cellular and subcellular levels in the human body.

Key words: Evolutionary background entities (EBEs); Evolution; Diversity; Animals; Symbiosis; Eukaryote; Prokaryote; Vertebrate; Mammals; Bacteria; Archaea; Fungi; Protists; Virus; Phage; Archaealphage; Bacteriophage; Membrane-enclosed microentities; Extracellular vesicles; Exosomes;

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1. Background

During the past years, partial hominal body-associated microorganisms such as bacteria, viruses, and fungi have been studied and reviewd separately according to anatomic sites, such as the skin,[8-14] the oral cavity,[15-22] the gut,[23-30] the respiratory tract,[31-35] the genitourinary tract,[36-39] and the amniotic cavity.[40-43] In recent novel evolution theories, the relationship between animals and their environments has been deciphered to be the interaction between animals and their environmental evolutionary entities at the same and/or different evolutionary levels;[1-3] and it is hypothesized that evolutionary entities at lower evolutionary levels are the evolutionary background entities of entities at higher evolutionary levels.[1,2] In order to understand the normal existence of evolutionary background entities, including various microorganisms, in the human body is becoming the first priority for elucidating the ecological and evolutiological relationships between humans and their host-associated evolutionary background entities, including hominal microorganisms. For example, humans can become carriers of plant viruses by coming into contact with them from edible plant foods such as vegetables and fruits, and can transmit these viruses to other plants via feces.[44] Human can also become carriers of nonhuman animal viruses by eating meat, animal viscera, milk or milk products, and eggs, and can transmit these viruses to other animals via feces. In other words, the human body can play a triple role—as a producer, carrier, and transmitter of viruses—in its biological, ecological, and evolutiological relationships with viruses. Moreover, the understanding that bacterial communities exhibit their compositional variation in different anatomic sites in the human body has been supported by evidence obtained using traditional culture-dependent methods or culture-independent molecular approaches.[9,45] Recently, host-associated microentities, or evolutionary background entities (EBEs) such as eukaryotic and prokaryotic monocellular entities including bacteria, archaea, and fungi, and subcellular entities such as viruses/phages and extracellular vesicles in vertebrates and invertebrates have been partially summarized.[5-7] In addition, EBEs in hominal body fluids such as human breastmilk have been reviewed recently.[4] In this article, I try to briefly review the evolutionary background entities (EBE) at the cellular and subcellular levels in different human anatomic sites and other body fluids.

2. The Skin and Hairs

2. 1 Bacteria

The skin is the largest organ of the human body and directly contacts the external environment through an area larger than 1.8 square meters. And its accessory structures include sweat glands, sebaceous glands, and hairs.[46] It is well known that the skin has many physiological functions, such as sensory functions including senses of pain, touch, and temperature, physical protection of internal organs, and regulation of body-temperature.

Studies using traditional culture methods have revealed that bacteria such as Staphylococcus epidermidis, Pseudomonas aeruginosa, and Streptococcus pyogenes are the predominant inhabitants of normal skin.[47-51] However, the diversity of the previously established resident skin bacteria at the species, genus, and phylum levels has been greatly expanded since the emergence of culture-independent approaches.[13] It is estimated that there may be up to one billion microorganisms in a single square centimetre of the human skin.[52] Gao and colleagues, using culture-independent approaches, revealed that species in the skin bacterial community belong to different phyla including Actinobacteria, Proteobacteria, Firmicutes, Bacteroidetes, Deinococcus-Thermus, Thermomicrobia, and Cyanobacteria, and more than one hundred gerna including Propionibacteria, Corynebacteria, Staphylococcus, and Streptococcus.[11] In orthodox medicine, the role of bacteria on the hominal skin has mainly been accounted for from a pathological perspective.[5-58] Recently, the question "how do skin microorganisms including bacteria, archaea, fungi, and viruses involve in the skin's physiological functions?" has attracted increasing attention.[59-63] For example, microbial communities and their metabolism on the skin are the major reason for the body odor of humans and nonhuman animals. The odorous organic compounds emitted by sweat are determined by skin glands and skin microorganisms,[64,65] and furthermore, skin bacteria-determined odour and yeast-produced carbon dioxide play an important role in the interaction between humans and environmental animals, as recently elucidated in studies on the host-seeking behaviour of mosquitoes.[66-70] Verhulst and colleagues showed that microorganisms on the human skin vary in their capability to produce volatiles that are attractive to malaria mosquitoes Anopheles gambiae sensu stricto.[66,68]

Recently, accumulating evidence obtained using culture-independent methods in healthy adults has revealed that the skin bacterial community composition, including previously undescribed organisms, and the skin fungal composition are much more diverse than that previously thought based on traditional culture techniques.[8-14,71-74]

2.1.1 The intra- and inter-individual variability

Intra- and inter-individual variability has also been observed in skin-associated bacterial communities.[8,55,73-77] Fierer and colleagues showed that bacterial communities on the hand surfaces differ recently between men and women.[74] Costello and colleagues revealed that bacterial communities on the forearm, palm, index finger, back of the knee, and sole of the foot vary in composition and that such site-to-site variation on skin surfaces also reflects differences in resistance to external bacterial invasion.[9] Moreover, the distribution of bacterial genera was found to be strongly symmetrical between the left and right sides.[8] However, several questions remain to be answered, such as when the sex variation of skin-associated bacterial communities begins, whether the difference is caused by internal factors or external agents or both, and the skin bacterial community changes during childhood, puberty, and old age.

2.1.2 The spatial and temporal variability

The skin bacterial community of healthy adults exhibits a high degree of spatial and temporal variability.[8-10] Dynamic changes in bacterial composition are also observed in skin-associated bacteria, with the proportions of the two genera Streptococcus and Staphylococcus being significantly different for samples obtained 1 month apart.[8] However, we do not yet know much about such spatial and temporal variability in childhood, puberty, and old age, which is expected to be studied in the future.

2.1.3 Infant skin bacterial microorganisms

Since the wide application of culture-independent methods in the study of human body-associated bacteria in the gut, reproduction tract, and adult skin, there had not been a study using such molecular techniques to investigate the skin bacteria of children, especially of infants, until Maria Dominguez-Bello and colleagues published their paper in 2010.[78]. However, the authors believed the traditional notion that "the healthy human fetus is thought to develop within a bacteria-free environment",[78] and, like many other researchers, assumed that the establishment of skin bacterial microorganisms occurred only during delivery and after birth. Nevertheless, Dominguez-Bello and colleagues' study [78] reconfirmed that external bacterial microorganisms from maternal source, as an important exogenous partners, are involved in the constitution of the neonatal skin bacterial community during and after the passage through the birth canal.

2.1.4 An interesting phenomenon of the initial neonatal skin bacterial community

An interesting phenomenon was released in Dominguez-Bello and colleagues' paper, but authors initially did not discuss it.[78] Although newborn skin samples were taken within seconds of delivery, before the umbilical cord was cut, the authors found that the bacterial communities (across all body habitats) of infants delivered via C-section were most similar to the skin communities of the mothers,[78] which was highly doubted to be of contamination,[79] and later attributed to hospital airborne bacterial contamination by the authors.[80,81] However, I argue that this interesting phenomenon strongly implies the possibility that skin bacterial community may be formed as early as during the fetal period. This assumption contradicts the traditional notion that healthy fetal growth and development is a sterile process, which will be discussed futher in another paper.

2.1.5 Factors affecting the skin bacterial communities

Many host factors have been recognized as being able to shape the skin microbial communities,[59,82] and some host behaviors, including delivery mode, hand washing and bathing at the individual level, have been found to be associate with the alteration of postnatal bacterial colonization on the skin and gut.[59,82]

Delivery mode

Two delivery methods, vaginal and Cesarean section (C-section) deliveries, were showed to have different effects on the initial exogenous bacterial colonization in the skin [78] and intestine.[83-86]

Hand washing

Hand washing was shown to be able to alter the bacterial community composition on hands, and its efficiency was influenced by different washing methods,[74,87] but Fierer and colleagues showed that its effect was temporary and did not change the sex variation of hand bacterial community.[74]

Bathing

Early and frequent bathing for newborns may influence postnatal bacterial colonization, which was suggested to be associate with some disorders in childhood.[88-92]

2.2 Archaea

In recent years, archaea in the skin microbiome have been identified and reviewed.[93-96] Probst and colleagues reported that up to 4.2% of the prokaryotic skin microbiome was made up of archaea.[95] Moreover, the authors described morphologically for this first time that archaeal cells were small cocci and their shape and size were similar to thaumarchaeal cells.[95]

2.3 Fungi

Zhang and colleagues showed that some fungal species, including Meyerozyma guilliermondii, Trichosporon asahii, Alternaria alternate, and Aureobasidium pullulans, were found on the skin of healthy individuals.[97] Paulino and colleagues revealed that the predominant fungal species in the healthy human skin was in the genus Malassezia, which included Malassezia restricta, M. globosa, M. sympodialis, M. pachydermatis, M. restricta, M. globosa, M. sympodialis, and M. furfur.[12]

Recently, Gehrmann and colleagues showed that M. sympodialis released extracellular vesicles carrying allergen. And in atopic eczema, exosomes from co-cultures of dendritic cell and M. sympodialis can induce IL-4 and TNF-α responses with a significantly higher IL-4 production.[98]

2.4 Viruses

In recent years, increasing numbers of viral species have been identified on the skin surface of healthy individuals or the normal skin surface of patients with some skin disorders. These include beta and gamma human papillomaviruses (β and γ-HPVs),[99-101] the Merkel cell polyomavirus,[102-105] the human polyomavirusV6 and human polyomavirus V7 in the genus of the human polyomavirus (HPyVs),[104] and circoviruses.[106]

2.5 Skin Hairs

2.5.1 Bacteria

The bacterial profiling of hominal hairs has been rarely investigated, but a recent study of Tridico and colleagues uncovered its direct practical significance in forensic science.[107] The authors revealed an interesting case, in which a cohabiting couple exhibited more similarity in their bacterial profiling of pubic hairs than before due to sexual intercourse that took place 18 hours prior to the collection of pubic hairs, despite their having a shower after intercourse.[107]

2.5.2 Viruses

Merkel cell polyomavirus DNA was detected in 50% of eyebrow hairs in HIV-positive men.[105]

3. The Oral Cavity

3.1 Bacteria

3.1.1 Oral microbiota in healthy individuals

Despite recent disputes, it is still believed by many researchers that acquiring the oral microbiome normally starts at birth.[17] The bacterial community of human oral cavity is complex in its composition, dynamic with age and diet, and varied in health and diseases.[20,22,108-115] In edentulous infants, their oral cultivable anaerobes were found to be relatively lower than in the oral cavities of human adults.[116] The standard culture-based studies have revealed that within several hours after birth, microorganisms such as streptococci (especially Streptococcus salivarius, Streptococcus oralis, and Streptococcus mitis biovar) from maternal and external sources constitute the initial colonizers in the oral cavity.[117-122] Following tooth eruption, the number and isolation frequency of obligately anaerobic bacteria increase, and Streptococcus mutans, Streptococcus sanguis, and Actinomyces species specifically appear in the oral cavity after teeth eruption.[122,123] When infants grow to the end of first year of life, their oral bacterial community already contains some species in the genera of Streptococcus, Neisseria, Veillonella, Staphylococcus, Actinomyces, Lactobacillus, Rothia, Fusobacterium, and Prevotella.[118,124,125] The bacterial composition patterns at different anatomic sites of the oral caviy, such as the dorsal and lateral surfaces of the tongue, saliva, dental plaque, gingival sulcus, gingival margin, buccal mucosa, and pharyngeal site, are different. For example, gram-positive bacilli, gram-positive cocci, and Veillonella are predominant in marginal plaque and plaque from the tooth surface, and Veillonella is predominant in saliva.[120,126,127] Bacteria in the genera of Actinomyces, Arachnia, Bacteroides, Bifidobacterium, Eubacterium, Fusobacterium, Lactobacillus, Leptotrichia, Peptococcus, Peptostreptococcus, Propionibacterium, Selenomonas, Streptococcus, Treponema, and Veillonella are commonly cultivable bacterial microorganisms isolated from different areas in the oral cavity.[120,127,128] Dewhirs and colleagues, using culture-independent approaches revealed that the oral microbiome is distributed in 13 phyla, including Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Euryarchaeota, Firmicutes, Fusobacteria, Proteobacteria, Spirochaetes, Synergistetes, and Tenericutes.[20] Zaura and colleagues showed that there is a core bacterial community in the oral cavity of unrelated healthy individuals, and the predominant oral microbiome sequences are distributed in the phyla of Firmicutes, Proteobacteria, Actinobacteria,

Bacteroidetes, and Fusobacteria, and the genera including Streptococcus, Granulicatella, Neisseria, Haemophilus, Corynebacterium, Rothia, Actinomyces, Prevotella, Capnocytophaga, Porphyromonas, and Fusobacterium.[129] Macovei and colleagues showed for the first time that non-tuberculous mycobacteria normally exist in the oral cavity and upper respiratory tract of healthy individuals.[130]

3.1.2 Different bacterial species in the oral cavity

The existing literature has clearly shown that as more and more human oral bacterial species have been recognized, the number of oral bacterial species has doubled from more than 300 species at the end of last century,[121,131] to 700 species in 2007,[115,132,133] and over 1100 in 2010.[20] Despite nearly half of the bacteria in saliva and dental plaque being uncultivable,[134] the concentrations of bacteria in different anatomic sites in the oral cavity are found to vary. For example, bacteria in saliva range from 10^8 to 10^{12} colony forming units/mL, and the number of anaerobic bacteria is 10 times that of aerobic bacteria.[135,136] In contrast, bacteria on tooth surfaces range 10^{10} to 10^{11} cfu/mL.[135,136]

3.1.3 Microbial community in saliva

The dominant microbial species in adult saliva were found in the following seven major phyla: Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes, candidate division TM7, Fusobacteria and Spirochaetes.[18,137] Cephas and colleagues showed that Streptococcus, Veillonella, Neisseria, Rothia, Haemophilus, Gemella, Granulicatella, Leptotrichia, and Fusobacterium were the predominant genera in infant saliva.[18] In contrast, the major genera in adult saliva were Haemophilus, Neisseria, Veillonella, Fusobacterium, Oribacterium, Rothia, Treponema, and Actinomyces.[18]

3.1.4 The inter- and intra-individual variability

Inter- and intra-individual variations of microbial communities have been found in the oral cavity of adult individuals.[18,19,129,137,138] The complex eubacterial communities in periodontal pockets also exhibit a substantial inter-individual variation.[22] Huang and colleagues showed that there was a distinguished pattern on the composition of plaque microbiomes, but not of salivary microbiomes, when comparing the oral microbial communities of patients with gingivitis to those of healthy subjects.[19] Sato and colleagues further showed that inter-individual variation of the bacterial community was more remarkable than intra-individual differences.[138]

3.1.5 The physiological and pathogenic roles

Our understanding of the roles of microorganisms in the oral health and diseases of humans has been greatly improved during the past four centuries. For example, oral malodor is usually the clinical reflection of oral microbial metabolism, which has been recognized to involve several molecular compounds such as volatile sulfur compounds (VSCs) including hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH), and dimethyl sulfide (CH_3SCH_3), and short-chain fatty acids including propionic acid and butyric acid, cadaverine, indole, and scatole.[139] Tannerella forsythia, Porphyromonas gingivalis, and Actinobacillus actinomycetemcomitans are considered putative pathogens contributing to periodontal diseases mainly because of their are frequently detected in high proportions in patients with periodontitis.[22,132,140-142] Lactobacilli appear in the oral cavity during the first years of life in childhood, and some strains have been shown to have close relationships with coronal caries among children and root caries among

adults.[21,134] Lactic and acetic acids produced during streptococcal carbohydrate metabolism generate a low pH that can interfere with the growth of other microorganisms and are inhibitory to anaerobes, especially Porphyromonas gingivalis.[131,143]

Moreover, considering the fact that more than 700 microorganism species coexist within the oral cavity and that the oral cavity is an opened "niche" or "habitat", a port of our body loading edible substance from the external environment,[2,115] we should know that a dynamic balance of microorganisms, or called the "microbial homeostasis," is the consequence of complicated interactions among those cellular, subcellular, and molecular entities,[2,3,121,131,144-146] and such balance is challenged all the time by various host internal and external factors.

3.2 Archaea

Archaeal species such as Methanobrevibacter smithii and Methanobrevibacter oralis in the phylum Euryarchaeota have been detected in the human oral cavity.[20,62,147-149] Archaea in the oral cavity have been found to associate with periodontitis.[62,150-154] However, the question "what is the archaeal physiological role?" remains to be answered.

3.3 Fungi

The fungal community, as an important member of the human microbiome in the oral cavity, has not attracted much attention from researchers until recently. Some fungal species have been found to be members of the normal oral microbiome.[17.20,155-162] Monteiro-da-Silva, Araujo and Sampaio-Maia revealed that the majority of fungal species in healthy adults belong to the genera Candida, Rhodotorula, Penicillium, Aspergillus, and Cladosporium.[156]

3.3.1 The inter- and intra-individual variability

Monteiro-da-Silva, Araujo, and Sampaio-Maia showed that the inter-individual variation of the oral fungal community was remarkable, but the intra-individual variation was not.[156] One of reasons for this may be that the 30-week observation period was not long enough to reflect the intra-individual variation.[156] In contrast, the intra-individual variation of the oral bacterial community can be observed at the hourly level.[137,138]

3.4 Viruses

Bacteriophage, or bacterial viruses, are the major constituenta of the viral community in the saliva, dental plaque, and oral cavity of healthy human subjects. The oral viral community plays a role in shaping the oral bacterial community.[15,16,163-165] Epstein-Barr virus, cytomegalovirus, human herpesvirus (HHV)-6, and HHV-7 have been detected in saliva from healthy adults and children.[165-168] TT virus DNA has been detected in saliva samples from normal, healthy individuals in Japan.[169] Pride and colleagues revealed that salivary viromes were different from those of human feces and the respiratory tract.[164] Human papillomavirus type 16 (HPV-16) has been detected in the oral specimens of healthy human individuals.[170] Despite the fact that the oral positive rate of HPV-16 in healthy individuals is less than 2%,[170] the oral sex should not be neglected as a practical route for transmitted HPV-16 infection.[170-172] In addition, Naidu and colleagues showed that the community of bacteriophage in dental plaque exhibited inter-individual variation.[163]

3.5 Extracellular vesicles

Extracellular vesicles (EVs) such as exosomes and other vesicular nanoparticles surrounded by bi-layered membrane in saliva of healthy individuals have been studied extensively from the morphological, physiological, pathological, and chemistry perspectives in recent years.[173-186] Gallo and colleagues revealed that exosomal microRNAs greatly outnumber circulating miRNAs in salivary miRNAs.[187,188] From the fimpological perspective, one of the most important achievements of studies on extracellular vesicles in recent years is Pfeffer and colleagues' finding that some extracellular vesicles released from eukaryotic cells contain viral functional miRNAs,[189] which was later supported by the studies on tumor cells.[190-195] It has been suggested that the miRNAs within extracellular vesicles released from eukaryotic cells are not of homogeneous eukaryotic origin, but are heterogeneous, and that the significance of extracellular vesicles in the human body is far beyond that in human health and diseases, which is worth exploring theoretically and laboratorially in the future.

4. The Nasopharyngeal Tract

4.1 Bacteria

4.1.1 The nasal cavity

The human nose and throat (or pharynx), although anatomically neighbored, are colonized by different bacterial communities respectively.[196] Studies based on traditional culture-dependent methods indicated that bacterial species belonging to the genera of Staplylococcus, Haemophilus, Streptococcus, Moraxella, Propionibacterium, Peptostreptococcus, and Prevotella were among those cultivable bacteria in the normal nasopharynx and nasal cavity,[196-202] and some bacterial species such as Haemophilus influenzae, Streptococcus pneumoniae, Branhamella catarrhalis and Streptococcus pyogenes were rarely isolated from the nasal cavities of healthy adults.[203] Frank and colleagues using culture-independent approaches showed that nasal bacterial species in healthy adults belonged to the phyla Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Cyanobacteria, and Tenericutes, and they distributed in various genera including Propionibacterium, Corynebacterium, Staphylococcus, Enterobacter, and Deinococcus.[204] The whole picture of the bacterial compositions in the human nose and throat has become much clearer since the recent application of culture-independent analyses to the study of the bacterial community in these anatomic sites. Moreover, culture-dependent syudies indicated that healthy sinuses are also not sterile.[205-208] Kalcioglu and colleagues showed that coagulase-negative staphylococci, alpha-hemolytic streptococci, and anaerobes were isolated from normal maxillary sinuses.[207]

4.1.2 The pharynx of healthy infants

Hokama and colleagues revealed that the respiratory bacterial compositions were dissimilar among healthy infants with different feeding methods.[209-211] The dominant bacteria in the throat flora isolated in both breastfed and formula-fed infants are alpha-haemolytic Streptococcus and gamma Streptococcus, and the incidence of pathogenic bacterial isolation

from normal breastfed infants is lower relative to healthy infants fed formula.[209-211] All Gambian infants were found to be colonized postnatally at some point by Streptococcus pneumoniae in the nasopharyngeal cavity.[212] Some pathogenic strains of Streptococcus pneumoniae are the otitis media pathogen and Streptococcus pneumoniae in the normal microbial communities of the upper respiratory tract are believed to be inihibited normally by other bacterial members such as Corynebacterium and Dolosigranuum,[213] which, however, is a dynamic course.[214]

4.1.3 The inter- and intra-individual variability

The inter- and intra-individual variation has been shown in the bacterial community composition at the human nares, oropharynx, saliva, axilla, and groin, which seemed associated with some other factors including sex and race.[196,204,214]

4.1.4 Nasal bacterial composition in sinusitis

Studies have shown that in the nasal cavity of patients with sinusitis, staphylococcus and diphtheroids decrease, while Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pygenes, and Moraxella catarrhalis relatively increase.[198,203,215,216] In acute maxillary sinusitis, Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, and Branhamella catarrhalis become the dominant isolated bacterial species.[217,218] In contrast, in chronic sinusitis, bacteria belonging to the genera of Prevotella, Fusobacterium, Peptostreptococcus, Staphylococcus, and Propionibacterium are dominant.[219]

4.2 Viruses

4.2.1 Virome in nasal/nasopharyngeal secretion

Winther and colleagues showed that picornavirus was usually detected in the sampling of nasal/nasopharyngeal secretion from healthy children, and one fifth of children with positive picornavirus in their nasal/nasopharyngeal secretion were asymptomatic.[220] Human bocavirus was first discribed by Allander et al in 2005 from nasopharyngeal aspirates of children with respiratory tract infection, and has also been detected in blood, fecal, and urine samples.[221-224] Human bocavirus (HBoV) has shown highly genetic diversity and includes HBoV1, HBoV2, HBoV3, and HBoV4.[225,226]

4.3 Extracellular vesicles

Recently, Ye and colleagues revealed that tumor cells in human nasopharyngeal carcinoma released exosomes that were associated with tumor progression and T-cell dysfunction.[227]

5. The gastrointestinal tract

5.1 Bacteria

Although bacterial communities in the human gastrointestinal tract have attracted much research attention during the past century, our existing knowledge on horminal gut-associated bacteria mainly focused on their etiological or pathological relations with some diseases, including preterm,[228-231] necrotizing enterocolitis,[232-236] inflammatory bowel disease,[237-243] diabetes,[244-247] obesity,[244,248-253] and cancer.[254-261] However, in a very recent review, Xu and Knight asked several critical questions: "Exactly what role does the microbiota play in obesity, diabetes and other diseases? Is the microbiota shift a result of changes in gut environment or a cause? Does microbiota initiate the effect, or mediate it?" [262] Clearly, finding the answers to these questions is far beyond our existing theoretical systems in the life sciences. During the past decades, some researchers have paid attention to the physiological roles of gut-associated bacteria in healthy individuals.[263-272] Since the 1990s, metabolism-based fermented food products have introduced our attention from previous understanding on their nutritional supply as foods to the therapeutic or preventive roles of some enteric beneficial bacterial species as bioactive agents or called probiotics in human health and disease.[273-276] The application of probiotic therapy has been documented in medical practice for the management of gastrointestinal disorders such as inflammatory bowel disease,[277-282] and specific diarrhoeal diseases,[283,284,285] as well as for atopic dermatitis,[286] improving hypertension [287] and prophylactic cancer.[288] In the following content, the discuss will briefly on bacterial communities in different anatomic segments of the gastrointestinal tract and several selected bacterial species.

5.1.1 The esophagus

As a part of the luminal organs of human digestive system, the esophagus anatomically connects mouth and stomach. In medicine, the esophagus has received somewhat attention mainly because this organ is liable to generate inflammation and cancer. Interestingly, although this luminal organ theoretically and anatomically provides a potential environment for some residential microorganisms, during the past decades there has not been much research attention paid to the bacterial community in the esophagus,[289.290] which was attributed to "the belief that bacteria are not responsible for esophageal diseases" as Pei pointed out.[291] Pei and colleagues, using molecular approaches, showed that bacterial species in the normal mucosal surfaces of the human esophagus belonged to six phyla including Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, and Fusobacteria; and the dominant genera were Streptococcus, Prevotella, and Veilonella.[291] Moreover, the esophagus-associated bacterial community exhibited an inter-individual variation in its diversity and composition.[291]

5.1.2 The stomach

The relative paucity of stomach-associated bacteria and the gastric harsh environment have led to the assumption that the human stomach does not harbor a complex microbial community. The application of culture-independent molecular methods has revealed that the bacterial diversity within the human gastric mucosa is greater than previously described. Bik and colleagues showed that one hundred twenty-eight phylotypes among eight bacterial phyla detected in human gastric mucosa can match that described by using culture-based methods. [292] And some bacterial species including Caulobacter, Actinobacillus, Corynebacterium, Rothia,

Gemella, Leptotrichia, Porphyromonas, Capnocytophaga, TM7, Flexistipes, and Deinococcus had not yet been described with culture-based analyses.[292] The cultivation of gastric fluid or mucosal biopsies has identified several bacterial species belonging to the phyla Firmicutes, Proteobacteria, Actinobacteria, and Fusobacteria, as well as yeasts in relatively low abundance.[293,294] Evaldson and colleagues showed that in the stomach and the proximal small bowel, the microorganisms found as normal flora were a reflection of the oral flora, and bacterial concentrations in this region were 10^2-10^5 cfu/ml intestinal content.[135]

5.1.3 The intestine

Since the 1980s, studies based on traditional bacteria culture methods have shown that the main groups of bacterial microorganisms in the normal intestine belong to the genera of Streptococcus, Lactobacillus, Bacteroides, Veillonella, Actinomyces, Haemophilus, and Corynebacterium;[295,296] and microbial cell population densities increase along the jejunum and ileum.[295,297] However, molecular methods that emerged in the 1990s have improved our previous knowledge of intestinal microbial communities.[298-301] The human gut harbors over 1,000 bacterial species, and each individual has at least 160 such species.[302,303,304] 60-80% of the total human gut microflora are uncultivable.[305] The predominant bacterial species in the human gut belong to the different genera such as Bacteroides, Eubacterium, Clostridium, Ruminococcus, Peptococcus, Peptostreptococcus, Bifidobacterium, and Fusobacterium. Bifidobacteria, lactobacilli, and bacteroides are the most common anaerobic microorganisms in the human gut.[135,306]

Gut microflora composition in the infant gut is less stable than that of adults.[307,308] In the colon, bacterial concentrations reported by different authors are around 10^{11} -10^{14} cfu/g faces, and the majority of more than 400 bacterial species belong to Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria.[298,302,307,309-314] Paliy and colleagues revealed that Clostridia in the fecal samples from adults were more prevalent than in samples from children, and Bacteroidetes and Proteobacteria in fecal samples from adults were less prevalent than in samples from children.[315] Swidsinski and colleagues reported that bacterial concentrations on mucosal surfaces were 10^6 to 10^7/ml when the biopsies were observed by fluorescent in situ hybridization.[316]

5.1.4 Prokaryotic bacterial species in meconium of healthy neonates

In fact, despite the detection of microbial DNA in meconium samples of premature newborns,[317] some lactic acid bacteria and other commensal bacteria belonging to the genera Enterococcus and Staphylococcus were isolated from meconium of healthy neonates who were delivered by either labor or cesarean section.[318-321] Most recently, Dong and colleagues compared the microbial community in the first feces of neonates delivered vaginally and via Cesarean section and found that neonatal meconium samples of newborns in both groups with different modes of delivery contained similar bacterial communities.[322]

5.1.5 The intra- and inter-individual variability, and more

The intra- and inter-individual variations have been found in the human gut-associated bacterial microbiome at different time-scales.[28,94,295,297,299,307,315,323] The inter-individual variation of gut-associated microbial communities can be observed in the infant intestinal tract, and the intra-individual variation in an adult's gut microflora is normally more remarkable at the time-scale of years.[307] Reyes and colleagues using sequencing technique, compared viral and bacterial communities in fecal samples from healthy adult female monozygotic twins and their mothers and showed that the similarity of fecal bacterial communities in co-twins and their mothers was significantly greater than that in unrelated individuals,[30,250] whereas facel viral genotypes showed a unique individual pattern without reflecting the genetic relationship.[30] Moreover, recently, Ellis and colleagues provided new evidence indicating that some commensal bacterial species are commonly shared in the distal gut microbiota of humans, cattle, and semi-captive chimpanzees living in the same geographical region.[324]

5.1.6 Factors influencing gut microbial communities

The human gut microbial communities can be affected by some factors, such as gastric bypass,[325] antibiotics,[231,326,327] inflammation,[26] pH,[310] foods,[262,328-334] probiotic bacteria,[335-337] mode of delivery,[86,338-340] maternal microbial community,[272] age,[327,341-345] and travel.[346]

5.1.7 Selected bacterial species from the gut-associated microbial communities

Helicobacter

Helicobacter are members of the family epsilonproteobacteria.[347] Since Marshall and Warren first isolated Helicobacter pylori from gastric biopsy samples in 1982,[348] we have learned that this small Gram-negative bacterium harbors in the gastric mucosa of half of the human population,[349-351] and that the presence of H. pylori does not affect the composition of the gastric community.[292] From the beginning, the appearance of Helicobacter pylori in the human stomach has generally been attributed to infection from external source. Its pathological role in clinical medicine has been the focus of many studies since the1980s. Indeed, accumulating evidence has shown that H. pylori colonization is associated with various forms of gastric disease, from mild gastritis to duodenal and gastric ulcers, as well as two forms of gastric cancer: mucosa-associated lymphoid tissue lymphoma and adenocarcinoma.[352-360] However, the appearance of Helicobacter pylori in apparently healthy individuals, including infants, is still not fully understood.[361-367]

Lactobacilli and Bifidobacteria

Lactobacilli and Bifidobacteria are Gram-positive microorganisms and belong to the lactic acid bacteria (LAB) family. Some specific LAB, such as L. rhamnosus GG and L. reuteri belonging to the genus Lactobacillus have been shown to stimulate human myeloid dendritic cells (MDCs) to secrete bioactive IL-12, a critical factor in switching naive or memory T cells to Th1 responses. Moreover, such IL-12 production from lactobacilli-activated MDCs cannot be reversed by simultaneous treatment with E. coli LPS.[368-370] Lactobacillus strains have been shown to exert different effects on human immune cells and can be divided into two groups: strongly and weakly IL-12- and TNF-α-inducing strains. For example, both L. rhamnosus GG and L. reuteri DSM12246 have been shown to induce low IL-12 and TNF-α responses, and only L. reuteri DSM12246 can induce a strong IL-10 response, indicating marked differences among

the bacteria in the induced IL-12/IL-10 ratio.[369] Bifidobacteria are among the first microorganisms to postnatally colonize the newborn gut.[371] Some strains of bifidobacteria in vitro haveb been showed to increase the release of interleukin 10 (IL-10) from dendritic cells (DCs).[372-373] Menard and colleagues found that some infant fecal Bifidobacterium species had different effects on the rodent immune system. For example, while B. adolescentis had no effect and B. breve had little effect,[374] one B. longum strain was found to induce splenocyte to secrete Th2 cytokines (high levels of IL-4 and IL-10), and the other two strains induced Th1 cytokines (high levels of IFN-γ and TNF-α).[374] Some probiotic strains of Bifidobacteria in combination with some probiotic strains of Lactobacilli have shown potential clinical value in treating diarrhea and obesity.[282,284,337] More interestingly, Andriantsoanirina and colleagues found that Bifidobacterium longum and Bifidobacterium breve isolates from preterm and full term neonates varied in their autoaggregation, surface hydrophobicity, and Caco-2 cells adhesion capabilities, which may reflect variations in bifidobacteria membrane structure and/or composition.[230]

Enterobacteriaceae

The members of the family Enterobacteriaceae are Gram-negative bacteria, such as E. coli and Klebsiella pneumoniae. In contrast to both the lactobacilli and the bifidobacteria, the bacteria in Enterobacteriaceae were found to consistently induce dendritic cells to release remarkably IL-10, and moderate amounts of IL-12 and TNF-α.[369] The development and maintenance of immune homeostasis indispensably depends on signals from the host affiliated evolutionary background entities. For example, mammals coexist with an estimated 300 to 500 different species of commensal bacteria that colonize the gastrointestinal tract in a symbiotic relationship [375] and the immune cells of the gut are indeed influenced by stimuli coming from these commensal microflora. Although the interactions between bacteria and immune cells are traditionally alleged to induce immune activation, in healthy individuals this interaction in fact leads to gut immune homeostasis accompanied by the tolerance to the microflora.[376]

Clostridia

Different species of the genus Clostridium such as Clostridium difficile, the Clostridium coccoides group and the Clostridium leptum subgroup have been detected in the human gut.[299,377] Norin**,** Midtvedt and Bjorksten believed that Clostridium difficile may be a normal part of the intestinal flora in infants.[377] Hayashi and colleagues revealed that the distribution of different species of the genus Clostridium along the gut was unequal, and the human fecal Clostridium coccoides group and the Clostridium leptum subgroup were undetectable in the upper gastrointestinal tract.[299]

5.2 Archaea

The archaeal diversity associated with the human gut and the possible roles of archaea in gut physiology and health have been reviewed recently.[62,378-380] Molecular studies have shown that there are methanoarchaea and non-methanogenic archaea, including Thermoplasma, Crenarchaeota, and halophilic archaea in the human intestinal tract.[381-384] Methanobrevibacter smithii and Methanosphaera stadtmanae are the two most abundant methanogens in the human gut and these two archaeal species belong to the order Methanobacteriales and the phylum Euryarchaeota.[378,380,385-389] Moreover, Methanobrevibacter smithii DNA was reported to be detected in the neonatal gut[307] and an age-associated variation in the diversity has been found in

the human gut methanogenic archaeal community and composition.[389,390] However, the physiological and pathological roles and the composition of the archaea community in the human gut are largely unknown,[391] which is attributed to several reasons, such as without archaea-specific DNA-extraction protocols, their abundance too below to be detected or more variable than that of fungi and bacteria, and racial difference.[307,378,381,387,389] Although to date, none of Archaea have been found to be involved in the pathogenesis of any human diseases,[392,393] a recent study showed that methanogen incidence in ulcerative colitis and Crohn's disease was reduced.[394] Moreover, Vianna and colleagues suggested that a novel, as-yet-uncultured methanogenic phylotype might be associated with oral infections.[395] Samuel and colleagues implied that some archaeal species in the gut microbial communities may be associated with the pathogenesis of obesity.[382] Recent studies revealed that human monocyte-derived dendritic cells can be induced by Methanosphaera stadtmanae and Methanobrevibacter smithii to release proinflammatory cytokines in different extents,[396] and mononuclear cells were induced by Methanosphaera stadtmanae to produce more TNF than by Methanobrevibacter smithii.[397]

5.3 Fungi

Although our knowledge of the human gut-associated fungal community is very little compared to that of gut bacteria,[384,398] Parfrey, Walters and Knight predicted that the study of gut fungi will likely reveal their ecological and evolutionary significance.[399] In fact, three decades ago, various fungal species were isolated from the intestine of some healthy infants and adults.[295,400] For example, Justesen and colleagues showed that Candida albicans was isolated from normal upper jejunal fluid of healthy adults.[295] Since the application of molecular approaches in the study of gut-associated microorganisms, the diversity and dynamics of the gut-associated fungal communities have been gradually uncovered in nonhuman animals and humans.[307,384,401-405] For example, Scupham and colleagues used a culture-independent method termed oligonucleotide fingerprinting of rRNA genes (OFRG) to describe the compositions of the fungal community in murine intestines and the found that the largest assemblages of fungal species belonged to the genera Acremonium, Monilinia, Fusarium, Cryptococcus/Filobasidium, Scleroderma, Catenomyces, Spizellomyces, Neocallimastix, Powellomyces, Entophlyctis, Mortierella, and Smittium and the order Mucorales.[405] Later, the diverse enteric fungal species in human healthy control individuals were revealed by Ott and colleagues using metagenomic 18S rDNA-based molecular techniques.[403] Most recently, Chehoud and colleagues showed that Cladosporium was more abundant in the fecal samples of healthy subjects than in those of patients with IBD (Crohn's disease or ulcerative colitis) and that the gut fungal communities were altered in patients with inflammatory bowel disease (Crohn's disease or ulcerative colitis),[384] and similar results were observed in dextran sulfate sodium (DSS)-colitis mouse models.[401]

5.4 Protists

Human gut-associated protists are largely unknown, and our existing knowledge of them mainly revolves around their pathogenic roles in certain diseases. Giardia intestinalis, Entamoeba histolytica, Cyclospora cayetanenensis, and Cryptosporidium spp. are the most common protozoan parasites in the human gut, and they are known to cause diarrhoeal disease, giardiasis, amoebiasis, cyclosporiasis, and cryptosporidiosis, respectively.[399,406-409] Most recently, Alvarado-Esquivel and colleagues reported that the seropositive rate of Entamoeba histolytica

infection in the Tepehuanos population in Mexico was between 28.2% and 41.8%,[410,411] suggesting that there are many unanswered questions in the field of protozoan ecology and evolutiology and they are worth exploring in the future.[399]

5.5 Viruses, Bacteriophages, and Archaealphages

5.5.1 Humans as the viral carrier and transmitter

It has been recognized for a long time that humans play a role in the spread of many infectious viral diseases, such as hepatitis A and viral gastroenteritis, as carriers and transmitters of viruses. Many pathogenic viruses have been isolated from the feces of patients, including rotavirus, astrovirus, calicivirus, hepatatis E virus, bocaviruses, certain coronavirus, and torovirus, as well as certain enteric adenovirus species.[412-417] In fact, the role of viruses in the human body goes beyond just their pathogenic effects. In the human gut, viruses present in the gastrointestinal content come from both internal and external sources to the host. However, there have been few studies on the non-pathogenic roles of enteric viruses in healthy humans. Between the 1980s and 1990s, there were several studies on the enteric viral community in both healthy humans and nonhuman animals. For example, some viral species such as parvovirus, astrovirus, picornavirus, and rotavirus were identified in the normal faeces of cats,[418] and particles with the morphological features of coronaviruses, rotavirus, papovavirus, torovirus, picornavirus, and other virus-like particles were identified in faecal samples from dogs,[419] Bacteriophages were also isolated from fecal specimens of healthy human individuals.[420,421]

Since the 1990s, intense research on the gastrointestinal bacterial profile in the healthy human body, partially for the purpose of searching probiotic bacteria, has stimulated the study of enteric viral communities in the human gut. Breitbart and colleagues used molecular methods to describe the composition and population structure of the human fecal viral community. [422] In 2006, Zhang and colleagues described a "large and diverse community of plant RNA viruses" in the feces of healthy human adults.[44] Interestingly, authors' initial purpose was to find pathogenic enteric RNA viruses through a metagenomic survey, but instead, 97% of the viral-like sequences resembled plant viruses, among which, pepper mild mottle virus was the most abundant viral stain.[44] Chikhi-Brachet and colleagues reported that group A rotavirus and astroviruses were identified in fecal samples from healthy individuals.[423] BK virus, a member of the polyomavirus family, is normally detected in the stool of healthy adults.[424] Coelho and colleagues showed that John Cunningham virus DNA was detected in 40% of normal colorectal mucosa from controls, but in colorectal tumor lesions, the rate increased to 90%.[425] Moreover, recent reviews have indicated that eukaryotic viruses and prokaryotic viruses are detected widely in invertebrates and vertebrates.[4-7] Based on this information, we can infer that humans may be carriers of other animals' viruses through the consumption of meats, animal viscera, milk or milk products and eggs, and transmitters of these viruses through feces. For example, picobirnavirus, a common animal RNA virus that can cause diarrhea, isresent in the stools of animals and healthy human individuals.[426-428] Circoviruses are known to infect birds, pigs, chimpanzee, cows, sheep, and dogs,[429-435] and multiple diverse circoviruses strains, including a strain specific to humans, have been detected in human feces.[436]

5.5.2 The complexity and dynamics of the interaction among different microentities within the gut

The interactions within the gastrointestinal tract actually take place at several different evolutionary levels, such as between endogenous bacterial species and exogenous bacterial species, between host eukaryotic cells and prokaryotic cells, between exogenous viruses and host cells, and between exogenous phages and commensal bacterial cells. Gut-associated viruses detected at any time points are actually a cross-sectional profile reflecting, theoretically, an assembly of various viral entities from heterogeneous sources including host-eukaryotic cells-released viruses, prokaryotic cells-released phages, and free viral entities. However, because of the the current technical limitations, it is difficult to distinguish them well. For example, while detecting the fecal viral community of carnivore, we cannot make a distinction between the fecal viruses from host eukaryotic cells of a predator and those from animal foods-contained eukaryotic cells for some viral entities that are the common evolutionary background entities of different animal species. This recognition is based on a fimpological standpoint that there is no complete similarity between any two evolutionary entities at any given evolutionary level.[1-3,146,437] Moreover, viral species detected from fecal samples may sometimes contain respiratory viruses (e.g. coronavirus) and hepatitis viruses, in addition to enteric viruses,[24] and archaeal phages (archaeal virus) in addition to bacterialphages.[438-441] Therefore, some previously believed viral pathogens detected in the human body may not be real etiological agents, but rather viral bystanders when re-examed from today's theoretical perspective.[24] Recently, Cotten and colleagues using novel, sensitive viral detection approaches showed that fecal samples of HIV-1 infected adult patients with diarrhea contained the RNA and DNA viruses (cosavirus, adenovirus, hepatitis B virus, human papillomavirus, norovirus, and torque teno virus) from eukaryotic cells, bacteriophages from prokaryotic lactococci, enterococci, and plant viruses, including tobacco mild green mosaic virus, paprika mild mottle virus, cucumber green mottle mosaic virus, tomato mosaic virus, and grapevine rupestris vein feathering virus.[24] Colson and colleagues found Marseillevirus-like sequences can be detected in human stools, which suggests the possibility of the presence of giant viruses of amoebae in humans.[442]

5.5.3 Virome in the infant gut

Viruses in the human body consist of prokaryotic viruses (bacteriophages and archaeal phages) and eukaryotic viruses. Breitbart and colleagues revealed that a viral community dominated by phages and with extremely low diversity was found in the feces of a healthy week-old infant. They also found that the most abundant fecal viral sequences did not originate from breast milk or formula, and that the overall viral community in the infant's gut was dynamic during the first 3 months of life, despite some viral species remaining stable.[422,443] Reyes and colleagues showed that the fecal viral community compositions of monozygotic twins and their mothers were similar and stable over time.[30] Torque Teno virus (TTV), the first known human circovirus, was detected in fecal samples from normal, healthy infants and adults.[444,445] Zhang and colleagues did not detect pepper mild mottle virus in the fecal samples of infants, although it was detected in the feces of healthy adults.[44]

5.5.4 The intra- and inter-individual variability in gut-associated viromes

The intra- and inter-individual variations in the human gut-associated viromes were observed.[29,30,446]

5.5.5 Factors influencing gut fecal viral composition

The composition of the adult human fecal virome was found influenced by diet,[29] infant formula feeding,[5,447] and fibres, probiotics, and synbiotics.[274,337]

5.5.6 Non-reproduction sexual behavior: ano-genital intercourse

As non-reproduction sexual behavior or habits occur commonly in gay, bisexual, and other men who have sex with men, the ano-genital intercourse has been shown to associate with the alteration of viral species composition in the anal canal and with high risk for both human immunodeficiency virus (HIV) and pathogenic human papillomavirus (HPV) infections in different racial populations such as Brazilian, Italian, Thai, and Dutch.[448-454] HPV, a group of double-stranded, nonenveloped, small DNA viruses, normally exists in the human body and at least 176 types of HPV have been isolated from different body sites.[455]

5.6 Extracellular vesicles

Extracellular vesicles, such as exosomes, were detected in the bile of rats [456] and chickens.[457] Moreover, human biliary EVs were shown to contain abundant miRNAs.[458] Colorectal cancer cells were shown to release extracellular vesicles, such as exosomes,[459] and colorectal cancer cell-derived exosomes were found to contain mRNAs, microRNAs, and natural antisense RNAs.[460]

6. The respiratory tract

6.1 Bacteria

Little attention was once paid to human indigenous microflora in the respiratory system despite the emergence of culture-independent techniques and their application in the microflora of the oral, gut, urogenital system, and skin because of the traditional notion that healthy lungs were sterile organs.[33,461-464] As a result, over past decades, our understanding of the role of microorganisms in the human lung has been limited to their pathogenic roles in various respiratory system diseases. For example, De Dooy and colleagues detected various bacterial species belonging to the genera Escherichia, Enterobacter, Haemophilus, Klebsiella, Streptococcus, Staphylococcus, Enterococcus, Mycoplasma, Micrococcus, and Capnocytophaga in the endotracheal fluid of infants. [465] And, however, these microorganisms were shown to be associated with preterm and ventilator-associated postnatal colonization.[465]

In ventilator-associated pneumonia, a high alveolar bacterial burden is considered by clinicians to be a diagnostic marker,[466,467] in which methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, Streptococcus pneumoniae, Haemophilus influenzae, and Enterobacteriaceae are believed to be common causative pathogens.[468] In fact, specific information about the normal microorganism profile in the respiratory tract was not

available until 2010 when two research teams from the United States and England using culture-independent microbiological techniques revealed that healthy lungs are not sterile.[469-471] Erb-Downward and colleagues indicated that there is a core pulmonary bacterial microbiome that is constituted of bacterial species in the genera such as Pseudomonas, Streptococcus, Prevotella, Fusobacterium, Haemophilus, Veillonella, and Porphyromonas.[31] This finding was later confirmed by other research groups.[31-35,472,473] Most recently, Macovei and colleagues showed for the first time that non-tuberculous mycobacteria normally exist in the oral cavity and upper respiratory tract of healthy individuals,[130] and the lung-associated microbiomes have become one of the hot research topics.[34,35,474-477] Charlson and colleagues using molecular methods showed that the bacterial profile in the lungs of healthy individuals was lower in biomass, but homogenous in composition to that found in the upper respiratory tract.[32] Moreover, the microorganism profile was found to change significantly in some clinical disorders, such as upper respiratory tract infection,[478] and chronic obstructive pulmonary disease (COPD),[31,470,479-482] cystic fibrosis,[483,484] non-cystic fibrosis bronchiectasis (NCFBr),[485] ventilator-associated pneumonia,[466] and asthma.[469,486]

6.1.1 The sources for lung-associated bacteria

Anatomically, the upper and lower airways of lung are connected luminally with oral, nasal, and pharyngeal cavities. Charlson and colleagues [32] compared bacteria in the upper and lower respiratory tracts of healthy lungs and did not find a difference in their community composition. Based on this, the authors suggested that bacteria in the low airway originated from the upper respiratory tract as a result of "microaspiration."[32] Morris and colleagues compared microorganisms in oral washes and bronchoscopic alveolar lavages collected from healthy individuals and found that most lung-associated bacteria were also found in the mouth; that some lung-associated specific bacteria such as Enterobacteriaceae, Haemophilus, Methylobacterium, and Ralstonia species were disproportionally represented in lungs; and that the lung-associated bacterium Tropheryma was not found in the mouth.[487] The authors revealed that the lung microbiome did not match that of the mouth entirely.[488] Bassis and colleagues compared microorganisms in oral wash, bronchoalveolar lavage fluid, nasal swab, and gastric aspirate samples collected from 28 healthy subjects and revealed that the bacterial communities of healthy lungs were significantly different from those in the mouth, nose, and stomach despite sharing some of the same bacterial species, and microbial immigration from the oral cavity was the significant source of the healthy lung microbiome.[488] Segal and colleagues argued that the similarity of the bacterial communities between the lung and the month might be due to oral bacterial contamination via bronchoscopy;[473] and the authors used the bronchoscopic technique via nasal route to reduce contamination with oral secretions and found a different lung microbiome.[473] However, how to eliminate the potential contamination of bacteria from the oral and nasal cavities when collecting bronchoscopic alveolar lavages samplings is still a challenge in studying the microbiomes in the human lung. In order to avoid this potential contamination, Sze and colleagues using the human lung tissue samples obtained from nonsmokers, smokers without COPD, patients with very severe COPD, and patients with cystic fibrosis confirmed that a detectable bacterial community normally exists within human lung tissue, and it changes in patients with very severe COPD.[479]

6.1.2 The intra- and inter-individual variability

The intra- and inter-individual variations in the bacterial communities of healthy lungs were found by different research groups.[488,489] Such inter-individual variation was also observed in the bronchoalveolar lavage fluid of lung transplant recipients.[34] Dickson and colleagues showed that in healthy human lungs, the intra-individual variation of the microbiota was significantly less than the inter-individual variation.[489]

6.2 Fungi

Our knowledge of the fungal community in healthy human lungs is inadequate. The presence of fungi in the respiratory system has been studied and accounted for mainly from a pathological perspective.[465,490-494] For example, fungal species in the genus Candida were detected in the endotracheal fluid of ventilated preterm infants.[465] However, over the past two years, the study on the pulmonary fungal community has become a hot field as a result of our increasing understanding that the pathological role cannot represent the whole significance of fungi in the lung.[494-496]

6.3 Viruses

It has been over a century since the notion of the pathogenic relationship between viruses and human diseases was accepted, and the viral presence in the respiratory system is mainly accounted for from a pathological perspective.[497-500] In recent years, the pulmonary bacterial and fungal communities have received more attention than the pulmonary viral profile. Considering that the lung normally harbors bacteria, fungi, and host eukaryotic cells, it is reasonable to hypothesize that there is a viral community including prokaryotic viruses (phages) and eukaryotic viruses in the healthy lung. The missed piece in the puzzle of human pulmonary Evolutionary Background Entities (EBEs) is expected to be described in the near future. Therefore, our current knowledge of the human pulmonary viral profile largely cames from the clinical studies from a pathological perspective. In some clinical investigations, there are even no normal controls, which cannot exclude the possibility that some detected viruses might be bystander agents, not exactly the relevant viral pathogens. Akhtar and colleagues reported that enterovirus, cytomegalovirus, adenovirus, herpes simplex virus, Epstein-Barr virus, influenza A, and influenza B were detected in tracheal aspirate samples from intubated pediatric patients with pneumonia or myocarditis.[501] Volz and colleagues reported that pathogenic human bocavirus (HBoV) were detected in patients with pneumonia.[502] Human bocavirus (HBoV) has been detected in the respiratory tract samples of children world-wide and usually co-existed with other respiratory viruses, such as respiratory syncytial virus, adenoviruses, and rhinoviruses.[222,415,502-504] Moreover, KI and WU, two newly identified members of the polyomavirus family, were found in respiratory fluids of children with respiratory infections and in healthy individuals.[505,506]

6.4 Extracellular vesicles

Although extracellular vesicles can be released by normal respiratory cells,[507,508] the current research attention is focusing on extracellular vesicles released by lung cancer cells and the various molecules encapsulated within these vesicles, such as proteins and microRNAs.[509-513] Extracellular vesicles in various lung diseases, primarily chronic obstructive pulmonary disease

(COPD) and lung cancer, were reviewed recently.[507,514] In the future, it may be shown that extracellular vesicles are detectable in normal bronchial lavage, but it may be a next challenge to distinguish the respiratory extracellular vesicles released by bacteria, virusesl, and fungi from released by host eukaryotic cells, including respiratory white blood cells, while considering the co-existence of bacteria, fungi, viruses, host white blood cells, and lung cells in the human healthy respiratoey tract.[31-35,496,515,516]

7. The Peritoneal Cavity

7.1 Bacteria

As early as three decades ago, when twelve healthy women underwent laparoscopic tubal sterilization, Spence and colleagues using culture methods found that anaerobic bacteria were isolated from the peritoneal cavity of three women.[517] The coexistence of spermatozoa and Chlamydia trachomatis in the peritoneal cavity of patients with salpingitis was observed by Friberg and colleagues.[518] Moreover, microorganisms were detected in the peritoneal cavity of patients suffering colon cancer.[519] In the traditional notion, the peritoneal cavity of a healthy human individual is sterile and the appearance of bacterial microorganisms should be the consequence of the primary peritonitis or secondary peritonitis.[520-522] Therefore, our existing knowledge of the peritoneal cavity-associated bacterial community composition is mainly from the study of patients. For example, recently, Pihl and colleagues showed that diverse bacterial species were detected from the peritoneal dialysis catheters used by patients without signs of infection and they belonged to the genera of Staphylococcus, Streptococcus, Propionibacterium, Proteus, Corynebacterium, Micrococcus, and Rothia.[521]

8. Human cerebrospinal fluid and brain tissue

8.1 Bacteria

The high concentration of lactate in cerebrospinal fluid from patients with meningitis is usually attributed to the metabolic products of pathogenic bacterial isolates from cerebrospinal fluid.[523,524] However, among those bacterial isolates from cerebrospinal fluid, some are pathogenic and some are not.[524,525] In clinical, these non-pathogenic bacteria in cerebrospinal fluid are usually attributed to contamination.[524-527] Therefore, to date, due to the traditional assumption that cerebrospinal fluid is normally bacteria-free, studies on bacterial profile in normal cerebrospinal fluid are rare. Additionally, the existing relevant literature is based on culture methods, and the investigations using cultural-independent approaches to explore the bacterial profile in cerebrospinal fluid samples taken from healthy individuals or healthy control groups are rare. Given that many previously assumed bacteria-free anatomic sites or body fluids, such as the endometrial cavity of a nonpregnant uterus,[528-533] the amniotic cavity,[534-538] follicular fluid,[539-541] and blood[542-548] in the healthy human body have been proved to actually be harbored by non-pathogenic bacteria, it is reasonable to hypothesize that there may be a

dynamic bacteria community at a low concentration in normal cerebrospinal fluid, which is worth investigating using culture-independent approaches in the future.

8.2 Fungi

Garges and colleagues reported that some fungal species were isolated from cerebrospinal fluid.[525]

8.3 Viruses

Several clinical studies have tried to establish a link between viral aetiology and clinical neurological symptoms by using polymerase chain reaction (PCR) to detect DNAs of HSV-1, HSV-2, CMV, EBV, VZV, and HHV-6 in brain tissues or cerebrospinal fluid samples.[549-553] Some human herpes viruses have been detected in normal human brain tissue, including human herpesvirus 6, 7, and 8 DNA.[554-559] Perez-Liz and colleagues detected human JC virus (JCV) DNA in normal brain tissue.[560] Therefore, from the fimpological perspective, it is hypothesized that there may be dynamic viral entities in normal cerebrospinal fluid, which is worth investigating in the future.

8.4 Extracellular vesicles

Recently, studies on extracellular vesicles and their contents, including proteins, lipids, nucleic acids and other molecular entities in cerebrospinal fluid, have focused on their roles in some neurodegenerative disorders such as Alzheimer disease,[561-571] Parkinson disease,[562,564,574] Creutzfeldt-Jakob disease in humans,[561,573,574] stroke,[575,576] and glioma.[577-581] However, extracellular vesicles have also been found to exist normally in human cerebrospinal fluid.[571,582-586] Tietje and colleagues found that extracellular vesicles in cerebrospinal fluid exhibit age-dependent declines.[585] Extracellular vesicles containing microRNAs and proteins have been detected in human embryonic cerebrospinal fluid.[583,586] The physiological function of the cerebrospinal fluid in the brain development of chick and rats suggests that extracellular vesicles and their contents, including proteins, lipids, nucleic acids, and other molecular entities in cerebrospinal fluid, may play a role in brain development.[583,586-589]

9. Blood

Recently, there has being an increasing concern about the safety of blood transfusion and blood products as more and more bacterial and viral entities are being uncovered in blood samples from healthy donors.[590-595] The following viewpoints should be stressed: (1) human blood normally harbors heterogeneous prokaryotic bacteria and subcellular entities such as eukaryotic or prokaryotic viruses or phages and extracellular vesicles, which has been supported by solid evidence; (2) the bacteria, viruses, extracellular vesicles, and molecular entities in blood constitute the blood-associated evolutionary background entities (EBEs) of the human body, which is dynamic and affected by host-external environmental factors (also called environmental EBEs); and (3) considering that human blood exhibits intra- and inter-individual variations, transfusion had never been, is not now, and will never be an entirely safe therapy.

9.1 Bacteria

9.1.1 The concept of the "sterility" of "normal and healthy" blood

It was once generally recognized that the bloodstream in healthy humans was a sterile environment.[546] In traditional medicine, if viable microorganisms are transiently present in blood without causing any clinical signs and symptoms, this is clinically diagnosed as "bacteremia." Interestingly, although asymptomatic bacteremia was found in the first day of life as early as the 1960s, it was considered to be transient in clinic and therefore not attracting much attention.[596] Moreover, asymptomatic bacteremia is common in end-stage renal disease patients[597] and hemodialysis patients,[598,599] which is attributed to the consequence of gut bacterial translocation.[597-599] If bacteremia is accompanied by clinical systemic inflammatory signs and symptoms, sepsis is diagnosed instead, which is a leading cause of morbidity and mortality worldwide.[600] Therefore, improving the positive results and decreasing false-negative results in blood culture is still a challenge in clinical diagnosis and research.[600-605] In fact, accumulating evidence has indicated that bacteremia may be present in the blood of healthy humans, despite the fact that culture-positive bacteremia may appear after toothbrushing in individuals with periodontal disease.[542-548,606] For instance, Tedeshi and colleagues reported that bacteria-like entities were present in the blood of clinically healthy individuals.[542] Haimowitz and colleagues reported that cultivable Streptococcus bovis were found in donated platelets from a 56-year-old woman with a history of well-controlled insulin-dependent diabetes mellitus and hypertension,[548] and cell wall-deficient organisms appeared in the blood of control subjects.[543,546,547] McLaughlin and colleagues even showed that pleomorphic microorganisms in the blood samples from healthy individuals can be observed under dark-field microscopy.[546]

9.1.2 Prokaryotic bacterial species in the umbilical cord blood of healthy neonates

In contrast, the significance of neonatal asymptomatic bacteremia has been ignored or underestimated despite some researchers suggesting that the prenatal life of offspring may not be sterile.[607,608] In 2005, Jimenez and colleagues published their astonishing finding,[609] in which, Gram-positive cocci were isolated from umbilical cord blood samples of 20 healthy neonates born by cesarean section; furthermore, the amounts of initial cultivable bacteria in umbilical cord blood from healthy neonates born by cesarean section were very low.[609].

9.2 Archaea

Unfortunately, to date, there is no much information about archaea in the blood of healthy human individuals available for review. It is reasonable predict from a fimpological perspective, that some archaeal species should normally coexist with prokaryotic bacteria in the blood of humans, while considering the mechanisms of gut bacterial translocation via circulation.[597-599]

9.3 Fungi

Fungal species in blood have mainly been investigated from a pathological perspective, such as in cancer patients.[610-612] To date, there has been no theoretical recognition for the possibility that some fungal species may exist in the blood of healthy human individuals. In recent years,

researchers have focused on improving molecular protocols for detecting fungal species in blood.[613-617]

9.4 Viruses

In the fimpological theories, viruses evolved as an independent evolutionary entity with a high diversity on Earth long before the emergence of primary cell-like organisms. The emergence of Virus Time miay have occurred between the Latest Universal Organic Molecular Ancestor (LUOMA) and the Earliest Universal Cellular Ancestor (EUCA), and Virus Time may have been preceded by proteins, lipids, carbohydrates, membranes, and polyribonucleotide.[1,146.437] Moreover, some independent vial strains remain in their original forms. Some free viral strains or species became extinct at some evolutionary time points, and their symbiotic strains continue to exist along the cellular path.[146,437,618,619-622] Therefore, the ancient viral polyribonucleotide, which is found within the genomes of extant prokaryotes and eukaryotes, can be called "viral fossils," a class of molecular fossils found within extant cells.[1,146,437] As an important environmental evolutionary entity, viruses exhibit geographic variation in their distribution, and this variation of Evolutionary Background Entities (EBEs) (also called Evoccasional Variation) [1] is also reflects in relevant evolutionary entities at higher evolutionary levels. For example, simian foamy virus (SFV),[622] human immunodeficiency virus (HIV),[623] hepatitis C virus (HCV), hepatitis B virus (HBV), [624,625] dengue viruses,[626,627] human parvovirus, [628-633] and hantavirus[634-636] exhibit diverse prevalence in the blood of different human populations. Moreover, non-pathogenic viruses in the human body have received increasing attention.[637,638]

9.4.1 Human Parvovirus

Human erythrovirus

Human erythrovirus, formerly called parvovirus B19 and discovered in 1975 by Yvonne Cossart in the blood of a healthy blood donor, [639] is a small, nonenveloped, linear, single-stranded DNA virus belonging to the genus Erythrovirus of the family Parvoviridae [640,641] and normally exists in the blood of healthy individuals.[595,631,641-646] Candotti and colleagues showed that the prevalence of human erythrovirus DNA in blood donor samples from four different populations in the United Kingdom, Ghana, South Africa, and Malawi was between 0.55 and 1.3%,[641] and 11 different erythrovirus strains were identified in blood donors from Kumasi, Ghana.[641] Manning and colleagues detected human erythrovirus DNA in both HIV-infected and HIV-uninfected individuals at autopsy.[632] In addition, erythrovirus has also been detected in blood samples from nonhuman mammals such as chimpanzees and gorillas.[225]

PARV4 and PARV5

Human parvovirus 4 (PARV4) and PARV5 are novel human parvovirus species and have been detected in individual plasma samples from healthy blood donors.[629,630,646,647] The prevalence of PARV4 in the healthy population in Shanghai, China was 16-22%.[630]

9.4.2 Torque Teno virus (TTV)

TTV, a single-stranded, circular DNA virus of approximately 3.8 kb, was first found in a Japanese patient with non-A, non-B, non-C hepatitis (named Torque Teno, initials T.T.) in 1997.[431,444,648,649] It was the first known human circovirus,[445] and belongs to the genus

Anellovirus of the family Circoviridae.[431] TTV viremia is widespread, with a very high incidence in general populations worldwide, and may be a common phenomenon in humans.[649-656] For example, in Japan, TTV DNA was identified in 92% of healthy individuals;[657] in Brazil, 62% of blood donors were TTV viremic;[651] and in Russia, 94% of healthy individuals in the Russian population were TTV positive.[658] Detectable TTV viremia was even found in neonates with 9 days of age,[659-662] and in cord blood,[663,664] and maternal blood, [663-665] although some other studies failed to confirm TTV in cord blood.[662,666] TTV has a wide genetic diversity, including five identified TTV groups.[444,654,661,667-672] For instance, in Brazil, at least seven strains of TTV were circulating among healthy persons,[673] and a single individual can even co-infect multiple TTV strains.[669,673] However, despite the low risk of TTV infection in healthy individuals,[674,675], the association of TTV infection with chronic obstructive pulmonary disease has recently been discussed.[676]

9.4.3 Human herpesvirus in the family Herpesviridae

Varicella zoster virus (VZV), also known as human herpesvirus-3 (HHV-3)

Varicella zoster virus (VZV), also known as human herpesvirus-3 (HHV-3), belongs to the genus Varicellovirus of the family Herpesviridae. Recently, Toi and colleagues reported that VZV DNA was detected in blood from immunocompetent individuals who were asymptomatic for VZV infection, but its frequency and viral load was low.[677]

Epstein-Barr virus (EBV), also known as human herpesvirus-4 (HHV-4)

Epstein-Barr virus, also called human herpesvirus-4 (HHV-4), is one of the most common DNA viruses in humans. It belongs to the genus Lymphocryptovirus of the family Herpesviridae, although the origin of its multiple strains is unknown.[678] Epidemiological studies have shown that the prevalence of EBV infections in healthy individuals is up to 100%.[168,678] The peripheral blood cells of healthy individuals have been found to carry EBV genome.[678-681] Epstein-Barr virus has also been detected in asymptomatic infants.[682-684] EBV has a wide genetic diversity, and some EBV species are considered to cause specific diseases such as infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma (NPC), immunodeficiency-associated lymphomas, peripheral T-cell lymphomas (PTLs), and Hodgkin's disease (HD).[685,686] Many studies on the relationship between EBV diversity and the geographical variation of the incidence of different EBV-associated tumours have shown that virus strains are geographically related, not disease restricted.[686-691] Therefore, although Epstein-Barr virus DNA is found in serum or plasma of infectious mononucleosis, nasopharyngeal carcinoma, posttransplant lymphoma, and nasal lymphoma,[692] it is uneasy to distinguish etiological EBV species from bystander EBVs. Moreover, some EBV species may play a role in the developmental and physiological processes of host eukaryotic cells.[693,694]

Human cytomegalovirus (HCMV), also known as human herpesvirus-5 (HHV-5)

Human cytomegalovirus (HCMV), also known as human herpesvirus-5 (HHV-5), belongs to the genus Cytomegalovirus of the family Herpesviridae. While our understanding of HCMV is still focused on its pathological roles in birth defects and developmental disabilities,[695-698] accumulating evidence from studies at the molecular levels [699,700] strongly implies its ecological and evolutionary roles and the need for further exploration.[701] It is a traditional notion that lifelong latent infection with HCMV is often established following asymptomatic primary infection.[702-706] The prevalence of CMV in apparently healthy Latvian blood donors was

2.6%.[707] In normal, healthy individuals, more than one HCMV viral species has been detected.[678,708,709] More than one human cytomegalovirus (HCMV) genotype has been detected in solid organ transplant recipients.[710,711] A possible explanation for this may be that different HCMV species came from both donor organ and host sources. Human cytomegalovirus glycoprotein N (gpUL73-gN) has been shown to have geographical origins in four main regions: Europe, China, Australia, and Northern America.[712,713] For example, the distribution of envelope glycoprotein O subtypes of human cytomegalovirus in Japanese children differs slightly from that of Caucasian populations.[713] During natural infection, envelope glycoprotein N subtypes of HCMV induce a strain-specific antibody response.[714]

Human herpesvirus-6 (HHV-6)

Human herpes virus 6 (HHV-6), a member of the β-Herpesviridae subfamily, was first isolated from human peripheral blood lymphocytes in 1986.[715,716] Kozireva and colleagues showed that the prevalence of HHV-6 in apparently healthy Latvian blood donors was 8.0%.[707] Politou and colleagues showed that the HHV-6 seroprevalence in healthy blood donors in Greece was 78.75%.[717] Tanaka-Taya and colleagues revealed that chromosomally integrated human herpesvirus-6 DNA was detected in the peripheral blood mononuclear cells of healthy individuals by fluorescence in situ hybridization.[718] Arbuckle and colleagues further showed that the integration sites were on chromosomes 17p13.3, 18q23, and 22q13.3 [719] Ohye and colleagues, using FISH, found that chromosomally integrated human herpesvirus-6 was located at the telomeric region.[720]

Human herpesvirus-7 (HHV-7)

Kozireva and colleagues showed that the prevalence of HHV-7 in apparently healthy Latvian blood donors was 43.3%.[707]

9.4.4 Hepatitis viruses

Hepatitis B virus (HBV)

Hepatitis B virus (HBV), a circular DNA virus, belongs to the genus Orthohepadnavirus of the family Hepadnavirus. The prevalence of HBV in blood varies among different populations. [624,625]

Hepatitis C virus (HCV)

Hepatitis C virus (HCV), an enveloped, positive-sense, single-stranded RNA virus, belongs to the genus Hepacivirus of the family Flaviviridae. Wang and colleagues first reported in 1992 that they detected replicative forms of hepatitis C virus RNA genomic sequences in peripheral blood mononuclear cells (PBMC)] and their finding were confirmed by later studies.[722,723]

Interestingly, Marukian and colleagues found that cell culture-produced hepatitis C virus does not infect peripheral blood mononuclear cells.[724]

Hepatitis D virus (HDV)

Hepatitis D virus, a small circular, enveloped RNA virus, belongs to the genus Deltavirus. The prevalence of HDV in blood exhibits a geographic variation.[625]

Hepatitis E virus (HEV)

Hepatitis E virus, non-enveloped, positive-sense, single-strand RNA virus, belongs to the genus Orthohepevirus of the family Hepeviridae. Recently, Hewitt and colleagues showed that

HEV is normally exist in the blood of some individuals in the English population without any clinical evidence of infection.[725]

Hepatitis G virus (HGV)/GB virus-C (GBV-C)

Hepatitis G virus (HGV), also known as GB virus-C (GBV-C), a single-stranded RNA virus discovered by different teams in the late 1990s, belongs to the genus Pegivirus of the family Flaviviridae.[726-728] The prevalence of GBV-C/HGV RNA in healthy blood donors in many countries around the world is around 2%.[729] The physiological role of GBV-C/HGV is unknown to date.[728-730] Martin and colleagues revealed an association between chronic hemodialysis and HGV.[731]

9.4.5 Human polyomaviruses

To date, 13 different human polyomaviruses such as KI, WU, Merkel cell polyomavirus, HPyV6, HPyV7, HPyV9, 10, and HPyV12 have been described and they belong to the family Polyomaviridae.[732-736] They have been detected in the plasm of healthy adults.[737] In addition, human polyomaviruses have also been detected in other specimens of the human body, such as the skin,[738] respiratory secretions,[733,735,737] faeces,[736,739] and urine.[737] Although several human polyomaviruses may be associated with several human malignant diseases,[734,738,740-742] their roles in human physiology and pathology are largely unknown.[738,743]

9.4.6 Marseillevirus

Popgeorgiev and colleagues detected Marseillevirus-like viral DNA in blood samples from 10 healthy French blood donors and thalassemia patients.[744] Moreover, the authors further observed this virus under transmission electron microscopy and by fluorescence in situ hybridization, and revealed that it was grown in human T lymphocytes.[744,745]

9.4.7 Human T-cell lymphotropic virus (HTLV)

Kozireva and colleagues showed that the 4.6% of HTLV-I seronegative, healthy Latvian blood donors were positive for the HTLV-I tax gene.[707]

9.5 Extracellular vesicles

During the past years, there have been many investigations focusing on plasma or serum extracellular vesicles containing miRNAs, proteins, and lipid. Extracellular vesicles in blood can be released extracellularly by multiple host eukaryotic cells, including peripheral blood mononuclear cells, T lymphocytes, B lymphocytes, platelets, and the endothelium,[746-759] and even by prokaryotic cells, including bacteria and archaea.[760-763]

Extracellular vesicles have been detected in the plasma of healthy human individuals or healthy control individuals, and their contents have been shown to include DNA, messenger RNAs (mRNAs), micro RNAs (miRNAs), tetraspanin molecules, and class I and class II MHC molecules.[184,764-774] Caby and colleagues showed that exosomes in the blood of healthy donors are a physiological phenomenon.[764] Recently, Beatty and colleagues revealed that exogenous exosomes containing abundant non-human small RNA sequences in the human plasma of healthy individuals were from bacterial species in the phylum Proteobacteria, fungal species in the order Hypocreales of the phylum Ascomycota, and dietary plants, in addition to those from

human host eukaryotic cells.[775] Extracellular miRNAs wrapped up in extracellular vesicles such as exosomes and apoptotic bodies can be shielded from degradation by ribonucleases present in blood,[746,749,764] and can be transferred to recipient cells to play a physiological or pathological role.[746,749,760] In fact, the pathological roles or diagnostic and prognostic biomarkers of plasma or serum extracellular vesicles and their contents of miRNAs have been studied in some human diseases,[748,751,767,776-780] such as Alzheimer's disease,[781,782] autism spectrum disorder,[783] cardiovascular diseases,[784-787] inflammatory bowel disease,[788] hepatitis C,[789] alcoholic hepatitis,[790] type 2 diabetes,[791] multiple sclerosis,[792-794] venous thromboembolism,[765,795] preeclampsia,[796-798] esophageal carcinoma,[766,768,799] bladder cancer,[800] breast cancer,[801,802] lung cancer,[803-806] hepatocellular carcinoma,[807] pancreatic cancer,[808] colorectal carcinoma,[769,770,772,774,809] ovarian cancer,[810,811] prostate cancer, [812,813] glioblastoma,[577,814-816] leukemia,[817,818] multiple myeloma,[819] and lymphoma.[820]

10. The amniotic cavity

The formation of amniotic fluid is mainly from early transfer across fetal skin, fetal urine, and lung fluid production.[821] As the important aquatic environment of the fetus, amniotic fluid is no longer considered a simple liquid containing only some bio-active molecules, but a complex aquatic media carrying various cellular, subcellular, and molecular entities, which constitutes a special window for our understanding of the mysterious embryonic and fetal growth and development.[821,822]

10.1 Bacteria

10.1.1 Prokaryotic bacterial species in amniotic fluids

In orthodox medicine, the presence of bacteria in amniotic fluid is traditionally believed to be a sign of a pathogenic condition, which is associated with spontaneous preterm labor, periventricular leukomalacia, and chronic lung disease of prematurity. Intrauterine inflammation, including endometritis and chorioamnionitis, is often considered synonymous with intrauterine infection.[41,823-831] DiGiulio and colleagues revealed that some bacterial species in the amniotic fluid of women with preterm pre-labor rupture of membranes were associated with the bacteria specifically harboring in the gastrointestinal tract, the oral cavity, and the vaginal tract.[826]

Finding bacteria in amniotic fluids

Habitually in clinic, if any bacterial species is detected in amniotic fluid, it is usually attributed to the consequence of either “infection” or contamination. Based on the fact that bacterial microrganisms commonly identified in amniotic fluid are vaginal commensals, ascending infection is usually suspected as a route of entry to the uterine cavity;[832] if clinical infection signs and symptoms also appeared, antibiotic and therapeutic abortion are among the clinical options for choosing; or “subclinical infection” would be the diagnosis if no any clinical signs and symptoms exist. Since the application of cesarean section in obstetrics, amniotic fluid samples can be taken sterilely and therefore, the phenomenon that bacteria appear in the third trimester has been uncovered. However, amniotic fluid in many studies was used to identify antenatal intrauterine infection.[537,825,833,834] As the technique of transabdominal amniocentesis emerged and became a standard obstetric procedure in the 1960s, amniotic fluid samples can be

taken sterilely at as early as the 14th week of gestation, which offers an unprecedented opportunity to early detect cultivable bacteria in amniotic fluid of midtrimester. During the past decades, the development and application of culture-independent molecular approaches in obstetrical microbiology has uncovered those uncultivable bacteria in amniotic fluid.

Since the 1990s, many authors have reported that some bacterial species have been isolated in amniotic fluid samples taken by transabdominal amniocentesis from healthy pregnant women. For example, Romero and colleagues in 1993 performed traditional bacterial culture for amniotic fluid samples taken by transabdominal amniocentesis from 90 women in spontaneous term labor with intact membranes; the prevalence of positive amniotic fluid cultures was 18.8%; and all neonates were free of clinical signs of infection.[534] Montuclard and colleagues performed quantitative aerobic and anaerobic cultures for amniotic fluid samples obtained by transabdominal amniocentesis between 14 and 27 weeks of gestation from151 healthy pregnant women with intact membranes and without preterm labor or signs of infection, and they isolated coagulase negative staphylococcus and alpha-hemolytic streptococcus in three amniotic fluid samples.[835] In a study of amniotic fluid specimens for bacterial and mycoplasmal cultures from 251 normal pregnant women at 24-43 weeks of gestation, Keski-Nisula and colleagues revealed that the prevalence of microbial presence in amniotic fluid was lowest in those women not in labor and with intact membranes, but the prevalence increased in those in labor or with ruptured membranes.[535] Mandar and colleagues investigated the presence of amniotic fluid microflora in 22 consecutive asymptomatic women with intact membranes at mid-gestation and found that three of the 22 women had microorganisms in their amniotic fluid samples.[536] After entering the 21st century, studies on microorganisms in amniotic fluid began to use culture-independent molecular approaches. Bearfield and colleagues indicated that 71% of samples of amniotic fluid taken from healthy women with intact membranes were positive for the presence of bacteria, including Streptococcus spp. and Fusobacterium nucleatum, using 16S rDNA PCR.[836] In the detection of Mycoplasma hominis or Ureaplasma urealyticum in midtrimester amniotic fluid of 15 and 19 weeks of gestation in 179 asymptomatic women by polymerase chain reaction coupled to enzyme-linked immunosorbent assay, Perni and colleagues showed that the positive rate of Ureaplasma urealyticum in amniotic fluid was 12.8%, and that of M hominis was 6.1%.[837] Around the same time, Nguyen and colleagues reported that the positive rate for Mycoplasma hominis in amniotic fluid of 456 women with European background at weeks 15-17 of pregnancy was 6.4%.[838] However, the microorganisms focused by Perni and Nguyen in amniotic fluids were only Mycoplasma hominis or Ureaplasma urealyticum, so information about the whole profile of microorganisms existing in the midtrimester amniotic fluid of healthy pregnant women is limited.

Bacterial profile in amniotic cavity

The most common bacterial species in the amniotic fluid of asymptomatic women detected by cultural methods and molecular approaches belonged to the genera of Lactobacillus, Staphylococcus, Streptococcus, Ureaplasma, Mycoplasma, Propionibacterium, Escherichia, Peptostreptococcus, Corynebacterium, Prevotella, Actinomyces, and Gardnerella.[319,534-538,836,839-841] Streptococci, staphylococci, and propionibacteria were also detected in chorioamnion samples of healthy mothers.[836] Indeed, we cannot always interpret the co-existence of bacteria, viruses, and extracellular vesicles in amniotic fluid from a pathological perspective and we have to confront the fact that they appear in normal pregnancy during the gestational course, from a fertilized single cell to a multi-cellular fetus. For this, we need a novel theory to account for it. In fact, during the past decades, the bacterial roles in the normal embryonic development have been

studied in invertebrate animals.[7,42,842-844] In contrast, such studies on vertebrate animals, especially mammals, have not attracted much attention. One reason for this is that we are theoretically fettered by the hypotheses of Pasteur's "germ-free animal" and Tissier's "germ-free human fetus".[42,845,846] However, the integration between animal embryonic development and bacterial microbiology in nature deals with prokaryotes and eukaryotes, which will unavoidably associate with the evolutionary relationship between them.[146]

10.1.2 Prokaryotic bacterial species in placentas

The notion that placenta is not sterile during normal pregnancy was first supported by the solid evidence presented by Onderdonk**,** Hecht and colleagues in 2008, who completed both bacterial culture and histological examination on more than a thousand of cesarean-delivered placentas.[847,839] Later on, this newly emerged recognition was also supported by other researchers' studies using standard culture-dependent procedures [848,849] and culture-independent approaches,[850,851] despite the fact that bacterial species were also detected more frequently in placentas of preterm gestations.[840,849,852-855] Fardini and colleagues provided experimental evidence in pregnant mice for the oral microbiome as a potential source of bacterial species in the placenta.[856] Aagaard and colleagues further showed that the placental microbial profiles most closely resembled microbes in the maternal oral cavity when compared to those in other human body sites including the oral, skin, airway (nasal), vaginal, and gut.[850] Thus, the oral-placenta route has been suggested to be the model of maternal bacterial transmission to the fetus.[42,850,856,857] Stout and colleagues using morphological techniques reported that Gram-positive and Gram -negative bacteria with diverse morphologies within the cytoplasm of cells in the basal plates of 27% of 195 placentas, which the authors inferred might be "a possible source of intrauterine colonization".[849] Cao and Mysorekar found bacteria in fetal extravillous trophoblasts (EVTs) in placental basal plate.[858] Zheng and colleagues revealed that there were different placental microbiome profiles between low birth weight and normal birth weight full-term neonates.[851] However, the extension of "placenta is not sterile" [839,847,849-851.858] into "uterus is not a sterile organ" [530-532,859] during both pregnancy and non-pregnancy still needs more laboratory evidence and theoretical explanations, because a series of new questions arose and require imperative answers, such as when is uterus sterile? When did uterus become a bacteria-colonized organ? What are the bacterial species in the utero-bacterial community? Where did those uterine bacteria come from? Are there any differences in the utero-bacterial composition between pregnancy and non-pregnancy? And can placental bacteria be simply attributed to the migrating consequence of maternal utero-bacteria? Clearly, some of these questions are far beyond the scope of clinical researchers' concern and the answers cannot be found in the existing medical theoretical system; and more than that, some questions even contradict or challenge our traditional notions.

10.1.3 Bacteria in fetal membranes

Bacterial species were also detected in the human fetal membranes, and their presentation did not associate with clinical manifestation of infection in the pregnancy.[860-862]

10.2 Archaea

DiGiulio and colleagues reported that they did not detect archaeal species in amniotic fluid of women with preterm pre-labor rupture of membranes.[826] However, it is still worth exploring the possibility of archaeal species in normal amniotic fluid during gestation.

10.3 Fungi

Overwhelming studies have focused on the human vaginal bacterial microorganisms, with far less data produced on the uterine fungal/yeast communities. DiGiulio and colleagues detected Candida species in the amniotic fluid of women with preterm pre-labor rupture of membranes.[826]

10.4 Viruses

During the past two decades, studies on viruses and phages in aquatic systems, such as marine and freshwater environments like oceans, lakes, springs, and rivers, have indicated that abundant viruses and phages can affect prokaryotic communities, such as bacteria and archaea, through lysis of prokaryotic cells and/or through horizontal gene transfer.[440,863-870] The pathological consequences of viral existence within amniotic fluid, such as preterm birth,[828,871-874] stillbirth,[43,875,876] sensorineural hearing loss,[877,878] and birth defects, have been recognized for a long time.[878,879]

10.4.1 Viruses in amniotic fluid from healthy pregnancies at term

Diverse viruses or viral nucleic acids have been reported to be detected in the amniotic fluid of healthy pregnancies at term in humans.[873,878,880-891] The most commonly detected viruses in amniotic fluid of normal pregnancies are adenovirus, human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), RSV, human papillomaviruses, herpes simplex virus (HSV), human herpesvirus type 6 (HHV6), human herpesvirus 7 (HHV7), parvovirus B19, and enteroviruses.[537,880,882,884,885,887,888,890-895] Wenstrom and colleagues found that 15% of women who delivered at term in the control group contained a single virus in the second-trimester amniotic fluid, while a single virus in the second-trimester amniotic fluid was detected in 8% of women with spontaneous pregnancy loss.[891] Cytomegalovirus has been found only in several controls and adenovirus has been detected in both cases and controls.[891] Baschat and colleagues showed that 6.4% of amniotic fluid samples were positive for viral genome.[885] In addition, Torque Teno virus (TTV) was detected in amniotic fluid [664] and TTV strains from infants were found not to be identical to the TTV strains from mothers.[660,896]

10.4.2 Viruses in placentas

Human endogenous retroviruses (HERVs)

In 1978, Nelson, Leong and Levy revealed that normal human placentas contain retrovirus-like particles and RNA-directed DNA polymerase activity,[897] which led to a shift in our understanding of the monopathological relationships between viruses and humans to a biological and evolutionary perspective.[898-900] It has been revealed that human endogenous retroviruses (HERVs) make up to 9% of the human genome and include more than 800 elements related to betaretroviruses.[898,901,902] The retroviral envelope proteins of human and murine, which are

called syncytins, can display different functions. For instance, Mangeney and colleagues showed that human syncytin-2 and mouse syncytin-B have immunosuppressive activity, while human syncytin-1 and mouse syncytin-A do not, but are able to induce cell–cell fusion,[900] and therefore, they may play a physiological role in placentation.[903] Noorali and colleagues found that the expression of syncytin-1 is localized in the syncytiotrophoblast layer and upregulated by progesterone.[904]

Cytomegalovirus (CMV)

Cytomegalovirus, parvovirus B19, and herpes simplex virus types 1 and 2 have been detected in placental specimens taken from full-term newborns,[876] which is believed to be a result of transplacental transmission of maternal viral sources.[876] A study on an experimental model showed that the migration of virus from the maternal to fetal side begins within 20 minutes and reaches a peak after 1-2 hours.[905]

10.5 Extracellular vesicles

Extracellular vesicles (also known as membrane-enclosed microentities in my other papers) have been detected in amniotic fluids of normal pregnant women.[906-911] Asea and colleagues reported that heat shock protein-containing exosomes were detected in mid-trimester amniotic fluid.[908] The syncytiotrophoblast and extravillous cytotrophoblasts make up the maternofetal interface,[912] and it has been shown that the placental syncytiotrophoblast secretes exosomes.[913-920] Hu and colleagues showed that miRNAs profile in the placenta of patients with severe pre-eclampsia was different from that in a normal placenta.[921] Stenqvist and colleagues found that bioactive FasL- and TRAIL-carrying exosomes secreted from human early and term placentas were able to cause apoptosis in activated immune cells.[922] Some researchers have suggested that the extracellular vesicles in amniotic fluids may come from both maternal and fetal sources.[907,909,911] There is evidence supporting this speculation because some exosomes in amniotic fluids have been found to contain a specific marker, CD24, which is a marker of extracellular vesicles in urine. Simce fetal urine is the main source of amniotic fluid, it is thought that CD24-contained exosomes in amniotic fluids are released by fetal renal epithelial cells.[907,911,923] In addition, exosomes have been found to be secreted by in vitro-produced embryos, as observed under a transmission electron microscope.[924,925] However, some exosomes in amniotic fluids do not contain CD24 and are thought to originate from the maternal side,[907,911] and maternal endometrial epithelial cells have been found to release exosomes/ microvesicles.[926] The importance of pregnancy-associated extracellular vesicles and their contents, such as proteins and microRNAs, in pregnancy has been studied and reviewed from both physiological and pathological perspectives recently.[924,926-933] For example, human placental microRNAs have been suggested to play a pathological role in preeclampsia [797,909,934-937] and a physiological role in placental and embryonic development.[926,938]

11. Other anatomic sites and body fluids in the human body

Bacteria, archaea, viruses/phages, extracellular vesicles (or called membrane-enclosed microentities), and fungi as the evolutionary background entities at the cellular and subcellular levels in the other anatomic sites and body fluids of the human body including human breastmilk, semen, follicular fluid, and the reproductive tract of men and women have been reviewd in the other two articles.[4,939]

12. Concluding Remarks

Since the emergence of culture-independent molecular approaches in the 1990s, our previously pitiable knowledge of the human body-associated microorganisms such as bacteria, viruses, and fungi has been enriched in an unprecedented pace, although the roles of these microorganisms were still mainly accounted for from Pasteur's pathogenic perspective. In Fimpology, the human body has been understood as the "niches" or "habitats" of evolutionary microentities including cellular, subcellular, and molecular entities.[1,2,4] In this article, the selected data from samples of healthy or asymptomatic human individuals in control groups of clinical investigations hace clearly revealed the following facts—that bacteria, archaea, fungi, viruses/phages, and extracellular vesicles as evolutionary background entities (EBEs) at the cellular and subcellular levels exist normally in the human skin, mucosa, and body fluids; and that human body-associated EBEs exhibit inter- and intra-individual variations in different anatomic sites such as the skin, oral cavity, gastrointestinal tract, nasopharyngeal tract, and respiratory tract. Describing the normally existing EBEs including various microorganisms in our bodies is the first priority for elucidating the ecological and evolutiological relationships between humans and host-associated evolutionary background entities. By putting our existing pieces together, we can theoretically easily find where the pieces are still missing, uncompleted, or outdated in the puzzle of EBEs in the human body, which will be enriched in the future.

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