The Fimpological View: The Future Synthesis of Biology, Ecology, and Evolutiology §

Shu-dong Yin
Cory H. E. R. & C. Inc. Burnaby, British Columbia, Canada
Email: sdyin@fimpology.com

Abstract

Recently, some pundits have called for a theoretical revolution in the life sciences, stating that it is outdated in the Modern Synthesis, our current view of evolution. However, the past decades, rapidly growing evidence has suggested that it may be time to turn data into knowledge. In the 1990s, several new interdisciplinary fields emerged that have partly addressed the deficiencies of the Modern Synthesis at the molecular, cellular and individual organism levels. However, as we continue to uncover more unknowns, the Modern Synthesis has faced increasing challenges, particularly when confronted with following three realities: (i) increasing evidences have indicated that the genetic introgression in both prokaryotes and eukaryotes is not only endogenous as what neo-Darwinians insisted on, but also from exogenous sources as what Lamarckians claimed; (ii) newly discovered sub-cellular and molecular entities that are the evolutionary consequence of natural selection have no place in traditional Darwinians' universal tree of life; and (iii) fertilized oocyte-mediated cytoplasmic heredity and pregnancy-associated eukaryotic integral cell inheritance are beyond the scope of DNA-centered modern genetics and genomics.

Additionally, the diversity and continuity of both abiotic and biological species throughout the evolutionary process require a unified theory. In this article, I discus these three challenges faced by the Modern Synthesis from a fimpological perspective, argue that it is time to upgrade "evolution" to "evolutiology," and propose that biology, ecology, and evolutiology should unite to form a new theoretical symphony for the future Synthesis.

Key words: biology, ecology, evolutiology, evolution, modern synthesis, evolutionary synthesis, neo-Darwinian synthesis, Evo-Devo, embryology, microbiology, integral cell inheritance, cytoplasmic inheritance, tree of life, molecular fossils, fimpology

Introduction

Since the early 20th century, Lamarck's theory of "the inheritance of acquired characteristics," which posits that evolutionary change is endowment is driven by an organism's experiences and environment, was discarded by many famous evolutionary biologists in the fields of genetics, biomathematics, zoology, paleontology and botany, they brought Darwinian natural selection and Mendelian genetics together to form the "Modern Synthesis" in the mid-20th century. Therefore, they are often referred to as "neo-Darwinians" and the theory they proposed is known as the "Modern Synthesis," "evolutionary synthesis," or "neo-Darwinian synthesis. " [1–6] Since then, the Modern Synthesis has been accepted as our modern understanding of how evolution works. In the Modern Synthesis, natural selection is the driving force for biological evolution; and the mutagenic traits are the objects that natural selection acts on.

Eleven years ago, Nobel laureate Sydney Brenner pointed out: "we are all conscious today that we are drowning in a sea of data and starving for knowledge," and "we need to turn data into knowledge." [7] Recently, a few evolutionary biologists strongly expressed the imperative necessity for a theoretical revolution in the new era of the life sciences.[4, 6, 8–16] Woese and Goldenfeld said, "It can no longer afford to keep the study of evolution within the narrow confines of the so-called modern evolutionary synthesis." [11] Koonin considered that "if the Modern Synthesis can be succinctly described as Darwinism in the Light of Genetics (often referred to as neo-Darwinism), then, the new stage is Evolutionary Biology in the Light of Genomics."[12] Boto argued that "selection and neutral variation, phylogeny and development, gradualism and innovation, vertical and horizontal inheritance: every one of these is a piece of an intricate puzzle, and it is thus necessary to piece them together to achieve a coherent understanding of evolution." [13] Prosser and colleagues believed that "the full potential of the ongoing revolution will not be realized if research is not directed and driven by theory."[17]

In the following content, I from a fimpological perspective discuss several newly emerged interdisciplinary fields and the following three challenges confronted by the Modern Synthesis: (i) Increasing evidence has indicated that the genetic introgression in both prokaryotes and eukaryotes is not only endogenous as neo-Darwinians insisted, but also from exogenous sources as Lamarckians claimed; (ii) newly discovered subcellular and molecular entities that are the evolutionary consequence of natural selection have no place in traditional Darwinian universal tree of life; and (iii) fertilized oocyte-mediated cytoplasmic heredity and pregnancy-associated eukaryotic integral cell inheritance are beyond the scope of DNA-centered modern genetics and genomics. Furthermore, I propos that now is the time to upgrade evolution to evolutiology; and that biology, ecology, and evolutiology should unite to form a theoretical symphony for the future synthesis.

Newly Emerged Interdisciplinary Studies

Since the 1990s, several new interdisciplinary fields have emerged for studying the relationships between developmental biology and evolutionary biology,[18] between developmental biology and ecology,[19] and between bacteriology and developmental biology.[20] These fields typically result from the combination of two different disciplines.

Evo-Devo — the study at the individual organism level

Evolutionary developmental biology, or "Evo-Devo", emerged in the 1980s as the integration of two disciplines—developmental biology and evolutionary biology. [18] The principle of Evo-Devo is that evolution arises from hereditable changes in development.[21] Evo-Devo aims to answer two major questions: (i) "how organisms evolve and change their shape and form" and (ii) "how alterations in gene expression and function lead to changes in body shape and pattern" [18] On the one hand, Evo-Devo has discarded the population-level model used in the Modern Synthesis and returned to the individual organism level, the foundation of traditional biology. On the other hand, Evo-Devo continues to study at the genetic level and therefore remains related to the Modern Synthesis.

However, even at the genetic level, there are also significant differences in understanding genes between Evo-Devo and the Modern Synthesis. For example, the Modern Synthesis sees spontaneous gene mutations, genetic recombination and genes drift in populations as the sources of genetic variation. In contrast, Evo-Devo revealed that changes in gene expression and function during development are influenced by individual internal and external factors and are the result of natural selection, and thus play a role in evolution. Evo-Devo argues that morphological evolution occurs through changes in embryonic development and predominantly relies on changes in the architecture of gene regulatory networks and the expression of numerous transcription factor genes.[10, 22–27]

Regulation of gene expression during development and its significance in evolution have been studied in Evo-Devo not only in multicellular eukaryotic organisms such as fishes,[28, 29] sea urchin,[30–33] and hemichordate Saccoglossus kowalevskii,[34] but also in prokaryotic organisms such as Escherichia coli.[35, 36] For instance, the expressions of genes for POU, LIMHD, Pax, Bar, Prox2, NK-2, T-box, MEF-2, Fox, Sox, Ets, and nuclear hormone receptor families have been analyzed during sponge embryogenesis,[37] and the spatial expression of SpHox7, SpHox8, SpHox9/10, SpHox11/13a and SpHox11/13b have been observed in sea urchin during larval development.[38] Other elements including small RNAs, riboswitches, RNA-binding proteins, sigma factors, protein-protein interactions, and DNA supercoiling have also been studied in Evo-Devo.[39, 40] While Evo-Devo has filled in the deficit at the molecular and individual level of the Modern Synthesis from a biological perspective, the shortage of the Modern Synthesis in macro- and micro-ecology remains, which Evo-Devo cannot address. Interestingly, 12 years ago Gilbert already highlighted the integration of ecology into developmental biology.[19] Combining Evo-Devo with

ecology may be a solution, but it raises the question "is Evo-Devo-Eco enough for the future Synthesis?"

The Integration of developmental biology into bacterial microbiology: bacterial group behavior in embryology

The study of the influence of bacteria on animal developmental processes is a newly emerged interdisciplinary field for the marriage of bacterial microbiology and developmental biology.[20, 41, 42] In the past two decades, accumulating evidence has shown that bacteria, as a critical evolutionary entity and environmental constituent, have a strong relationship with animal development.[41, 43–47] For example, many species of fish obtain luminescent bacteria such as Photobacterium phosphoreum to form their light organs.[48] Adult hydrothermal vent tubeworms (Vestimentifera, Siboglinidae) are nutritionally dependent on their bacterial symbionts during the early juvenile stages of the tubeworms.[49] It is also known that ruminants depend on their microorganism symbionts for digestion. To date, no animal species has been found to produce enzymes for the digestion of structural carbohydrates such as cellulose, hemicellulose and pectins.[50] However, wild ruminants have evolved the ability to digest fibrous plant materials, which depends on their harbored ruminal prokaryotic bacteria, eukaryotic fungi, and protists, but not on the function of the host eukaryotic cells of the ruminants themselves.[316] Approximately 75%-80% of the total energy in cows comes from short-chain fatty acids (SCFAs), which are formed through microbial fermentation.[50]

Symbiotic bacteria in the human body were first described by Antoni van Leewenhuock (1632-1723), a Dutch science giant, as early as the 1670s using his single-lens microscope. Since then, and even during the time of Pasteur and Koch, human symbiotic bacteria were overlooked for more than three centuries. The revitalization of the study on human symbiotic microorganisms occurred in the1990s, which can be attributed to the emergence and rapid development of microecology and cultivation-independent methods. Over the past decades, symbiotic bacteria have been widely studied in humans,[51–64] and many non-human animals such as rodents,[65–66] canine,[67–68] feline,[69] cow,[70, 71] sheep,[72, 73] swine,[74–76] birds,[77–79] worms,[80–83] leech,[84, 85] insects,[86–93] and nematodes.[94]

Despite many descriptive studies on symbiotic bacteria, their significance in biology and ecology has gradually attracted researchers' attention. Eleven years ago, Margaret McFall-Ngai called for the integration of developmental biology into bacterial microbiology due to her increasing awareness of the influence of bacteria on animal development.[20] McFall-Ngai asserted that "without such an integration these two fields will run the risk of missing important clues to both the evolution of animal–bacterial interactions and the mechanisms underlying animal developmental processes."[20] McFall-Ngai asked two critical questions: "what portions of an animal's life cycle are affected by interactions with coevolved bacterial partners? And, how are these

interactions integrated into the developmental program of a given host animal species?" [20] Doubtlessly, McFall-Ngai pointed out a new and correct direction for the development of developmental biology. However, following this path will confront many known and unknown problems. For instance, as we know that eukaryotic organisms are the starting line for the research of developmental biology, and that bacterial microorganisms are the most diverse prokaryotes on Earth, the integration between developmental biology and bacterial microbiology in nature involves prokaryotes and eukaryotes, which will inevitably be related to the evolutionary relationship between them. In fact, the deficiency of the traditional Darwinian universal tree of life has suggested that bacterial microbiology alone may not be sufficient to support the extension of developmental biology, which will be discussed further in the following content.

Combination of microbiology with ecology

In 2007, Prosser and colleagues emphasized the importance of another newly emerged discipline, microbial ecology, the combination of microbiology with ecology.[17] Recently, Koonin and Wolf pointed out "the combination of genomics and microbiology is indeed critical in the advent of this new age of evolutionary biology." [5] Woese emphasized Beijerinck's view of combination of macro-biology, microbiology, micro-ecology, and evolution. [11] It is true that uniting traditional biology and its subfields with micro-ecology is a correct direction for the future synthesis, but it is still not enough. In addition, there has not been any evolutionary theory to bridge the gap between microbial ecology and macrobial ecology [17, 95]. The same problem also exists between macro-biology and microbiology. Interestingly, although prokaryotic bacteria were discovered Antoni van Leewenhuock in the17th century, their place in the traditional Darwinian universal tree of life was not recognized till the 1970s, when Carl Woese discovered Archaea. [96–98] Since then, Bacteria, Archaea, and Eukarya have been recognized as the three domains of life.[99]

In fact, the initial understanding on evolution was established based the observation of natural plant and animal species and fossils; and therefore the lowest starting point of evolution was at the eukaryotic cell level since August Weismann (1834-1914), the German biologist who established the first theoretical bridge between Darwin's evolutionary theory and the cell theory. However, the prokaryote-rooted recognition in the traditional Darwinian universal tree of life has faced significant challenges in recent years,[100, 101] especially, when facing newly discovered sub-cellular and molecular entities, whose evolutionary significance clearly exceeds the traditional scope of microbiology, biochemistry, biophysics, and cytology. For instance, the largest viruses, Pandoraviruses, recently discovered by Philippe and colleagues, [102] and the second largest viruses, Mimivirus, discovered by Raoult's team 10 years ago, [103, 104] suggest that the current three domains of life (bacteria, archaea, and eukarya) may require revision. On the other hand, the combination of anthropology with human genetics and genomics over the past decades has raised many new questions about the origin, evolution, and dispersal of modern humans on Earth, for which we lack a theory that can

account for both social and biological perspectives. Therefore, we need a novel theoretical bridge to span the vast gaps between ‘macro’ and ‘micro’, ‘abiotic’ and ‘biotic’, ‘individuality’ and ‘population’, and ‘extant’ and ‘ancient’; without it, we will be unable to accurately predict evolutionary trends.

Challenges Faced by the Modern Synthesis

I. The genetic introgression from both endogenous and exogenous sources: DNA–centered inheritance has both ‘hard’ and ‘soft’ characters

Since H. J. Muller discovered in 1927 that mutation could caused by ionizing radiation, for years, spontaneous mutations at single-nucleotides under natural conditions, genetic recombination, and genetic drift have been accepted by neo-Darwinians as the source of genetic variation.[105, 106]

Because the Modern Synthesis holds that the hereditary material is resistant to environmental influences (except, of course, mutagenic effects), the nucleotide sequence of DNA passed to offspring is constant, a ‘hard inheritance’, and only changes by rare random mutation.[2, 107–109]

The Modern Synthesis completely discards Lamarckians’ concept that nucleotide sequence of DNA passed to offspring is changeable under the impact of environment, for which Ernst Mayr coined the term ‘soft inheritance’; therefore, “Neo-Darwinism may be defined as the Darwinian theory of evolution without recourse to any kind of soft inheritance.” [110] In the Modern Synthesis, mutations (genetic novelties) chosen by natural selection arise by chance, and usually are small genetic variations within populations; therefore, these kinds of evolutionary changes are tiny and are called ‘microevolution’. Large evolutionary changes, such as a new species or divergence that are called ‘macroevolution’, are the consequence of the accumulation of microevolution over many generations; and moreover, genetic mutations within existing chromosomes have been seen as the only source of new selectable genetic variation. Indeed, if we see the Modern Synthesis as the metaphor of a bridge for evolution, it was actually an arch bridge depending on merely two piers: one was at the molecular level; and another was at the macroorganism level.

However, controversies and questions around the above two conclusions have not stopped, such as “under what conditions does geographic isolation constitute a reproductive isolating barrier?” [111] “how does a given evolutionary principle or phenomenon actually operate in an individual case?” [1] Moreover, while the synthesis narrowed the gap between the experimental geneticists and the naturalists, the evolutionary relationships between species and their environment have been drifted apart more than before. The picture described by the Modern Synthesis for evolution is incomplete.

Since the rediscovery of the Mendel Law in 1900, biologists soon discovered that chromatin in nucleus is the hereditary material, which ordinarily looks like a ball of

tangled string, but begins to turn into rod like chromosomes during cell division. Chromosomes can show a unique banding pattern after special dye. It was a much clearer understanding than before that the genes described by Mendel should located in chromatin or chromosomes. However, at that time the dominant comprehension among geneticists was that "genes were preprogrammed, and like beads on a string, occupied a fixed place on chromosomes and displayed a fixed function." [112]. That was why although transposable elements (TEs) were discovered by Barbara McClintock in the 1940s,[113] their significance and importance were not accepted for many years until in 1983; and some 30 years after her discovery, McClintock was awarded the Nobel Prize in Physiology or Medicine. Clearly, the tremendous evolutionary gap between the molecular world and the macroorganism world had been underestimated or ignored in the Modern Synthesis, which would seem unbridgeable if an overpass did not have underwater piers. Love also noticed that "the synthetic theory of evolution did not capture multiple levels of biological organization." [114]

Recently, Weissing, Edelaar, and van Doorn pointed out that such 'gap' exists "between micro-evolution (that mainly occurs at or below the species level) and macro-evolutionary processes like adaptive radiations that largely occur above the species level." [115]

After entering the 21st century, the inadequacy of the Modern Synthesis has become more and more dazzling, and has encountered some criticisms.

Marc Kirschner and John Gerhart argued that the Modern Synthesis lacked a pillar to explain the feasibility of evolutionary change.[116]

Mary West-Eberhard stated straightforwardly that "The synthesis was not a monolithic affair" for it refused the natural selection operating on the molecular level such as acting on genotype or the gene.[2]

Denis Noble argued that the Modern Synthesis formed "barriers to the integration of physiological science with evolutionary theory." [117]

Indeed, the organ-centered physiological systems and human individuals have been studied by modern physiology since the 19th century; however, both are the two remarkable deficiencies in the Modern Synthesis.

According to the famous saying of the French physiologist Claude Bernard (1813-1878) "medicine is the science of sickness; physiology is the science of life; thus physiology must be the scientific basis of medicine," [118] It is clearly that such barriers created by the Modern Synthesis have hindered not only the integration of physiology and evolutionary theory, but also delayed the combination of medical science with evolutiology.

The molecular and evolutionary developmental biologist Sean Carroll humorously complained that [the Modern Synthesis] "forces the explanation toward mathematics and descriptions of genes, and away from butterflies and zebras." [105]

It's not difficult to understand that the literature of William Shakespeare can be studied not only through reading the words, sentences, paragraphs, plots, and even studying the author's writing styles, but also through calculating the change in alphabet letters' frequencies.

Similarly, the biological evolutionary history on this planet can also be studied not only at the various levels of sub-cellular entities, cellular organisms, individuals, and

social populations, but also at the molecular level through the changes in gene frequencies, because they all have constituted various facets of biological evolution over the past 3.5 billion years.

Since the discovery of transposable elements and horizontal gene transfer between the 1940s and the 1950s,[113, 119–121] and endogenous retroviruses in the late 1960s and early 1970s,[122] accumulating evidence has indicated that genetic alteration in both prokaryotes and eukaryotes is not only endogenous, as what neo-Darwinians insisted, but also from introgression from exogenous sources, as Lamarckians claimed.[123–145] For instance, over the past decades, experimental evidence has shown that at the cellular level, horizontal gene transfer may occur from a prokaryote to a prokaryote,[146–150] from a prokaryote to a eukaryote,[142, 143, 145, 147] from a eukaryote to a prokaryote,[139, 151] or from a eukaryote to a eukaryote.[152, 153]

II. Sub-cellular and molecular entities have no place in traditional Darwinians' universal tree of life

It was Antoni van Leewenhuock who opened the first window of the microorganism world for human beings in the17th century; however, the evolutionary relationship between bacteria and traditional biology was not generally recognized until the late 1970s.[154] The electron microscope, invented by Germans Ernst Ruska and Max Knoll, has opened the second window for watching subcellular entities of the microorganism world since the 1930s, which made it possible to obtain clear images of many entities smaller than cells. Viruses and exosomes are two examples of them. Viruses are usually about 20–200 nm long; [155, 156] and exosomes are between 30 nm and 1000 nm in diameter.[157–159] The third window for watching the micro world from an evolutionary perspective has been opened by a series of discoveries of evolutionary molecular entities, including RNA and prion, which allows us to watch those bioactive molecules beyond the traditional scope of biochemistry and biophysics. Indeed, as we dig deeper into the micro world, the border of microorganisms gradually disappeared; and the sub-cellular level is connected with the molecular level through evolutionary mechanisms.

Viruses—no place in Darwinians' universal tree of life

The discovery of viruses should be attributed to the original curiosity of Louis Pasteur, who in the late 19th century hypothesized that pathogenic organisms smaller than bacteria might exist because many infectious diseases could not be detected and explained by his bacteriological techniques and theory. Interestingly, as bacteria once did, viruses were also first linked only with diseases in plants, humans, and non-human animals. It is well known that rabies, measles, smallpox, chickenpox, mumps, yellow fever, AIDS, hepatitis, and H1N1flu are all caused by relevant pathogenic viruses.

Since the late 20th century, the ubiquity and diversity of viruses have been gradually uncovered; viruses are believed to be the most abundant evolutionary subcellular entities

on Earth, with an estimated number of 10^{30-31}. [12, 160–163] It has been a truly astonishing, puzzling, and inspiring finding since the 1980s that the viral abundance exceeds bacterial abundance in different marine and freshwater systems.[155, 164, 165] In fact, viruses have been shown to play a major role in lateral gene transfer mechanisms.[150, 166–176] Unlike cellular organisms, viruses cannot replicate on their own and are totally dependent on their host cells' machinery to make copies of themselves. Therefore, viruses are usually considered to have no place in Darwinians' universal tree of life [177–179] because it is an evolutionary tree for cellular life,[170] which was previously believed to be a drawback of the universal tree of life.[180]

Another major reason for debating the position of viruses in the tree of life is that the origin of viruses is unclear.[173, 181–183] Some researchers believe that viruses originated from cells,[184, 185] which could go back at least to the last universal common ancestor (LUCA) of the cells because viruses were found in archaeal, bacterial, and eukaryal cells;[186–188] and moreover, Michael Bishop and Harold Varmus even discovered the cellular origin of retroviral oncogenes, for which they both were awarded the Nobel Prize in 1989. However, on the other hand, it has also been shown that eukaryotic cells can acquire genes from viruses. For example, syncytins (syncytin-1 and -2), a protein expressed mainly in placental syncytiotrophoblasts, is encoded by the envelope gene of a human endogenous defective retrovirus, HERV-W.[189, 190] Therefore, the answer for the question of the origin of viruses cannot be found at the cellular level. Recently, the giant viruses, such as Pandoraviruses [102] and Mimivirus [103, 104] have made the origin of viruses more complicated, and further challenged Darwinians' universal tree of life. Moreover, unlike the phylogenetic comparison in bacterial communities via 16S rRNA, it is impossible to apply it in viruses due to the lack of a universal marker gene,[191] which has further impeded our understanding of the viral world.

In my opinion, viruses evolved as an independent evolutionary entity with high diversity long before the emergence of primary cell-like organisms; the emergences of Virus Time might have occurred between the Latest Universal Organic Molecular Ancestor (LUOMA) and the Earliest Universal Cellular Ancestor (EUCA); and Virus Time might have been preceded by proteins, lipids, carbohydrates, membranes, and polyribonucleotide.[100, 101] Moreover, some independent vial strains remain in their original forms. Some free viral strains or species became extinct at later evolutionary time points, and their symbiotic strains continue to exist along the cellular path.[169,181,182,192] Therefore, the ancient viral polyribonucleotide, which is present within the genomes of extant prokaryotes and eukaryotes, could be named 'viral fossils', one class of molecular fossils present within extant cells.[100, 101] Recently, Emerman and Malik proposed a new discipline called 'Paleovirology' to study ancient extinct viruses (called 'paleoviruses') and the their effects on the evolution of their hosts.[176] Doubtlessly, although viruses have no place in Darwinians' tree of cellular life, they play an important role in both pre-life and life evolution and have an unshakable place in the pre-cellular universal tree.[100, 101]

Other evolutionary sub-cellular entities—no place in Darwinians' Universal Tree of Life

Over the past decades, another class of sub-cellular entity that has attracted much research attention is various types of membrane-enclosed microentities, such as ectosomes, exosomes, microvesicles and apoptotic bodies.[157–159, 193–199] For instance, in eukaryotic cells, as a membrane-enclosed microentity, exosomes are a heterogeneous population of vesicles with a diameter of 30 to 1000 nm,[157–159] and are formed intracellularly through endocytic invagination and then released into the extracellular space through a multivesicular body (MVB) transmission mechanism.[194] To date, exosomes have been shown to be secreted by different eukaryotic cell types, such as red blood cells,[200–204] peripheral blood mononuclear cells (PBMC),[205] dendritic cells,[198, 206] microphages,[207, 208] T lymphocytes,[207, 209] B lymphocytes,[210–212] platelets,[207, 213–215] reticulocytes,[207] prostate acinar cells,[216] intestinal epithelial cells,[217] renal epithelial cells,[218] tracheobronchial epithelial cells,[219] endothelial cells,[220] neural cells,[221] stem cells/progenitor cells,[159, 222–226] syncytiotrophoblast,[227–231] and fungal cells,[232–236] such as Cryptococcus neoformans,[234, 237–239] Malassezia sympodialis,[235] Saccharomyces cerevisiae,[233, 236] and Histoplasma capsulatum.[233]

In addition, prokaryotic, Gram-negative, and Gram-positive bacteria also secrete a membrane-coated subcellular entity, called bacterial membrane vesicles (MVs).[240, 242–244, 253] The size of bacterial MVs ranges from 50 to 250 nm in diameter.[245, 246] The membrane of MVs consists of two layers: an outer leaflet of lipopolysaccharide (LPS) and an inner leaflet of phospholipids.[244] MVs are formed through the 'bulging and pinching off' of the outer membrane in most Gram-negative bacteria,[240, 244, 253] and they serve as vehicles for trafficking bioactive molecules such as proteins, lipids, and nucleic acids (including mRNAs and miRNAs).[198, 242–244, 246–250] MVs have been shown to be able to fuse with the outer membrane of Gram-negative cells such as Salmonella typhi, S. enterica, and Escherichia coli, but not with Gram-positive membranes.[245, 251] Although bacterial membrane vesicles were described four decades ago,[245, 253] their biological significances was not widely recognized until recent years. Membrane-enclosed vesicles have been shown to have evolutionary significance, for instance, in promoting intercellular communication.[198, 252–255] Recently, the role of exosomes in immune stimulatory-, inhibitory-, or tolerance-inducing functions has been attracting much attention.[212] Therefore, membrane-enclosed subcellular vesicles have some similarities in many characteristics with enveloped viruses.[193]

Indeed, from an evolutionary perspective, the ubiquitous existence of membrane-coated subcellular vesicles such as MVs and exosomes in prokaryotes and eukaryotes strongly suggests that there may be ancestors of these subcellular vesicles, and the origin of membrane-coated subcellular vesicles is also unclear. Although membrane-coated subcellular vesicles have no place in Darwinians' tree of cellular life, they may have emerged between the Earliest Universal Cellular Ancestors (EUCAs) and the Latest Universal Organic Molecular Ancestors (LUOMAs).[100, 101]

Evolutionary molecular entities—no place in Darwinians' universal tree of life

Thirty years ago, Sidney Altman and Thomas R. Cech published their finding that RNA, a polyribonucleotide, can also function as a catalytic enzyme in addition to its well-known role as a template for replication and read-out of genetic information.[256, 257] For this discovery, they were awarded the Nobel Prize in chemistry in 1989. The dual functions of RNA have provided new evidence for our further understanding of evolution and the root of Darwinians' tree of life at the molecular level. Additionally, the recent discoveries of microRNAs (miRNAs) and prions have completely changed our traditional understandings of them in biochemistry and genetics.

microRNAs (miRNAs)

In 1993, Lee, Feinbaum, and Ambros published their finding that the small RNAs encoded by the Caenorhabditis elegans gene lin-4 displayed regulatory functions,[258] which was later believed to be the first time the noncoding RNAs world was opened.[259, 260] Over the past two decades, it has been recognized that (i) these small RNAs belong to a large family of noncoding RNAs (approximately 22-24 nt) known as microRNAs (miRNAs); (ii) miRNAs play a role in regulating gene expression by causing targeted post-transcriptional gene silencing, which directly influences virtually all biological processes and often results in physiological or pathological consequences; (iii) miRNAs are found in the intracellular spaces of both prokaryotes and eukaryotes, and in extracellular spaces including various body fluids; and (iv) miRNAs are also found in subcellular entities such as viruses and membrane-coated vesicles including microvesicles and exosomes.[194, 261–275] Moreover, since the first description of viral microRNA (miRNAs) by Pfeffer and colleagues in 2004,[262, 276] more than 225 miRNAs have been discovered in double-stranded DNA viruses, mainly herpesviruses and polyomaviruses,[275, 277] which our existing knowledge cannot account for.

Protein World

One of the important discoveries of the 20th century was the finding of prions, which not only impacted our understanding of medical etiology, but also modified our comprehension of evolution. American Stanley Prusiner first added prions, a kind of pathogenic protein "to the list of well-known infectious agents including bacteria, viruses, fungi, and parasites." [278] Since S. Prusiner was awarded the Nobel Prize in Physiology or Medicine in 1997, the following newly emerged understandings from the study of prions have further challenged the Modern Synthesis: (i) prions are self-replicating protein entities. Like RNAs' ability to act as both templates and catalytic enzymes, prions can also act as templates for their own synthesis in addition to their well-known catalytic activity.[279–283] Furthermore, prions can mediate protein conformation-based

inheritance,[14, 284–293] which has clearly indicated that at the molecular level, oligopeptides can also play a role as hereditary information carriers in addition to polyribonucleotides such as RNA and DNA; (ii) the switching of a protein from the [psi−] state to the prion state [psi+] is environment-driven and results in phenotypic alterations that are the consequence of protein folding variations rather than polyribonucleotide-associated changes;[294–301] and (iii) recently, the notion that prions are nonpathogenic has also been proposed.[302, 303] In addition, recently, the evolutionary relationship between inorganic metal elements and organic molecules has caught the attention of some researchers;[304] for example, Mulkidjanian and Galperin proposed the "Zinc World" hypothesis on the role of zinc sulfide (ZnS) in the evolution of organic entities such as RNA and protein.[305–307]

III. Fertilized oocyte–mediated cytoplasmic heredity and pregnancy–associated eukaryotic whole cell inheritance

At the molecular level, modern DNA-centered genetics is no longer recognized as the only factor in the hereditary transmission of characters.[14,284,285,287–293,302,308] Moreover, at the cellular level, cytoplasmic heredity and whole-cell inheritance are also thought to be involved in the transmission of characters from the mother to both male and female offspring.[117,136,309–311] Fertilized oocyte-mediated cytoplasmic heredity and pregnancy-associated eukaryotic whole-cell inheritance are two phenomena that are missed in DNA-centered Mendelian genetics. According to Mendel's Law of Heredity and modern DNA-centered genetics, it has been generally accepted for over a century that female and male play an equal role in biological heredity. Recently, six models of pregnancy-associated eukaryotic cell transmission between mother and offspring have demonstrated their significance in biology and ecology from the fimpological perspective.[312,313]

Based on the above understanding, a model for female-relayed whole-cell and cytoplasmic inheritance further illustrates that eternal embryonic/fetal stem cells and maternal oocytoplasm could be transferred to the offspring generation by generation along the pregnancy-associated female path. Moreover, both fertilized oocyte-mediated cytoplasmic inheritance (FOMCI) and pregnancy-associated whole-cell inheritance (PAWCI) are determined by reproductive female offspring, but not by reproductive male offspring because their continuity stops at male offspring, indicating that female and male actually play an unequal role in biological heredity. [314] Clearly, modern genetics alone fails to reveal the real dispersal patterns of FOMCI and PAWCI, and therefore, is not enough to reflect the multiple roles the female plays in biological heredity, which is not only a deficiency of our understanding on biological heredity, but also a scarcity in the Modern Synthesis.

Upgrading Evolution Theory to Evolutiology

Ernst Mayr said: "Our understanding of the world is achieved more effectively by conceptual improvements than by the discovery of new facts, even though the two are not mutually exclusive." [315] To date, our entire knowledge and studies on the life sciences have focused on three major class questions: (1) questions dealing with the distribution and taxonomy, and the bio-functions, reproduction, inheritance, growth, and development of extant macro- and micro-biological species have constituted the initial driving power for traditional biology and its sub-branches including anatomy, botany, zoology, microbiology, genetics, genomics, developmental biology, embryology, physiology, and fetology; (2) questions about the relationship and interaction between a given species or entity and its relevant environmental species or entities gave birth to ecology in the 19th century; and (3) what are the regular patterns or principles for connections between extant species and ancient species in geological time scale? And what are the mechanisms for speciation, continuity, extinct and diversity of species? These questions have resulted in our recognition of evolution, for which, our theoretical exploration and decipherment initiated mainly by Lamarck, Darwin and Wallace have been accumulating for more than two centuries. The Modern Synthesis, as one of milestones of evolution theories in the life sciences in the 20th century, symbolizes the wisdom of many masters including Theodosius Dobzhansky, Thomas Hunt Morgan, Herman Muller, Ronald Fisher, George Gaylord Simpson, G. Ledyard Stebbins and Ernst Mayr. However, after entering the 21st century, the Modern Synthesis is no longer enough to express our latest understanding of evolution. From a fimpological view, evolution is happening all the time at every evolutionary level. Studying evolution is not only a theoretical exploration, but also an experimental research. There is no chasm in the entire evolution process, but only temporary gaps in our understanding. Now is the time to upgrade evolution to evolutiology. One direction for the future Synthesis should be to integrate with biology, ecology, and evolutiology to form a new theoretical system, in which biology, ecology, and evolutiology constitute a three-dimensional (3-D) profile to reflect the continuing evolutionary process of entities and environments from the past to the present, and then to the future.

Concluding Remarks

Since the fast development of ecology in the 1980s, traditional biology and its branches have been revealed to be closely associated with ecology and its branches. Moreover, after studying evolution for more than one and half centuries, now is the time to upgrade "evolution" to "evolutiology," around which, some relevant theoretical explorations will be elucidated later in other articles. Therefore, the future novel theoretical system for the life sciences should cover the content of three major disciplines: biology, ecology, and evolutiology, and form a novel theoretical system for the future synthesis.

[§ This revision of "The Fimpological View: The Future Synthesis of Biology, Ecology, and Evolutiology" was finished on January 12, 2023]

References

1. Ernst Mayr. The growth of biological thought: diversity, evolution, and inheritance. Pp: 566–570. Belknap Press. USA. 1982
2. West-Eberhard MJ. Colloquium Paper: Systematics and the Origin of Species: Developmental plasticity and the origin of species differences. Proc Natl Acad Sci USA 2005; 102(suppl 1): 6543–9
3. Hey J, Fitch WM, Ayala FJ. Systematics and the origin of species: an introduction. Pro Natl Acad Sci USA. 2005; 102(Suppl 1): 6515–9
4 Pigliucci M. An extended synthesis for evolutionary biology. Ann N Y Acad Sci. 2009; 1168: 218–28
5. Koonin EV, Wolf YI. Evolution of microbes and viruses: a paradigm shift in evolutionary biology? Front Cell Infect Microbiol. 2012; 2: 119
6. Noble D. Physiology is rocking the foundations of evolutionary biology. Exp Physiol. 2013; 98(8): 1235–43
7. Brenner S. Nature's gift to science. Nobel Lecture, December 8, 2002. Available from: http://nobelprize.org/nobel_prizes/medicine/laureates/2002/brenner–lecture.pdf (Accessed on August 8, 2007)
8. Pigliucci M. Do we need an extended evolutionary synthesis? Evolution. 2007; 61(12): 2743–9
9. Rose MR, Oakley TH. The new biology: beyond the Modern Synthesis. Biol Direct. 2007; 2: 30
10. Carroll SB. Evo-devo and an expanding evolutionary synthesis. A genetic theory of morphological evolution. Cell. 2008; 134(1): 25–36
11. Woese CR, Goldenfeld N. How the microbial world saved evolution from the scylla of molecular biology and the charybdis of the modern synthesis. Microbiol Mol Biol Rev. 2009; 73(1): 14–21
12. Koonin EV. Darwinian evolution in the light of genomics. Nucleic Acids Res. 2009; 37: 1011–3414.
13. Boto L. Horizontal gene transfer in evolution: facts and challenges. Proc R Soc B. 2010; 277(1683): 819–27
14. Koonin EV. Does the central dogma still stand? Biol Direct. 2012; 7: 27
15. Witzany G, Baluska F. Life's code script does not code itself. The machine metaphor for living organisms is outdated. EMBO Rep. 2012; 13(12): 1054–1056
16. Baluska F, Witzany G. At the dawn of a new revolution in life sciences. World J Biol Chem. 2013; 4(2): 13–5
17. Prosser JI, Bohannan BJM, Curtis TP, Ellis RJ, Firestone MK, Freckleton RP, et al. The role of ecological theory in microbial ecology. Nature Reviews Microbiology. 2007; 5(5): 384–92

18. Goodman CS, Coughlin BC. Special feature: the evolution of evo-devo biology. Proc Natl Acad Sci USA. 2000; 97(9): 4424–5
19. Gilbert S. Ecological developmental biology: Developmental biology meets the real world. Dev Biol. 2001; 233(1): 1–12
20. McFall-Ngai MJ. Unseen forces: the influence of bacteria on animal development. Dev Biol. 2002; 242(1): 1–14
21. Gilbert SF, McDonald E, Boyle N, Buttino N, Gyi L, Mai M, et al. Symbiosis as a source of selectable epigenetic variation: taking the heat for the big guy. Phil Trans R Soc B. 2010; 365(1540): 671–8
22. Peterson KJ, Davidson EH. Special Feature: Regulatory evolution and the origin of the bilaterians. Proc Natl Acad Sci USA. 2000; 97(9): 4430–3
23. Smith KK. Time's arrow: heterochrony and the evolution of development. Int J Dev Biol. 2003; 47(7–8): 613–21
24. Prud'homme B, Gompel N, Carroll SB. Emerging principles of regulatory evolution. Proc Natl Acad Sci USA. 2007; 104(suppl 1): 8605–12
25. Oliveri P, Tu Q, Davidson EH. Global regulatory logic for specification of an embryonic cell lineage. Proc Natl Acad Sci USA. 2008; 105(16): 5955–62
26. Ettensohn CA. Lessons from a gene regulatory network: echinoderm skeletogenesis provides insights into evolution, plasticity and morphogenesis. Development. 2009; 136(1): 11–21
27. Arenas-Mena C. Indirect development, transdifferentiation and the macroregulatory evolution of metazoans. Phil Trans R Soc B. 2010; 365(1540): 653–69
28. Derome N, Bernatchez L. The transcriptomics of ecological convergence between 2 limnetic coregonine fishes (Salmonidae). Mol Biol Evol. 2006; 23(12): 2370–8
29. Jeukens J, Bittner D, Knudsen R, Bernatchez L. Candidate genes and adaptive radiation: Insights from transcriptional adaptation to the Limnetic Niche among Coregonine fishes (Coregonus spp., Salmonidae). Mol Biol Evol. 2009; 26(1): 155–66
30. Smith J, Davidson EH. Regulative recovery in the sea urchin embryo and the stabilizing role of fail–safe gene network wiring. Proc Natl Acad Sci USA. 2009; 106(43): 18291–6
31. Oliveri P, Walton KD, Davidson EH, McClay DR. Repression of mesodermal fate by foxa, a key endoderm regulator of the sea urchin embryo. Development. 2006; 133(21): 4173–81
32. Morris VB. Origins of radial symmetry identified in an echinoderm during adult development and the inferred axes of ancestral bilateral symmetry. Proc R Soc B. 2007; 274(1617): 1511–6
33. Rottinger E, Saudemont A, Duboc V, Besnardeau L, McClay D, Lepage T. FGF signals guide migration of mesenchymal cells, control skeletal morphogenesis of the skeleton and regulate gastrulation during sea urchin development. Development 2008; 135(2): 353–65
34. Aronowiczand J, Lowe CJ. Hox gene expression in the hemichordate Saccoglossus kowalevskii and the evolution of deuterostome nervous systems. Integr Comp Biol 2006; 46(6): 890–901
35. Riordan JT, Tietjen JA, Walsh CW, Gustafson JE, Whittam TS. Inactivation of alternative sigma factor 54 (RpoN) leads to increased acid resistance, and alters locus of

enterocyte effacement (LEE) expression in Escherichia coli O157 : H7. Microbiology. 2010; 156(3): 719–30
36. Tenaillon O, Denamur E, Matic I. Evolutionary significance of stress–induced mutagenesis in bacteria. Trends Microbiol. 2004; 12(6): 264–70
37. Degnan BM, Leys SP, Larroux C. Sponge development and antiquity of animal pattern formation. Integr Comp Biol. 2005; 45(2): 335–41
38. Arenas-Mena C, Cameron A, Davidson E. Spatial expression of Hox cluster genes in the ontogeny of a sea urchin. Development. 2000; 127(21): 4631–43
39. Martinez–Nunez MA, Perez-Rueda E, Gutierrez–Rios RM, Merino E. New insights into the regulatory networks of paralogous genes in bacteria. Microbiology. 2010; 156(1): 14–22
40. Poli D, Jacobs M, Cooke TJ. Auxin regulation of axial growth in bryophyte sporophytes: its potential significance for the evolution of early land plants. Am J Bot. 2003; 90(10): 1405–15
41. Hooper LV, Gordon JI. Commensal host–bacterial relationships in the gut. Science. 2001; 292(5519): 1115–8
42. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host–microbial relationships in the intestine. Science 2001; 291(5505): 881–4
43. Douglas AE. Mycetocyte symbiosis in insects. Biol Rev. 1989; 64(4): 409–34
44. Cebra JJ. Influences of microbiota on intestinal immune system development. Am J Clin Nutr. 1999; 69(5): S1046–51
45. Umesaki Y, Setoyama H. Structure of the intestinal flora responsible for development of the gut immune system in a rodent model. Microbes Infect. 2000; 2(11): 1343–51
46. Moran NA, Baumann P. Bacterial endosymbionts in animals. Curr Opin Microbiol. 2000; 3(3): 270–5
47. Phillips ML. Interdomain interactions: dissecting animal-bacterial symbioses. BioScience. 2006; 56(5): 376–81 Available from http://labs.medmicro.wisc.edu/mcfall–ngai/media/bioscimay06.pdf
48. Dunlap PV, Ast JC. Genomic and phylogenetic characterization of luminous bacteria symbiotic with the deep-sea fish Chlorophthalmus albatrossis (Aulopiformes: Chlorophthalmidae). Appl Environ Microbiol. 2005; 71(2): 930–9
49. Nussbaumer AD, Fisher CR, Bright M. Horizontal endosymbiont transmission in hydrothermal vent tubeworms. Nature. 2006; 441(7091): 345–8
50. Collinder E, Bjornhag G, Cardona M, Norin E, Rehbinder C, Midtvedt T. Gastrointestinal host-microbial interactions in mammals and fish: Comparative studies in man, mice, rats, pigs, horses, cows, elk, reindeer, salmon and cod. Microb Ecol Health Dis. 2003; 15: 66–78
51. Zoetendal EG, Akkermans AD, De Vos WM. Temperature gradient gel electrophoresis analysis of 16S rRNA from human fecal samples reveals stable and host–specific communities of active bacteria. Appl Environ Microbiol. 1998; 64(10): 3854–9
52. Matsuki T, Watanabe K, Tanaka R, Fukuda M, Oyaizu H. Distribution of bifidobacterial species in human intestinal microflora examined with 16S rRNA gene-targeted species–specific primers. Appl Environ Microbiol. 1999; 65(10): 4506–12

53. Suau A, Bonnet R, Sutren M, Godon J-J, Gibson GR, Collins MD, Dore J. Direct analysis of genes encoding 16S rRNA from complex communities reveals many novel molecular species within the human gut. Appl Environ Microbiol. 1999; 65(11): 4799–807
54. Schwiertz A, Blay GL, Blaut M. Quantification of different Eubacterium spp. in human fecal samples with species–specific 16S rRNA–targeted oligonucleotide probes. Appl Environ Microbiol. 2000; 66(1): 375–82
55. Harmsen HJM, Raangs GC, He T, Degener JE, Welling GW. Extensive set of 16S rRNA–based probes for detection of bacteria in human feces. Appl Environ Microbiol. 2002; 68(6): 2982–90
56. Shen J, Zhang B, Wei G, Pang X, Wei H, Li M, Zhang Y, Jia W,. Zhao L. Molecular profiling of the Clostridium leptum subgroup in human fecal microflora by PCR-denaturing gradient gel electrophoresis and clone library analysis. Appl Environ Microbiol. 2006; 72(8): 5232–8
57. Vanhoutte T, De Preter V, De Brandt E, Verbeke K, Swings J, Huys G. Molecular monitoring of the fecal microbiota of healthy human subjects during administration of lactulose and Saccharomyces boulardii. Appl Environ Microbiol. 2006; 72(9): 5990–7
58. Weng L, Rubin EM, Bristow J. Application of sequence–based methods in human microbial ecology. Genome Res 2006; 16(3): 316–22
59. Rudi K, Zimonja M, Kvenshagen B, Rugtveit J, Midtvedt T, Eggesbo M. Alignment–independent comparisons of human gastrointestinal tract microbial communities in a multidimensional 16S rRNA gene evolutionary space. Appl Environ Microbiol. 2007; 73(8): 2727–34
60. Li M, Wang B, Zhang M, Rantalainen M, Wang S, Zhou H, et al. Symbiotic gut microbes modulate human metabolic phenotypes. Proc Natl Acad Sci USA. 2008; 105(6): 2117–22
61. Leuckfeld I, Olsen I, Geiran O, Bjortuft O, Paster BJ. Subgingival microflora in chronic obstructive pulmonary disease. Microbial Ecology in Health & Disease. 2009; 21: 183–92
62. Turroni F, Foroni E, Pizzetti P, Giubellini V, Ribbera A, Merusi P, et al. Exploring the diversity of the bifidobacterial population in the human intestinal tract. Appl Environ Microbiol. 2009; 75(6): 1534–45
63. Paliy O, Kenche H, Abernathy F, Michail S. High–throughput quantitative analysis of the human intestinal microbiota with a phylogenetic microarray. Appl Environ Microbiol. 2009; 75(11): 3572–9
64. Hong PY, Lee BW, Aw M, Shek LP, Yap GC, Chua KY, Liu WT. Comparative analysis of fecal microbiota in infants with and without eczema. PLoS One. 2010; 5(4): e9964
65. Vasquez N, Suau A, Magne F, Pochart P, Pelissier MA. Differential effects of Bifidobacterium pseudolongum strain Patronus and metronidazole in the rat gut. Appl Environ Microbiol. 2009; 75(2): 381–6
66. Sonoyama K, Fujiwara R, Takemura N, Ogasawara T, Watanabe J, Ito H, Morita T. Response of gut microbiota to fasting and hibernation in Syrian hamsters. Appl Environ Microbiol. 2009; 75(20): 6451–6

67. Suchodolski JS, Camancho J, Steiner JM. Analysis of bacterial diversity in the canine duodenum, jejunum, ileum, and colon by comparative 16S rRNA gene analysis. FEMS Microbiol Ecol. 2008; 66(3): 567–78
68. Suchodolski JS, Morris EM, Allenspach K, Jergens A, Harmoinen J, Westermarck E, Steiner JM. Prevalence and identification of fungal DNA in the small intestine of healthy dogs and dogs with chronic enteropathies. Vet Microbiol. 2008; 132(3-4): 379–88
69. Ritchie LE, Steiner JM, Suchodolski JS. Assessment of microbial diversity along the feline intestinal tract using 16S rRNA gene analysis. FEMS Microbiol Ecol. 2008; 66(3): 590–8
70. Dowd SE, Callaway TR, Wolcott RD, Sun Y, McKeehan T, Hagevoort RG, Edrington TS. Evaluation of the bacterial diversity in the feces of cattle using 16S rDNA bacterial tag-encoded FLX amplicon pyrosequencing (bTEFAP). BMC Microbiology. 2008; 8: 125
71. Khafipour E, Li S, Plaizier JC, Krause DO. Rumen microbiome composition determined using two nutritional models of subacute ruminal acidosis. Appl Environ Microbiol. 2009; 75(22): 7115–24
72. McSweeney CS, Palmer B, Bunch R, Krause DO. Isolation and characterization of proteolytic ruminal bacteria from sheep and goats fed the tannin–containing shrub legume Calliandra calothyrsus. Appl Environ Microbiol. 1999; 65(7): 3075–83
73. Koike S, Handa Y, Goto H, Sakai K, Miyagawa E, Matsui H, Ito S, Kobayashi Y. Molecular monitoring and isolation of previously uncultured bacterial strains from the sheep rumen. Appl Environ Microbiol. 2010; 76(6): 1887–94
74. Collier CT, Smiricky-Tjardes MR, Albin DM, Wubben JE, Gabert VM, Deplancke B, Bane D, Anderson DB, Gaskins HR. Molecular ecological analysis of porcine ileal microbiota responses to antimicrobial growth promoters. J Anim Sci. 2003; 81(12): 3035–45
75. Konstantinov SR, Awati AA, Williams BA, Miller BG, Jones P, Stokes CR, Akkermans ADL, Smidt H, de Vos WM. Post-natal development of the porcine microbiota composition and activities. Environmental Microbiology. 2006; 8(7): 1191–9
76. Castillo M, Martin-Orue SM, Nofrarias M, Manzanilla EG, Gasa J. Changes in caecal microbiota and mucosal morphology of weaned pigs. Vet Microbiol. 2007; 124(3–4): 239–47
77. Hansson I, Persson M, Svensson L, Engvall EO, Johansson KE. Identification of nine sequence types of the 16S rRNA genes of Campylobacter jejuni subsp. jejuni isolated from broilers. Acta Vet Scand. 2008; 50: 10
78. Lu J, Domingo JWS, Lamendella R, Edge T, Hill S. Phylogenetic diversity and molecular detection of bacteria in gull feces. Appl Environ Microbiol. 2008; 74(13): 3969–76
79. Eeckhaut V, Van Immerseel F, Pasmans F, Brandt ED, Haesebrouck F, Ducatelle R, et al. Anaerostipes butyraticus sp. nov., an anaerobic, butyrate–producing bacterium from Clostridium cluster XIVa isolated from broiler chicken caecal content, and emended description of the genus Anaerostipes. Int J Syst Evol Microbiol. 2010; 60(5): 1108–12
80. Schramm A, Davidson SK, Dodsworth JA, Drake HL, Stahl DA, Dubilier N. Acidovorax–like symbionts in the nephridia of earthworms. Environ Microbiol. 2003; 5(9): 804–9

81. Horn MA, Schramm A, Drake HL. The earthworm gut: an ideal habitat for ingested N2O-producing microorganisms. Appl Environ Microbiol. 2003; 69(3): 1662–69
82. Egert M., Marhan S, Wagner B, Scheu S, Friedrich MW. Molecular profiling of 16S rRNA genes reveals diet–related differences of microbial communities in soil, gut, and casts of Lumbricus terrestris L. (Oligochaeta: Lumbricidae). FEMS Microbiol Ecol. 2004; 48(2): 187–97
83. Davidson SK, Stahl DA. Transmission of Nephridial bacteria of the earthworm Eisenia fetida. Appl Envir Microbiol. 2006; 72(1): 769–75
84. Siddall ME, Perkins SL, Desser SS. Leech mycetomes endosymbionts are a new lineage of alphaproteobacteria related to the Rhizobiaceae. Mol Phylogenet Evol. 2004; 30(1):178–86
85. Perkins SL, Budinoff RB, Siddall MK. New gammaproteobacteria associated with blood–feeding leeches and a broad phylogenetic analysis of leech endosymbionts. Appl Environ Microbiol. 2005; 71(9): 5219–24
86. Brune A, Friedrich M. Microecology of the termite gut: structure and function on a microscale. Curr Opin Microbiol. 2000; 3(3): 263–9
87. Schmitt–Wagner D, Friedrich MW, Wagner B, Brune A. Phylogenetic diversity, abundance, and axial distribution of bacteria in the intestinal tract of two soil–feeding termites (Cubitermes spp.). Appl Environ Microbiol. 2003; 69(10): 6007–17
88. Graber JR, Breznak JA. Folate cross-feeding supports symbiotic homoacetogenic spirochetes. Appl Environ Microbiol. 2005; 71(4): 1883–9
89. Kikuchi Y, Meng XY, Fukatsu T. Gut symbiotic bacteria of the genus Burkholderia in the broad–headed bugs Riptortus clavatus and Leptocorisa chinensis (Heteroptera: Alydidae). Appl Environ Microbiol. 2005; 71(7): 4035–43
90. Lindh JM, Terenius O, Faye I. 16S rRNA gene-based identification of midgut bacteria from field-caught Anopheles gambiae Sensu Lato and A. funestus mosquitoes reveals new species related to known insect symbionts. Appl Environ Microbiol. 2005; 71(11): 7217–23
91. Herlemann DPR, Geissinger O, Brune A. The termite group I phylum is highly diverse and widespread in the environment. Appl Envir Microbiol. 2007; 73(20): 6682–5
92. Lee AH, Husseneder C, Hooper-Bui L. Culture-independent identification of gut bacteria in fourth–instar red imported fire ant, Solenopsis invicta Buren, larvae. J Invertebr Pathol. 2008; 98(1): 20–33
93. Gunawan S, Tufts DM, Bextine BR. Molecular identification of hemolymph-associated symbiotic bacteria in red imported fire ant larvae. Curr Microbiol. 2008; 57(6): 575–9
94. Ladygina N, Johansson T, Canback B, Tunlid A, Hedlund K. Diversity of bacteria associated with grassland soil nematodes of different feeding groups. FEMS Microbiol Ecol. 2009; 69(1): 53–61
95. Zengler K. Central role of the cell in microbial ecology. Microbiol Mol Biol Rev. 2009; 73(4): 712–29
96. Woese CR, Fox GE. Phylogenetic structure of the prokaryotic domain: the primary kingdoms. Proc Natl Acad Sci USA. 1977; 74(11): 5088–90
97. Woese CR, Magrum LJ, Fox GE. Archaebacteria. J Mol Evol. 1978; 11(3): 245–51
98. Woese CR. Bacterial evolution. Microbiol Rev. 1987; 51(2): 221–71

99. Woese CR, Kandler O, Wheelis ML. Towards a natural system of organisms: Proposal for the domains Archaea, Bacteria, and Eucarya. Proc Natl Acad Sci USA. 1990; 87(12): 4576–9
100. Yin S-d. The fimpological comprehension for definitions of life and species. The Journal of Theoretical Fimpology. in process
101. Yin S-d. The universal pattern of evolutionary entities and its circulatory ladder-like pyramid feature. The Journal of Theoretical Fimpology. in process
102. Philippe N, Legendre M, Doutre G, Coute Y, Poirot O, Lescot M, et al. Pandoraviruses: Amoeba viruses with genomes up to 2.5 Mb reaching that of parasitic eukaryotes. Science. 2013: 341(6143): 281–6
103. La Scola B, Audic S, Robert C, Jungang L, de Lamballerie X, Drancourt M, et al. A giant virus in amoebae. Science. 2003; 299(5615): 2033
104. Raoult D, Audic S, Abergel C, Ronesto P, Ogata H, La Scola B, et al. The 1.2–megabase genome sequence of Mimivirus. Science. 2004; 306(5700): 1344–50
105. Lynch M. Colloquium Papers: The frailty of adaptive hypotheses for the origins of organismal complexity. Proc Natl Acad Sci USA. 2007; 104 (Suppl 1): 8597–604
106. Mustonen V, Lassig M. Fitness flux and ubiquity of adaptive evolution. Proc Natl Acad Sci USA. 2010; 107(9): 4248–53
107. E. Julius Dasch (Editor in Chief). MacMillan Encyclopedia of Earth Science. Vol. 1. p. 552. MacMillan Reference. Simon Schuster Macmillan. New York. USA.1996
108. Stanley A Rice. Encyclopedia of Evolution. pp. 276–278. Facts on File, Inc. New York. USA. 2007
109. Ernst Mayr. The growth of biological thought: diversity, evolution, and inheritance. p. 687–689, 698–707. Belknap Press. USA.1982.
110. Ernst Mayr. The growth of biological thought: diversity, evolution, and inheritance. Pp: 537–539. Belknap Press. USA.1982
111. Sobel JM, Chen GF, Watt LR, Schemske DW. The biology of speciation. Evolution. 2010; 64(2): 295–315
112. Bridget Travers, Jeffery Muhr. McClintock, Barbra (1902-1992) in World of Scientific discovery. pp. 426–427. Gale Research Inc. USA.1994
113. McClintock B. The origin and behavior of mutable loci in maize. Proc Natl Acad Sci USA. 1950; 36(6): 344–55
114. Love AC. Evolutionary morphology and Evo-devo: hierarchy and novelty. Theory Biosci. 2006; 124(3–4): 317–33
115. Weissing FJ, Edelaar P, van Doorn GS. Adaptive speciation theory: a conceptual review. Behav Ecol Sociobiol. 2011; 65(3): 461–80
116. Marc W. Kirschner, John C. Gerhart. The Plausibility of life: Resolving Darwin's dilemma. Pp13, 28–31 Yale University Press. USA. 2005
117. Noble D. Neo-Darwinism, the Modern Synthesis and selfish genes: are they of use in physiology? J Physiol. 2011; 589(5): 1007–15
118. Paul Sreathern. A brief history of medicine: from Hippocrates to gene therapy. Pp. 214–215. Carroll & Graf Publishers. New York. USA. 2005
119. Avery OT, MacLeod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Induction of transformation

by a desoxyribonucleic acid fraction isolated from pneumococcus type III. J Exp Med. 1944; 79(2): 137–58
120. Watanabe T. Infective heredity of multiple drug resistance in bacteria. Bacteriol Rev. 1963; 27: 87–115
121. Aminov RI. Horizontal gene exchange in environmental microbiota. Front Microbiol 2011; 2: 158
122. Weiss RA. The discovery of endogenous retroviruses. Retrovirology. 2006; 3: 67
123. Ochman H, Lawrence JG, Groisman EA. Lateral gene transfer and the nature of bacterial innovation. Nature. 2000; 405(6784): 299–304
124. Kidwell M G, Lisch D R. Perspective: transposable elements, parasitic DNA, and genome evolution. Evolution. 2001; 55(1): 1–24
125. Dobrindt U, Hacker J. Whole genome plasticity in pathogenic bacteria. Curr Opin Microbiol. 2001; 4(5): 550–7
126. Nekrutenko A, Li WH. Transposable elements are found in a large number of human protein–coding genes. Trends Genet. 2001; 17(11): 619–21
127. Welch RA, Burland V, Plunkett G, Redford P, Roesch P, Rasko D, Buckles EL, Liou SR, Boutin A, Hackett J, et al. Extensive mosaic structure revealed by the complete genome sequence of uropathogenic Escherichia coli. Proc Natl Acad Sci USA. 2002; 99(26): 17020–4
128. Andersson JO. Lateral gene transfer in eukaryotes. Cell Mol Life Sci. 2005; 62(11): 1182–97
129. Kleter GA, Peijnenburg AA, Aarts HJ. Health considerations regarding horizontal transfer of microbial transgenes present in genetically modified crops. J Biomed Biotechnol. 2005; 2005(4): 326–52
130. Hao W, Golding GB. The fate of laterally transferred genes: Life in the fast lane to adaptation or death. Genome Res. 2006; 16(5): 636–43
131. Kamikawa R, Inagaki Y, Sako Y. Direct phylogenetic evidence for lateral transfer of elongation factor–like gene. Proc Natl Acad Sci USA. 2008; 105(19): 6965–9
132. Becq J, Gutierrez MC, Rosas-Magallanes V, Rauzier J, Gicquel B, Neyrolles O, et al. Contribution of horizontally acquired genomic islands to the evolution of the tubercle bacilli. Mol Biol Evol. 2007; 24(8): 1861–71
133. Pace JK 2nd., Gilbert C, Clark MS, Feschotte C. Repeated horizontal transfer of a DNA transposon in mammals and other tetrapods. Proc Natl Acad Sci USA. 2008; 105(44): 17023–8
134. Keeling PJ, Palmer JD. Horizontal gene transfer in eukaryotic evolution. Nat Rev Genet. 2008; 9(8): 605–18
135. Didelot X, Darling A, Falush D. Inferring genomic flux in bacteria. Genome Res. 2009; 19(2): 306–3
136. Brandvainand Y, Wade MJ. The functional transfer of genes from the mitochondria to the nucleus: the effects of selection, mutation, population size and rate of self–fertilization. Genetics. 2009; 182(4): 1129–39
137. Gilbert C, Schaack S, Pace JK 2nd, Brindley PJ, Feschotte C. A role for host–parasite interactions in the horizontal transfer of transposons across phyla. Nature. 2010; 464(7293): 1347–50

138. Munoz-Lopez M, Garcia–Perez JL. DNA transposons: nature and applications in genomics. Curr Genomics. 2010; 11(2): 115–28
139. Wu DD, Zhang YP. Eukaryotic origin of a metabolic pathway in virus by horizontal gene transfer. Genomics. 2011; 98(5): 367–9
140. Moran Y, Fredman D, Szczesny P, Grynberg M, Technau U. Recurrent horizontal transfer of bacterial toxin genes to eukaryotes. Mol Biol Evol. 2012; 29(9): 2223–30
141. Wallau GL, Ortiz MF, Loreto EL. Horizontal transposon transfer in eukarya: detection, bias, and perspectives. Genome Biol Evol. 2012; 4(8): 689–99
142. Alsmark C, Foster PG, Sicheritz-Ponten T, Nakjang S, Martin Embley T, Hirt RP. Patterns of prokaryotic lateral gene transfers affecting parasitic microbial eukaryotes. Genome Biol. 2013; 14(2): R19
143. Gilbert C, Cordaux R. Horizontal transfer and evolution of prokaryote transposable elements in eukaryotes. Genome Biol Evol. 2013; 5(5): 822–32
144. Walsh AM, Kortschak RD, Gardner MG, Bertozzi T, Adelson DL. Widespread horizontal transfer of retrotransposons. Proc Natl Acad Sci USA. 2013; 110(3): 1012–6
145. Whitehead MP, Hooley P, W Brown MR. Horizontal transfer of bacterial polyphosphate kinases to eukaryotes: implications for the ice age and land colonisation. BMC Res Notes. 2013; 6: 221
146. Jin Q, Yuan Z, Xu J, Wang Y, Shen Y, Lu W, et al. Genome sequence of Shigella flexneri 2a: Insights into pathogenicity through comparison with genomes of Escherichia coli K12 and O157. Nucleic Acids Res. 2002; 30(20): 4432–41
147. Klotz MG, Loewen PC. The molecular evolution of catalatic hydroperoxidases: evidence for multiple lateral transfer of genes between prokaryota and from bacteria into eukaryota. Mol Biol Evol. 2003; 20(7): 1098–112
148. Rohmer L, Fong C, Abmayr S, Wasnick M, Larson-Freeman TJ, Radey M, et al. Comparison of Francisella tularensis genomes reveals evolutionary events associated with the emergence of human-pathogenic strains. Genome Biol. 2007; 8: R102
149. Johnson TJ, Kariyawasam S, Wannemuehler Y, Mangiamele P, Johnson SJ, Doetkott C, et al. The genome sequence of avian pathogenic Escherichia coli strain O1:K1:H7 shares strong similarities with human extraintestinal pathogenic E. coli genomes. J Bacteriol. 2007; 189(8): 3228–36
150. Asadulghani M, Ogura Y, Ooka T, Itoh T, Sawaguchi A, Iguchi A, et al. The defective prophage pool of Escherichia coli O157: prophage-prophage interactions potentiate horizontal transfer of virulence determinants. PLoS Pathog 2009; 5(5):e1000408
151. Doolittle RF, Feng DF, Anderson KL, Alberro MR. A naturally occurring horizontal gene transfer from a eukaryote to a prokaryote. J Mol Evol. 1990; 31(5): 383–8
152. Khaldi N, Collemare J, Lebrun MH, Wolfe KH. Evidence for horizontal transfer of a secondary metabolite gene cluster between fungi. Genome Biol. 2008; 9(1): R18
153. Mallet LV, Becq J, Deschavanne P. Whole genome evaluation of horizontal transfers in the pathogenic fungus Aspergillus fumigatus. BMC Genomics. 2010; 11: 171
154. McInerney JO, Cotton JA, Pisani D. The prokaryotic tree of life: past, present... and future? Trends Ecol Evol. 2008; 23(5): 276–81
155. Fuhrman JA. Marine viruses and their bioeochemical and ecological effects. Nature. 1999; 399(6736): 541–8

156. Van Etten JL, Lane LC, Dunigan DD. DNA viruses: the really big ones (giruses). Annu Rev Microbiol. 2010; 64: 83–99
157. Mause SF, Weber C. Microparticles: Protagonists of a novel communication network for intercellular information exchange. Circ Res. 2010; 107(9): 1047–57
158. Anand PK. Exosomal membrane molecules are potent immune response modulators. Commun Integr Biol. 2010; 3(5): 405–8
159. Yuan A, Farber EL, Rapoport AL, Tejada D, Deniskin R, Akhmedov NB, et al. Transfer of microRNAs by embryonic stem cell microvesicles. PLoS One. 2009; 4(3): e4722
160. Breitbart M, Rohwer F. Here a virus, there a virus, everywhere the same virus? Trends Microbiol. 2005; 13(6): 278–84
161. Suttle CA. Viruses in the sea. Nature. 2005; 437(7057): 356–61
162. Angly FE, Felts B, Breitbart M, Salamon P, Edwards RA, Carlson C, Chan AM, Haynes M, Kelley S, Liu H, et al. The marine viromes of four oceanic regions. PLoS Biol. 2006; 4(11): e368
163. Clokie MRJ, Mann NH. Marine cyanophages and light. Environmental Microbiology. 2006; 8(12): 2074–82
164. Bergh O, Børsheim KY, Bratbak G, Heldal M. High abundance of viruses found in aquatic environments. Nature 1989; 340(6233): 467–8
165. Parada V, Sintes E, van Aken HM, Weinbauer MG, Herndl GJ. Viral abundance, decay, and diversity in the meso– and bathypelagic waters of the North Atlantic. Appl Environ Microbiol 2007; 73(14): 4429–38
166. Sano E, Carlson S, Wegley L, Rohwer F. Movement of viruses between biomes. Appl Envir Microbiol 2004; 70(10): 5842–6
167. Weinbauer MG, Rassoulzadegan F. Are viruses driving microbial diversification and diversity? Environ Microbiol. 2004; 6(1): 1–11
168. Sogin ML, Morrison HG, Huber JA, Welch DM, Huse SM, Neal PR, et al. Microbial diversity in the deep sea and the underexplored "rare biosphere". Proc Natl Acad Sci USA. 2006; 103(32): 12115–20
169. Koonin EV, Senkevich TG, Dolja VV. The ancient Virus World and evolution of cells. Biol Direct. 2006; 1: 29
170. Brussow H. The not so universal tree of life or the place of viruses in the living world. Philos Trans R Soc Lond B Biol Sci. 2009; 364(1527): 2263–74
171. Forterre P, Prangishvili D. The great billion–year war between ribosome– and capsid–encoding organisms (cells and viruses) as the major source of evolutionary novelties. Ann N Y Acad Sci. 2009; 1178: 65–77
172. Demongeot J, Glade N, Moreira A, Vial L. RNA relics and origin of life. Int J Mol Sci. 2009; 10(8): 3420–41
173. Forterre P, Prangishvili D. The origin of viruses. Res Microbiol. 2009; 160(7): 466–72
174. Yutin N, Wolf YI, Raoult D, Koonin EV. Eukaryotic large nucleo–cytoplasmic DNA viruses: clusters of orthologous genes and reconstruction of viral genome evolution. Virol J. 2009; 6: 223
175. Villarreal LP, Witzany G. Viruses are essential agents within the roots and stem of the tree of life. J Theor Biol. 2010; 262(4): 698–710

176. Emerman M, Malik HS. Paleovirology-modern consequences of ancient viruses. PLoS Biol. 2010; 8(2): e1000301
177. Lawrence JG, Hatfull GF, Hendrix RW. Imbroglios of viral taxonomy: genetic exchange and failings of phenetic approaches. J Bacteriol 2002; 184: 4891–905
178. Moreira D, Lopez-Garcia P. Ten reasons to exclude viruses from the tree of life. Nat Rev Microbiol 2009; 7(4): 306–11
179. Van Regenmortel MH. Logical puzzles and scientific controversies: the nature of species, viruses and living organisms. Syst Appl Microbiol 2010; 33(1): 1–6
180. Forterre P. Three RNA cells for ribosomal lineages and three DNA viruses to replicate their genomes: a hypothesis for the origin of cellular domain. Proc Natl Acad Sci USA. 2006; 103(10): 3669–74
181. Serwer P. Proposed ancestors of phage nucleic acid packaging motors (and cells). Viruses. 2011; 3(7): 1249–80
182. Bell PJ. The viral eukaryogenesis hypothesis: a key role for viruses in the emergence of eukaryotes from a prokaryotic world environment. Ann N Y Acad Sci. 2009; 1178: 91–105
183. Forterre P. The origin of viruses and their possible roles in major evolutionary transitions. Virus Res. 2006; 117(1): 5–16
184. Dorothy H. Crawford. The Invisible Enemy: A Natural History of Viruses. 18–19pp. Oxford University Press. Oxford, UK. 2000
185. Forterre P. Defining life: the virus viewpoint. Orig Life Evol Biosph. 2010; 40(2): 151–60
186. Krupovic M, Bamford DH. Order to the viral universe. J Virol. 2010; 84(24): 12476–9
187. Prangishvili D, Stedman K, Zillig W. Viruses of the extremely thermophilic archaeon Sulfolobus. Trends Microbiol. 2001; 9(1): 39–43
188. Colson P, Gimenez G, Boyer M, Fournous G, Raoult D. The giant Cafeteria roenbergensis virus that infects a widespread marine phagocytic protist is a new member of the fourth domain of life. PLoS One. 2011; 6(4): e18935
189. Mi S, Lee X, Li X, Veldman GM, Finnerty H, Racie L, et al. Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. Nature. 2000; 403(6771): 785–9
190. Dupressoir A, Marceau G, Vernochet C, Benit L, Kanellopoulos C, Sapin V, Heidmann T. Syncytin-A and syncytin-B, two fusogenic placenta-specific murine envelope genes of retroviral origin conserved in Muridae. Proc Natl Acad Sci USA. 2005; 102(3): 725–30
191. Caporaso JG, Knight R, Kelley ST. Host-associated and free-living phage communities differ profoundly in phylogenetic composition. PLoS One. 2011; 6(2): e16900
192. Mueser TC, Hinerman JM, Devos JM, Boyer RA, Williams KJ. Structural analysis of bacteriophage T4 DNA replication: a review in the Virology Journal series on bacteriophage T4 and its relatives. Virol J. 2010; 7: 359
193. Meckes DG Jr, Raab-Traub N. Microvesicles and viral infection. J Virol. 2011; 85(24): 12844–54

194. Zhu H, Fan GC. Extracellular/circulating microRNAs and their potential role in cardiovascular disease. Am J Cardiovasc Dis. 2011; 1(2): 138–49
195. Thery C. Exosomes: secreted vesicles and intercellular communications. F1000 Biol Rep. 2011; 3: 15
196. Oliveira DL, Nakayasu ES, Joffe LS, Guimarães AJ, Sobreira TJ, Nosanchuk JD, et al. Biogenesis of extracellular vesicles in yeast: Many questions with few answers. Commun Integr Biol. 2010; 3(6): 533–5
197. An Q, van Bel AJ, Hückelhoven R. Do plant cells secrete exosomes derived from multivesicular bodies? Plant Signal Behav. 2007; 2(1): 4–7
198. Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, et al. Eradication of established murine tumors using a novel cell–free vaccine: dendritic cell–derived exosomes. Nat Med. 1998; 4(5): 594–600
199. Stein JM, Luzio JP. Ectocytosis caused by sublytic autologous complement attack on human neutrophils. The sorting of endogenous plasma–membrane proteins and lipids into shed vesicles. Biochem J. 1991; 274(Pt 2): 381–6
200. Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). J Biol Chem. 1987; 262(19): 9412–20
201. Rieu S, Geminard C, Rabesandratana H, Sainte-Marie J, Vidal M. Exosomes released during reticulocyte maturation bind to fibronectin via integrin alpha4beta1. Eur J Biochem. 2000; 267(2): 583–90
202. Carayon K, Chaoui K, Ronzier E, Lazar I, Bertrand–Michel J, Roques V, et al. Proteolipidic composition of exosomes changes during reticulocyte maturation. J Biol Chem 2011; 286(39): 34426–39
203. Martin-Jaular L, Nakayasu ES, Ferrer M, Almeida IC, Del Portillo HA. Exosomes from Plasmodium yoelii-infected reticulocytes protect mice from lethal infections. PLoS One 2011; 6(10): e26588
204. Nantakomol D, Dondorp AM, Krudsood S, Udomsangpetch R, Pattanapanyasat K, et al. Circulating red cell-derived microparticles in human malaria. J Infect Dis 2011; 203(5): 700–6
205. Hunter MP, Ismail N, Zhang X, Aguda BD, Lee EJ, Yu L, et al. Detection of microRNA expression in human peripheral blood microvesicles. PLoS One 2008; 3(11): e3694]
206. Hao S, Bai O, Li F, Yuan J, Laferte S, Xiang J. Mature dendritic cells pulsed with exosomes stimulate efficient cytotoxic T-lymphocyte responses and antitumour immunity. Immunology 2007; 120(1): 90–102
207. Denzer K, Kleijmeer MJ, Heijnen HF, Stoorvogel W, Geuze HJ. Exosome: from internal vesicle of the multivesicular body to intercellular signaling device. J Cell Sci 2000; 113(Pt 19): 3365–74
208. Bhatnagar S, Shinagawa K, Castellino FJ, Schorey JS. Exosomes released from macrophages infected with intracellular pathogens stimulate a proinflammatory response in vitro and in vivo. Blood 2007; 110(9): 3234–44
209. Zhang H, Xie Y, Li W, Chibbar R, Xiong S, Xiang J. CD4(+) T cell–released exosomes inhibit CD8(+) cytotoxic T–lymphocyte responses and antitumor immunity. Cell Mol Immunol 2011; 8(1): 23–30

210. Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, Melief CJ, Geuze HJ. B lymphocytes secrete antigen-presenting vesicles. J Exp Med 1996; 183(3): 1161–72
211. Zumaquero E, Munoz P, Cobo M, Lucena G, Pavon EJ, Martin A, et al. Exosomes from human lymphoblastoid B cells express enzymatically active CD38 that is associated with signaling complexes containing CD81, Hsc-70 and Lyn. Exp Cell Res 2010; 316(16): 2692–706
212. Vallhov H, Gutzeit C, Johansson SM, Nagy N, Paul M, Li Q, et al. Exosomes containing glycoprotein 350 released by EBV-transformed B cells selectively target B cells through CD21 and block EBV infection in vitro. J Immunol 2011 186(1):73–82
213. Heijnen HF, Schiel AE, Fijnheer R, Geuze HJ, Sixma JJ. Activated platelets release two types of membrane vesicles: microvesicles by surface shedding and exosomes derived from exocytosis of multivesicular bodies and alpha-granules. Blood 1999; 94(11): 3791–9
214. Yin W, Ghebrehiwet B, Peerschke EI. Expression of complement components and inhibitors on platelet microparticles. Platelets 2008; 19(3): 225–33
215. Flaumenhaft R, Dilks JR, Richardson J, Alden E, Patel–Hett SR, Battinelli E, et al. Megakaryocyte-derived microparticles: direct visualization and distinction from platelet-derived microparticles. Blood 2009; 113(5): 1112–21
216. Tavoosidana G, Ronquist G, Darmanis S, Yan J, Carlsson L, Wu D, et al. Multiple recognition assay reveals prostasomes as promising plasma biomarkers for prostate cancer. Proc Natl Acad Sci USA 2011; 108(21): 8809–14
217. van Niel G, Raposo G, Candalh C, Boussac M, Hershberg R, Cerf–Bensussan N, et al. Intestinal epithelial cells secrete exosome-like vesicles. Gastroenterology 2001; 121(2): 337–49
218. Knepper MA, Pisitkun T. Exosomes in urine: who would have thought...? Kidney Int 2007; 72(9): 1043–5
219. Kesimer M, Scull M, Brighton B, DeMaria G, Burns K, O'Neal W, et al. Characterization of exosome-like vesicles released from human tracheobronchial ciliated epithelium: a possible role in innate defense. FASEB J 2009; 23(6): 1858–68
220. Deregibus MC, Cantaluppi V, Calogero R, Lo Iacono M, Tetta C, Biancone L, et al. Endothelial progenitor cell derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. Blood 2007; 110(7): 2440–8
221. Fitzner D, Schnaars M, van Rossum D, Krishnamoorthy G, Dibaj P, Bakhti M, et al. Selective transfer of exosomes from oligodendrocytes to microglia by macropinocytosis. J Cell Sci 2011; 124: 447–58
222. Sahoo S, Klychko E, Thorne T, Misener S, Schultz KM, Millay M, et al. Exosomes from human CD34(+) stem cells mediate their proangiogenic paracrine activity. Circ Res 2011; 109(7): 724–8
223. Gatti S, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, Tetta C, et al. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. Nephrol Dial Transplant 2011; 26(5): 1474–83

224. Grange C, Tapparo M, Collino F, Vitillo L, Damasco C, Deregibus MC, et al. Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche. Cancer Res 2011; 71(15): 5346–56
225. Prokopi M, Pula G, Mayr U, Devue C, Gallagher J, Xiao Q, et al. Proteomic analysis reveals presence of platelet microparticles in endothelial progenitor cell cultures. Blood 2009; 114(3): 723–32
226. Bruno S, Grange C, Deregibus MC, Calogero RA, Saviozzi S, Collino F, et al. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. J Am Soc Nephrol. 2009; 20(5): 1053–67
227. Sabapatha A, Gercel-Taylor C, Taylor DD. Specific isolation of placenta-derived exosomes from the circulation of pregnant women and their immunoregulatory consequences. Am J Reprod Immunol. 2006; 56(5–6): 345–55
228. Germain SJ, Sacks GP, Sooranna SR, Sargent IL, Redman CW. Systemic inflammatory priming in normal pregnancy and preeclampsia: the role of circulating syncytiotrophoblast microparticles. J Immunol. 2007; 178(9): 5949–56
229. Luo SS, Ishibashi O, Ishikawa G, Ishikawa T, Katayama A, Mishima T, et al. Human villous trophoblasts express and secrete placenta-specific microRNAs into maternal circulation via exosomes. Biol Reprod. 2009; 81(4): 717–29
230. Messerli M, May K, Hansson SR, Schneider H, Holzgreve W, Hahn S, et al. Feto-maternal interactions in pregnancies: placental microparticles activate peripheral blood monocytes. Placenta. 2010; 31(2): 106–12
231. Southcombe J, Tannetta D, Redman C, Sargent I. The immunomodulatory role of syncytiotrophoblast microvesicles. PLoS One 2011; 6(5): e20245
232. Rodrigues ML, Nimrichter L, Oliveira DL, Nosanchuk JD, Casadevall A. Vesicular trans-cell wall transport in fungi: a mechanism for the delivery of virulence-associated macromolecules? Lipid Insights. 2008; 2: 27–40
233. Albuquerque PC, Nakayasu ES, Rodrigues ML, Frases S, Casadevall A, Zancope-Oliveria RM, et al. Vesicular transport in Histoplasma capsulatum: an effective mechanism for trans-cell wall transfer of proteins and lipids in ascomycetes. Cell Microbiol. 2008; 10(8): 1695–710
234. Rodrigues ML, Nimrichter L, Oliveira DL, Frases S, Miranda K, Zaragoza O, et al. Vesicular polysaccharide export in Cryptococcus neoformans is a eukaryotic solution to the problem of fungal trans-cell wall transport. Eukaryot Cell. 2007; 6(1): 48–59
235. Gehrmann U, Qazi KR, Johansson C, Hultenby K, Karlsson M, Lundeberg L, et al. Nanovesicles from Malassezia sympodialis and host exosomes induce cytokine responses-novel mechanisms for host-microbe interactions in atopic eczema. PLoS One. 2011; 6(7): e21480
236. Oliveira DL, Nakayasu ES, Joffe LS, Guimaraes AJ, Sobreira TJ, Nosanchuk JD, et al. Characterization of yeast extracellular vesicles: evidence for the participation of different pathways of cellular traffic in vesicle biogenesis. PLoS One. 2010; 5(6): e11113
237. Panepinto J, Komperda K, Frases S, Park YD, Djordjevic JT, Casadevall A, et al. Sec6–dependent sorting of fungal extracellular exosomes and lac–case of Cryptococcus neoformans. Mol Microbiol. 2009; 71(5): 1165–76

238. Eisenman HC, Frases S, Nicola AM, Rodrigues ML, Casadevall A. Vesicle-associated melanization in Cryptococcus neoformans. Microbiology. 2009; 155(Pt 12): 3860–7
239. Nicola AM, Frases S, Casadevall A. Lipophilic dye staining of Cryptococcus neoformans extracellular vesicles and capsule. Eukaryot Cell. 2009; 8(9): 1373–80
240. Mayrand D, Grenier D. Biological activities of outer membrane vesicles. Can J Microbiol. 1989; 35(6): 607–13
241. Beveridge TJ. Structures of gram–negative cell walls and their derived membrane vesicles. J Bacteriol. 1999; 181(16): 4725–33
242. Schooling SR, Beveridge TJ. Membrane vesicles: an overlooked component of the matrices of biofilms. J Bacteriol. 2006; 188(16): 5945–57
243. Mashburn-Warren LM, Whiteley M. Special delivery: vesicle trafficking in prokaryotes. Mol Microbiol. 2006; 61(4): 839–46
244. Mashburn-Warren L, Howe J, Garidel P, Richter W, Steiniger F, Roessle M, et al. Interaction of quorum signals with outer membrane lipids: insights into prokaryotic membrane vesicle formation. Mol Microbiol. 2008; 69(2): 491–502
245. Mashburn-Warren L, McLean RJ, Whiteley M. Gram-negative outer membrane vesicles: beyond the cell surface. Geobiology. 2008; 6(3): 214–9
246. Kadurugamuwa JL, Beveridge TJ. Virulence factors are released from Pseudomonas aeruginosa in association with membrane vesicles during normal growth and exposure to gentamicin: a novel mechanism of enzyme secretion. J Bacteriol. 1995; 177(14): 3998–4008
247. Yaron S, Kolling GL, Simon L, Matthews KR. Vesicle–mediated transfer of virulence genes from Escherichia coli O157: H7 to other enteric bacteria. Appl Environl Microbiol. 2000; 66(10): 4414–20
248. Renelli M, Matias V, Lo RY, Beveridge TJ. DNA–containing membrane vesicles of Pseudomonas aeruginosa PAO1 and their genetic transformation potential. Microbiology. 2004; 150(Pt 17): 2161–9
249. Kuehn MJ, Kesty NC. Bacterial outer membrane vesicles and the host–pathogen interaction. Genes Dev. 2005; 19(22): 2645–55
250. Lee EY, Choi DY, Kim DK, Kim JW, Park JO, Kim S, et al. Gram–positive bacteria produce membrane vesicles: proteomics-based characterization of Staphylococcus aureus-derived membrane vesicles. Proteomics. 2009; 9(24): 5425–36
251. Kadurugamuwa JL, Beveridge TJ. Membrane vesicles derived from Pseudomonas aeruginosa and Shigella flexneri can be integrated into the surfaces of other Gram-negative bacteria. Microbiology. 1999; 145(8): 2051–60
252. Thery C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. Nat Rev Immunol. 2009; 9(8): 581–93
253. Giri PK, Kruh NA, Dobos KM, Schorey JS. Proteomic analysis identifies highly antigenic proteins in exosomes from M. tuberculosis–infected and culture filtrate protein–treated macrophages. Proteomics. 2010; 10(17): 3190–202
254. da Silveira JC, Veeramachaneni DN, Winger QA, Carnevale EM, Bouma GJ. Cell-secreted vesicles in equine ovarian follicular fluid contain miRNAs and proteins: a possible new form of cell communication within the ovarian follicle. Biol Reprod. 2011 Nov 23

255. Bard MP, Hegmans JP, Hemmes A, Luider TM, Willemsen R, Severijnen LA, et al. Proteomic analysis of exosomes isolated from human malignant pleural effusions. Am J Respir Cell Mol Biol. 2004; 31(1): 114–21
256. Guerrier-Takada C, Gardiner K, Marsh T, Pace N, Altman S. The RNA moiety of ribonuclease P is the catalytic subunit of the enzyme. Cell. 1983; 35(3 Pt 2): 849–57
257. Cech TR. RNA splicing: three themes with variations. Cell. 1983: 34(3): 713–6
258. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin–14. Cell 1993; 75(5): 843–54
259. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science 2001; 294(5543): 853–8
260. Kato M, Slack FJ. microRNAs: small molecules with big roles – C. elegans to human cancer. Biol Cell 2008; 100(2): 71–81
261. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 2004; 116(2): 281–97
262. Pfeffer S, Zavolan M, Grasser FA, Chien M, Russo JJ, Ju J, et al. Identification of virus-encoded microRNAs. Science. 2004; 304(5671): 734–6
263. Volinia S, Calin GA, Liu C-G, Ambs S, Cimmino A, Petrocca F, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA. 2006; 103(7): 2257–61
264. Morita T, Mochizuki Y, Aiba H. Translational repression is sufficient for gene silencing by bacterial small noncoding RNAs in the absence of mRNA destruction. Proc Natl Acad Sci USA. 2006; 103(13): 4858–63
265. Huang J, Wang F, Argyris E, Chen K, Liang Z, Tian H, et al. Cellular microRNAs contribute to HIV–1 latency in resting primary CD4 + T lymphocytes. Nat Med 2007; 13(10): 1241–7
266. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova–Agadjanyan EL, et al. Circulating microRNAs as stable blood–based markers for cancer detection. Proc Natl Acad Sci USA. 2008; 105(30): 10513–8
267. Wang K, Zhang S, Marzolf B, Troisch P, Brightman A, Hu Z, et al. Circulating microRNAs, potential biomarkers for drug–induced liver injury. Proc Natl Acad Sci USA. 2009; 106(11): 4402–7
268. Cordes KR, Srivastava D. MicroRNA regulation of cardiovascular development. Circ Res 2009; 104(6): 724–32
269. Mallanna SK, Rizzino A. Emerging roles of microRNAs in the control of embryonic stem cells and the generation of induced pluripotent stem cells. Dev Biol 2010; 344(1):16–25
270. Qin L, Chen Y, Niu Y, Chen W, Wang Q, Xiao S, et al. A deep investigation into the adipogenesis mechanism: profile of microRNAs regulating adipogenesis by modulating the canonical wnt/beta–catenin signaling pathway. BMC Genomics. 2010; 11: 320
271. Buchold GM, Coarfa C, Kim J, Milosavljevic A, Gunaratne PH, Matzuk MM. Analysis of microRNA expression in the prepubertal testis. PLoS One. 2010; 5(12): e15317
272. Karali M, Manfredi A, Puppo A, Marrocco E, Gargiulo A, Allocca M, et al. MicroRNA–restricted transgene expression in the retina. PLoS One. 2011; 6(7): e22166

273. Curry E, Safranski TJ, Pratt SL. Differential expression of porcine sperm microRNAs and their association with sperm morphology and motility. Theriogenology. 2011; 76(8): 1532–9
274. Joshi SR, McLendon JM, Comer BS, Gerthoffer WT. MicroRNAs-control of essential genes: Implications for pulmonary vascular disease. Pulm Circ. 2011; 1(3): 357–64
275. Grundhoff A, Sullivan CS. Virus-encoded microRNAs. Virology. 2011; 411(2): 325–43
276. Cullen BR. Viral and cellular messenger RNA targets of viral microRNAs. Nature. 2009; 457(7228): 421–425
277. Plaisance-Bonstaff K, Renne R. Viral miRNAs. Methods Mol Biol 2011; 721: 43–66
278. Nobelprize.org. Physiology or Medicine for 1997-Press Release. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1997/press.html Accessed on August 6, 2013
279. Wickner RB, Shewmaker F, Edskes H, Kryndushkin D, Nemecek J, McGlinchey R, et al. Prion amyloid structure explains templating: how proteins can be genes. FEMS Yeast Res. 2010; 10(8): 980–91
280. Ross ED, Edskes HK, Terry MJ, Wickner RB. Primary sequence independence for prion formation. Proc Natl Acad Sci USA. 2005; 102(36): 12825–30
281. Lee DH, Granja JR, Martinez JA, Severin K, Ghadiri MR. A self-replicating peptide. Nature. 1996; 382(6591): 525–8
282. Lee DH, Severin K, Yokobayashi lee DH, Severin K, Yokobayashi Y, Ghadiri MR. Emergence of symbiosis in peptide self–replication through a hypercyclic network. Nature. 1997; 390(6660): 591–4
283. Issac R, Ham YW, Chmielewski J. The design of self-replicating helical peptides. Curr Opin Struct Biol. 2001; 11(4): 458–63
284. Li L, Lindquist S. Creating a protein-based element of inheritance. Science. 2000; 287(5453): 661–4
285. Derkatch IL, Bradley ME, Hong JY, Liebman SW. Prions affect the appearance of other prions: The story of [PIN(+)]. Cell. 2001; 106(2): 171–82
286. Uptain SM, Lindquist S. Prions as protein–based genetic elements. Annu Rev Microbiol. 2002; 56: 703–41
287. Shorter J, Lindquist S. Prions as adaptive conduits of memory and inheritance. Nat Rev Genet. 2005; 6(6): 435–50
288. Wickner RB, Edskes HK, Shewmaker F, Nakayashiki T. Prions of fungi: Inherited structures and biological roles. Nat Rev Microbiol. 2007; 5(8): 611–8
289. Derkatch IL, Liebman SW. Prion-prion interactions. Prion. 2007; 1(3): 161–9
290. Halfmann R, Alberti S, Lindquist S. Prions, protein homeostasis, and phenotypic diversity. Trends Cell Biol. 2010; 20(3): 125–33
291. Kelly AC, Shewmaker FP, Kryndushkin D, Wickner RB. Sex, prions, and plasmids in yeast. Proc Natl Acad Sci USA. 2012; 109: E2683–90
292. Didonna A. Prion protein and its role in signal transduction. Cell Mol Biol Lett. 2013; 18(2): 209–30
293. Telling GC. The importance of prions. PLoS Pathog. 2013; 9(1): e1003090

294. True HL, Lindquist S. A yeast prion provides a mechanism for genetic variation and phenotypic diversity. Nature. 2000; 407(6803): 477–83
295. True HL, Berlin I, Lindquist SL. Epigenetic regulation of translation reveals hidden genetic variation to produce complex traits. Nature. 2004; 431(7005): 184–7
296. Sideri TC, Stojanovski K, Tuite MF, Grant CM. Ribosome–associated peroxiredoxins suppress oxidative stress–induced de novo formation of the [PSI+] prion in yeast. Proc Natl Acad Sci USA. 2010; 107(14): 6394–9
297. Halfmann R, Lindquist S. Epigenetics in the extreme: prions and the inheritance of environmentally acquired traits. Science. 2010; 330(6004): 629–32
298. Halfmann R, Jarosz DF, Jones SK, Chang A, Lancaster AK, Lindquist S. Prions are a common mechanism for phenotypic inheritance in wild yeasts. Nature. 2012; 482(7385): 363–8
299. Li L, Kowal AS. Environmental regulation of prions in yeast. PLoS Pathog. 2012; 8(11):e1002973
300. Calo S, Billmyre RB, Heitman J. Generators of phenotypic diversity in the evolution of pathogenic microorganisms. PLoS Pathog. 2013; 9(3): e1003181
301. Manuelidis L. Infectious particles, stress, and induced prion amyloids: A unifying perspective. Virulence. 2013; 4(5): 373–83
302. Nair P. Nonpathogenic prions. Proc Natl Acad Sci USA. 2013; 110(17): 6612
303. Debets AJM, Dalstra HJP, Slakhorst M, Koopmanschap B, Hoekstra RF, Saupe ST. High natural prevalence of a fungal prion. Proc Natl Acad Sci USA. 2012; 109(26):10432–7
304. Dupont CL, Butcher A, Valas RE, Bourne PE, Caetano-Anolles G. History of biological metal utilization inferred through phylogenomic analysis of protein structures. Proc Natl Acad Sci USA. 2010; 107(23): 10567–72
305. Mulkidjanian AY. On the origin of life in the zinc world: 1. Photosynthesizing, porous edifices built of hydrothermally precipitated zinc sulfide as cradles of life on Earth. Biol Direct 2009; 4: 26
306. Mulkidjanian AY, Galperin MY. On the origin of life in the zinc world. 2. Validation of the hypothesis on the photosynthesizing zinc sulfide edifices as cradles of life on Earth. Biol Direct 2009; 4: 27
307. Mulkidjanian AY, Galperin MY. On the abundance of zinc in the evolutionarily old protein domains. Proc Natl Acad Sci USA. 2010; 107(36): E137
308. Adams IR, Meehan RR. From paramutation to paradigm. PLoS Genet. 2013; 9(5): e1003537
309. Maurel M–C, Kanellopoulos–Langevin C. Heredity-venturing beyond genetics. Biol Reprod 2008; 79(1): 2–8
310. Cohen J, Alikani M. The biological basis for defining bi-parental or tri-parental origin of offspring from cytoplasmic and spindle transfer. Reprod Biomed Online. 2013; 26(6): 535–7
311. Tartakoff AM, Aylyarov I, Jaiswal P. Septin–containing barriers control the differential inheritance of cytoplasmic elements. Cell Rep. 2013; 3(1): 223–36
312. Yin S-d. About fimpology. The Journal of Theoretical Fimpology. 2013; 1(1): e-20130316-1. Available from: http://www.fimpology.com (Search Google Scholar)

313. Yin S-d. Six models of pregnancy–associated eukaryotic cell transmission among fetus, mother and infant. The Journal of Theoretical Fimpology. 2013; 1(2): e-20120609-1-2-3. Available from: www.fimpology.com (Search Google Scholar)
314. Yin S-d. The female may play more roles in biological heredity than the male does: Female–relayed integral cell and cytoplasmic inheritance. The Journal of Theoretical Fimpology. 2013; 1(3): e-20120717-1-3-6. Available from: http://www.fimpology.com (Search Google Scholar)
315. Ernst Mayr. The growth of biological thought: diversity, evolution, and inheritance. p.23. Belknap Press. USA.1982.
316. Russell JB, Rychlik JL. Factors that alter rumen microbial ecology. Science. 2001; 292(5519): 1119–22