The Second Time of Combining Darwin with Pasteur: Beyond Questioning Human Fetus in Uterus—Sterile, or Not §

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Abstract

In Fimpology, the human body is understood as the "niches" or "habitats" of evolutionary microentities, including cellular, subcellular, and molecular entities.[1-4] In the recent reviews, bacteria, archaea, fungi, viruses/phages, and extracellular vesicles were revealed to exist normally in the human body as evolutionary background entities (EBEs) at the cellular and subcellular levels.[3,4] The earliest source of hominal EBEs can be traced back to the prenatal period. Evidence and facts uncovered in studies on fetus and neonates in the past decades support the novel concept that "fetuses are not sterile," which challenges the traditional dogma that the human fetal growth and development occurs within a sterile environment. It was traditionally thought that during normal pregnancy, the fetal respiratory tract, gastrointestinal tract, skin, vaginal tract and amniotic fluid are all sterile, and that the birth of a fetus marks the point at which the respiratory tract, gastrointestinal tract, skin, and vaginal tract become colonized by external microorganisms. However, our current theories in the life sciences cannot answer the question of "when, how, and why did host-associated microorganism communities including fungi, bacteria, archaea, viruses, and protists occur in our bodies?" One reason for this may be the lack of a critical unification between Darwin's evolution theory and Pasteur's Germ Theory. From the fimpological perspective, the late 1970s, when the evolutionary relationship between bacteria and traditional biology was acknowledged, marked the first time Darwin and Pasteur's theories were combined.[5] Today, while we recognize that Lamarck, Darwin and Wallace's evolution theories, Mendel's law of biological heredity, and Pasteur's Germ Theory are all movements of the symphony of evolution, one of the tasks we have to complete is to theoretically unite Darwin's evolution theories with Pasteur's viruses, fungi, protists, and molecular prions for the second time, for which, the UPOEE model in Fimpology was proposed in 2013.[1] In this article, the following three novel concepts are proposed from the fimpological perspective: (1) the growth and development of a fertilized egg, an embryo, and fetus is not an automatic solo process of host eukaryotic cell lineages, but the complex

interactions that occur at different developmental stages between host eukaryotic cell lineages and their environmental microentities such as bacteria, fungi, viruses, and extracellular vesicles at the cellular, subcellular, and molecular levels; (2) There are two stages of non-host derived bacterial colonization normally experienced by human embryos, fetuses, and infants. One is the primary or prenatal colonization, which occurs during the embryonic or prenatal period, and the other is the secondary or postnatal colonization, which occurs during and after birth; and (3) I hypothesize for the first time that the human embryo and fetus may release bacteria during normal gestation, and these host-derived bacteria may be the unrecognized non-maternal source of bacteria in the amniotic cavity.

Key words: Evolutionary background entities (EBEs); Evolution; Darwin; Pasteur; Diversity; Animals; Plants; Modern Synthesis; Evolvamity; Evoclash; Eukaryote; Prokaryote; Vertebrate; Mammals; Bacteria; Archaea; Fungi; Viruses; Extracellular vesicles; Prions; Embryos; Fetus; Gnotobiotics; Germ-free; the primary colonization; the secondary colonization

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1. Introduction

During the past decades, in spite of recent myriad studies using newly emerged culture-independent molecular methods to describe the gastrointestinal microbiota of children and adults, only a few researchers have paid their attention to the prenatal microorganism profile in the gut of fetus.[6-18] One of the most reasonable excuses for this ignorance may be that none of the existing theories in the life sciences could be used to elucidate the significance and mechanisms of prenatal microorganism in fetuses. For instance, Pasteur's germ theory revealed a pathogenic relationship between bacterial agents and their host organisms, and what modern embryological biology has elucidated is a solo course performed by an embryo from a host eukaryotic zygote cell as the micro-entity at the cellular level to a fetus as the macro-entity at the macroorganism individual level, during which nothing has to do with microorganisms from the traditionally biological and physiological perspective.

In a recent paper, Rodríguez and colleagues stressed that "the dogma that the fetus resides in a sterile environment is being challenged by recent findings…increasing evidence on early microbial contact suggest that human intestinal microbiota is seeded before birth."[19] Gritz and Bhandari wrote that "colonization of mucosa in the digestive, respiratory, urogenital tracts, as well as the skin begins at, or perhaps even before, the time of birth when a newborn is exposed to a mother's microbiota." [20] Indeed, some anatomic sites of the human body were once believed to be sterile and this notion was also supported by results of traditional, culture-dependent studies. For example, the normal lungs were once believed to be germ-free.[21-23] Moreover, the hypothesis that the human amniotic cavity is sterile has been generally accepted for more than a century.[24-26] Although studies sometimes revealed bacterial coexistence in amniotic fluids, placentas, and fetal membranes, these results were usually accounted for from the pathological perspective or the consequence of their external transmission during pregnancy.[27-39] Therefore, in the NIH-initiated Human Microbiome Project (HMP), the lung and the

amniotic cavity were not included in the list of initial sites for investigation.[40-43] However, in recent years, bacterial communities in the lungs of healthy individuals and the amniotic cavity, including amniotic fluid, placenta, and fetal membranes of normal pregnancy, have been uncovered by culture-independent approaches.[4,23,44-49] Funkhouser and Bordenstein argued straightforwardly that "we can no longer ignore the fact that exposure to microbes in the womb is likely and may even be a universal part of human pregnancy, serving as the first inoculation of beneficial microbes before birth."[24] Most recently, Rodriguez and colleagues further asked, "we need to be able to not only understand 'who is there', but also be able to determine 'what they are doing' and how these functions interact with the host." [19] Indeed, while challenging the old doctrine, we have to confront the following newly arisen questions, such as what is the bacterial composition community in the embryo, fetus, and amnion fluid during normal pregnancy? Where do these bacteria come from? When do they appear earliest? What are their roles in normal pregnancy? And what discriminates between non-pathogenic and pathogenic bacteria in fetus and amnion fluid? Clearly, some of the above questions belong to the descriptive study, for which, to date, only a few pieces have been found due to ethical and technical limitations. Undeniably, the whole profile of bacterial composition and its dynamics in normal the embryo, fetus, and amnion fluid during ten months of gestation are still two of those unsolved, attractive puzzles. On the other hand, some questions need a theoretical exploration ahead because their answers cannot be found within the frame of our existing theoretical systems of the life sciences.[50] In this article, I try to propose some novel hypotheses as a theoretical examination for the future development while questioning whether the human fetus in the uterus is sterile or not.

2. The traditional notion: a human fetus normally develops in utero, a sterile environment

Recently, Funkhouser and Bordenstein revealed that it was French pediatrician Henry Tissier who first declared that "human infants develop within a sterile environment and acquire their initial bacterial inoculum while traveling through the maternal birth canal" in 1900, [24,51] which, however, should be attributed to the development of the idea of "germ-free" animals proposed first by Pasteur in 1885.[52] Moreover, the founders of bacteriology including Pasteur and Fernbach, also believed that inner plant tissues were sterile, since then, this opinion has been accepted by many researchers, although bacteria were often observed within fruits, seeds, and plant shoot tissues, which usually were attributed to contamination from external environment.[53-55] Indeed, Tissier's assumption has taken root deeply in the life sciences, and even in recent years, it is often cited or restated by many authors in their articles. This traditional notion was not only a theoretical hypothesis that existed for more than a century, but also supported by most laboratory studies, which indicated that traditional bacterial cultural methods did reveal that amniotic fluid was normally "sterile." However, in the last decade of the 20th century, especially after the application of culture-independent molecular approaches in medical microbiology, the presumptive sterility of normal fetuses has being challenged by accumulating novel findings.[4,19,20,26,56]

3. The sources of bacteria, viruses, and extracellular vesicles in the amniotic cavity

Most recently, bacteria, viruses, and extracellular vesicles as evolutionary background entities at the cellular and subcellular levels in the human amniotic cavity have been reviewed,[4] in which, it has been indicated that evolutionary background entities (EBEs), including microorganisms, normally exist in fetal blood, the fetal gastrointestinal tract, amniotic fluid, and even chorioamnion.[37,38,57-65] If we accept the notion that bacterial colonization in the fetal gut occurred before birth via ingesting bacteria in amniotic fluid, the following questions will arise and to be answered imperatively: When, where, and how do bacteria in amniotic fluid come from? What is their composition? Is bacterial community in amniotic fluid stable or dynamic? What determines their role to be physiological or pathogenic? Is it true that bacterial colonization occurs in the whole fetal skin and mucous membrane exposed to amniotic fluid? Or, do bacteria appear not only in the fetal gut, but also present in the fetal respiratory tract, genital tract and circulatory system during gestation? What is the ecological significance of a "germ-harboring" fetus? Can we extend the recognition of a "germ-harboring" human fetus to the "germ-free" nonhuman animals? If so, how do we account for the un-revealed evolutionary significance? And how do we bridge the huge gap between "germ-free" non-human animal and a "germ-harboring" fetus?

3.1 The proposed source and routes of bacterial access to the uterus in the existing literature

In fact, although we cannot answer the whole bunch of questions above right now, there is still much indirect information or data that could be used to elucidate this novel recognition. In this section, I will focus the question "where do bacteria, viruses, and extracellular vesicles in amniotic fluid come from?" Although the researchers who believed that "human amniotic fluid is normally sterile" accounted for the coexistence of bacteria in human amniotic fluid mainly from the pathological perspective, they cannot explain why some pregnant women do not develop a clinical intra-amniotic infection despite the coexistence of bacteria in amniotic fluid.[66] The following three major routes were proposed in the existing literature for pathogenic bacterial accessing to the uterus [66]: (1) Bacterial ascending into the uterus from the lower tract, which is believed to be the most common route of uterine bacterial infection. For instance, the coexistence of E. coli in amniotic fluid has been considered to be the consequence of E. coli entering the uterus from the lower genital tract through an ascending route.[67-70] Although Rezeberga and colleagues believed that a barrier constituted by "a long and closed cervix, thick cervical mucus, intact fetal membranes, and a competent maternal immune system" can play a role against the intrauterine migration of normal and pathogenic cervicovaginal flora in healthy women,[71,72] the barrier's efficiency is physiologically dynamic or unstable, as revealed in the studies on sperm transport.[73-76] (2) Bacterial descending into the uterus from the peritoneal cavity. As early as 1982, when twelve healthy women underwent laparoscopic tubal sterilization, Spence and colleagues using culture methods

found that anaerobic bacteria were isolated from the peritoneal cavity of three women.[77] Friberg and colleagues observed the coexistence of spermatozoa and Chlamydia trachomatis in the peritoneal cavity of patients with salpingitis.[78] Experimental studies have revealed that during the sexual intercourse, the peristaltic contractions of the female genital tract help not only sperm, but also seminal and vaginal bacteria move through the cervix into the uterus,[79,80] which means that the female upper reproductive tract is routinely exposed to vaginal microorganisms and subsequently some bacteria even enter the peritoneal cavity through the fallopian tubes; (3) Hematogenous transmission. In fact, the pathogenic association between maternal sourced bacteria and pregnancy was already observed before, in which two routes of maternal bacterial hematogenous transmission were proposed. The first route is the bacterial hematogenous transmission from the maternal oral cavity to the amniotic cavity via maternal circulation.[38,81,82] As early as the early 1980s, Kornman and colleagues reported that oral bacterial species in the subgingival space of women were found to reach the amniotic fluid via the bloodstream, particularly in the presence of gingivitis or peridontitis during pregnancy.[81] Dasanayake and colleagues also argued that oral bacteria can enter the uterine environment through the bloodstream and may influence the delivery process.[83] Some normal oral bacterial inhabitants including Acinetobacter spp., Peptostreptoccus spp., and Leptotrichia spp. were isolated from intrauterine samples, [84] and some bacterial species in the genera of Fusobacterium, Bergeyella, Eikenella, and Capnocytophaga found in the amniotic cavity were not found in the maternal urogenital tract, but in the oral cavity;[38,82] therefore, maternal periodontal disease was suggested to associate with preterm labor.[84] This bacterial hematogenous transmission route has been proved in a mice model.[82,85,86] In order to check where the bacteria in amniotic fluid come from, Jimenez and colleagues divided pregnant mice into two groups: one group was orally inoculated with a genetically labeled Enterococcus faecium, and the other group was not given bacterial oral administration. [58] And they found that labeled Enterococcus faecium was detected in meconium. [58] And the second route is bacterial hematogenous transmission from the maternal gut to the amniotic cavity via maternal circulation. Rautava and colleagues showed that probiotic Bifidobacterium lactis and Lactobacillus rhamnosus GG migrated from the maternal gut into amniotic fluid, placenta, and the fetal intestine.[31] Rescigno and colleagues found that dendritic cells can penetrate the gut epithelium to directly take up bacteria from the gut lumen.[87] Once being inside or attached to dendritic cells or other lymphocyte types, bacteria could spread to other locations via the bloodstream due to the circulation of lymphocytes within the mucosal-associated lymphoid tissue system.[58] Jimenez and colleagues explained that bacteria can have a transient spread from the digestive tract to extradigestive locations such as amniotic fluid, and therefore, they were swallowed by fetal mice and appeared in meconium.[58,86]

3.2 The hypothesis from the fimpological perspective for the unrecognized source of bacteria in the amniotic cavity

Generally, maternal bacteria have been recognized as the only bacterial source accounting for bacterial appearance in the amniotic cavity during pregnancy. However,

considering the fact that some bacterial species and some subcellular entities including viruses and extracellular vesicles have been found normally in human semen,[56,88-90] I argue that theoretically, the possibility of seminal bacteria as the second bacterial source entering the amniotic cavity via sexual intercourse cannot be excluded. Moreover, from the fimpological perspective, I hypothesize for the first time that embryo and fetus are an unrecognized source of bacteria in the amniotic cavity. These two non-maternal bacterial sources for bacteria in the amniotic cavity will be discussed in other articles later.

3.3 The source of viruses in the amniotic cavity

Traditionally, viruses appeared in the amniotic cavity were considered to be the consequence of viral invasion.[91] The pathological consequences of amniotic fluid viral invasion, such as preterm birth,[84,92-94] stillbirth, [95-99] and birth defects have been recognized for a long time in clinical medicine.[100] However, since 1978 when Nelson, Leong and Levy revealed that normal human placentas contained retrovirus-like particles and RNA-directed DNA polymerase activity,[101] diverse viruses or viral nucleic acids have been reported being detected in the amniotic fluid of normal pregnancy of humans.[91,102-107] The hematogenous transplacental path and the ascending trans-cervix path from the lower genital tract were believed to be the major two routes for the entrance of maternal viruses into the amniotic cavity.[91,97,98,108] In addition, the seminal source is the second viral source for viral appearance in the amniotic cavity.[4,97,108,109]

3.4 The source of extracellular vesicles in the amniotic cavity

Extracellular vesicles are constituted by various types of membrane-enclosed microentities, including ectosomes, exosomes, microvesicles, and apoptotic bodies,[110-115] In fimpology, extracellular vesicles, together with eukaryotic viruses and prokaryotic phages, have been classified as microentities at the subcellular level. These microentities are the evolutionary background entities (EBEs) of prokaryotic and eukaryotic cells.[1,2,50,116] Studies have revealed that extracellular vesicles have also been detected in the amniotic fluids of humans and other mammal species,[4,117-122] and the source of these extracellular vesicles in amniotic fluids is believed to be the maternal body and the fetal themselves.[4,118,120,122] For example, maternal endometrial epithelial cells have been found to release exosomes/microvesicles, [123] and some extracellular vesicles in amniotic fluids have been found to carry a marker of extracellular vesicles released from fetal renal epithelial cells called "CD24".[118,120,122] Moreover, the evidence of secreting exosomes has been found in in vitro-produced embryos, as observed under a transmission electron microscope.[4,124,125] Considering the fact that extracellular vesicles can also be released by prokaryotic cells such as Gram-negative and Gram-positive bacteria [50,126] and that bacteria exist normally in the amniotic cavity, [4] theoretically, I argue that prokaryotic bacteria may be another source of extracellular vesicles in amniotic fluids. Similar to the circumstance of extracellular vesicles in the healthy human respiratory tract,[4] it may be a challenge to distinguish the extracellular vesicles in the amniotic cavity released by bacteria from those released by maternal and fetal eukaryotic cells, especially considering

the co-existence of prokaryotic and eukaryotic cells in the healthy human amniotic cavity.[4]

Therefore, amniotic fluid, which is normally the important aquatic environment of the fetus, is no longer a previously assumed simple fluid containing only some bio-active molecules, but a complex aquatic medium carrying various cellular, subcellular, and molecular entities. This complex medium constitutes a special "window" for observing and understanding mysterious embryonic and fetal growth and development. Indeed, we cannot always interpret the co-existence of bacteria, viruses, and extracellular vesicles in amniotic fluid from a pathological perspective and must confront the fact that they appear during normal pregnancy, from a fertilized single cell to a multicellular fetus. In fact, the role of bacteria in the normal embryonic development of invertebrate animals has been studied in the past decades, [24,127-130] but such study in vertebrate animals, especially mammals, has not attracted much attention. One reason for this lack of attention may be that we are theoretically fettered by the hypotheses of Pasteur's "germ-free animal" and Tissier's "germ-free human fetus." [24,25,52]

4. Gnotobiotic nonhuman animal and plant models

Undoubtedly, the most serious impact of the novel concept—"fetus isn't sterile", as recently pointed out by Reid and colleagues—is that it contradicts the theoretical base of gnotobiotics.[131] Based on the assumption that the growth and development of a fertilized cell might be a sterile course in a sterile environment, gnotobiotic or germ-free nonhuman animal and plant models have been developed gradually over the past decades.

Gnotobiotic animal models, or "germ-free" animal models, are those animals that are maintained after birth "either free from external microbial contaminants or live in association with known elements of the flora."[52] Since the 1950s, gnotobiotic animal models have been established in many nonhuman animal species [132] such as mice,[133-138] pigs,[139,140-144] lambs,[145-147] salmonid fish,[148] zebrafish, [149,135] sea bass,[150] and Atlantic cod.[151]. These gnotobiotic animal models, or "germ-free" animal models have been widely used in life science studies over the past decades.[139,143,146,152-161] In addition, gnotobiotic plant models have also been established in several plant species such as canola, tomato, radish, wheat, and potato.[162,163] The importance of bacterial colonization in the postnatal growth, development, and lifespan of animals has been revealed in the gnotobiotic animal models. For example, Rawls and colleagues showed that Zebrafish raised axenically suffered severe deterioration in gut development in terms of enterocytic structure and function, and displayed early lethality.[159] Brummel and colleagues showed that the lifespan of Drosophila was enhanced after secondary colonization by exogenous bacteria.[164] In fact, gnotobiotics or "germ-free" in nonhuman animal models, is based on two prerequisites: (1) those animals were "germ-free" before birth, and (2) they were maintained "germ-free" after birth. The second prerequisite was an extension of the first one, which was also the theoretical base of all published papers on gnotobiotics for accounting for their results. However, today the first theoretical prerequisite of gnotobiotics is challenged for the following reasons: (1) "germ-free" animal models were initially defined using traditional bacterial culture methods, not culture-independent

approaches, and (2) Reid and colleagues revealed that "to our knowledge, there are no studies on the bacterial load of germ-free derived animals at their fetal stage."[131]

In fimpology, there are two stages of non-host derived bacterial colonization experienced normally by animal embryos, fetuses, and infants. One is primary or prenatal colonization, which occurs during the embryonic or prenatal period and is mainly source from the mother. The other is secondary or postnatal colonization, which occurs during and after birth and is sourced from both the mother and the non-maternal environment.

If the above two prerequisites of gnotobiotics were to change as follows: (1) those animals experienced primary colonization by maternal-derived microorganisms before birth, and (2) they were kept away from secondary colonization by external microorganisms, including bacteria, archaea, fungi, and protists, after birth, the interactions between prokaryotic and eukaryotic cells within "germ-free" animal models would be much more complicated than previously understood. Therefore, a new challenge for researchers is how to control and rule out the influence of primary colonization while deciphering the results of postnatal colonization experiments. Germ-free animals will continue to be used as a unique laboratory tool for in vivo studies on secondary colonization of microorganisms in the future.

5. The critical questions to be answered since Leeuwenhoek's time

As early as the 17th century, microbial cells in the human body first attracted the Netherlander Antoni van Leeuwenhoek's (1632-1723) attention when he examined scrapings of his tongue and teeth under lenses he made and discovered the normal existence of bacterial microorganisms within his oral cavity. Leeuwenhoek became the earliest man to reveal that there are naturally occurring bacteria in the human body that are invisible to the naked eye. However, the mysterious role of microorganisms in our bodies wasn't uncovered until the middle of the 19th century when the French chemist and biologist Louis Pasteur (1822-1895) published his Germ Theory. Pasteur believed that fermentation, putrefaction, and infection were all caused by microbes or bacilli, and furthermore, different bacilli seemed to cause different diseases. Therefore, the first role of microorganisms in our bodies wasn labeled "pathogens," and this pathogenic role of bacteria was observed not only in diseases of humans but also in those of nonhuman animals and plants. Since the advent of the great Germ Theory, humans have launched an anti-bacteria "war" along the path pointed by Pasteur's Germ Theory. Although several hundred bacteria had been identified by the beginning of the 20th century, there were still many severe infections, such as smallpox, rabies, and measles, for which no bacterial cause could be found. Meanwhile, when the knowledge of pathogenic agents expanded into the submicroscopic level, the concept of virus, a subcellular bioactive entity, was proposed, and its image was finally described after the invention of the electron microscope by Germans Ernst Ruska and Max Knoll in the1930s. Viral diseases and relevant pathogenic viruses were also gradually recognized and illustrated morphologically.

Since then, humans' enthusiasm for digging and fighting pathogenic microorganisms, including bacteria and viruses, has never waned. However, while we celebrate one victory after another in fighting microorganism pathogens, several important questions that have been ignored unintentionally since Leeuwenhoek's time are "what are the roles of microorganisms in our healthy bodies?" Or in other words, "why do bacteria exist in our healthy bodies?" "Do bacteria play roles in the human not only pathologically, but also physiologically?" Indeed, answering these questions is becoming more and more imperative today. Moreover, considering that an adult human body is formed from a fertilized eukaryotic egg created by the combination of a female oocyte and a male spermatozoon, we have to answer when and how the huge microorganism community, including fungi, bacteria, archaea, viruses, and protists, is formed in our bodies, and furthermore, such questions also apply to nonhuman animals and plants. Is the appearance of microorganisms in the human body a unique phenomenon that only occurs in humans? If not, can we trace its existence back in nonhuman animals and plants according to the Darwinian Tree of Life? And if the outcome is what we expected, what role do host-associated microorganisms play in biological evolution?

6. Darwin and Pasteur: two different contributors in helping our understanding of the symphony of evolution

Darwin and Pasteur are undoubtedly two giants in the history of science. Both of them had many similarities and differences. For example, they were born in the same century, and Pasteur was only 13 years younger than Darwin. When Darwin and Wallace jointly announced their grand theory in 1858, Pasteur was 36 years old. Nither of them had an educational background in medicine. Darwin's father had hoped Darwin to become a doctor at first; but Darwin couldn't tolerate the agonizing screams of surgical patients operated on without anesthesia. By the first surgery in England was carried out under an anesthetic ether in 1846, Darwin was already 37 years old. Pasteur studied science during his undergraduate and postgraduate studies and obtained a doctorate in physics and chemistry in 1847.[217] Moreover, they made their unique contributions to the life sciences. In fact, what both Darwin and Pasteur studied were essentially two different forms of life: macroorganisms such as humans, nonhuman animals, and plants, and bacterial microorganisms. Darwin created the evolution theory, which for the first time theoretically uncovered the evolutionary nexus between human beings and other nonhuman animals. Pasteur proposed his Germ Theory, which for the first time revealed that diseases were caused by bacteria and there is a pathogenic connection between bacterial microorganisms and diseases of humans and nonhuman animals, resulting in the birth of microbiology and its branches, including medical microbiology, veterinary microbiology, and botany microbiology.

During the past one and half centuries, the importance of the combination between Darwin's theory and Pasteur's study has seldom been stressed, one of the major reasons may be that Pasteur's pathogenic agents have expanded from initially only bacterial member to the current assembly consisting of viruses, fungi, protists, and prions, and that

these pathogens belong to different evolutionary levels, and their morphology, structures, and functions are extremely varied. Therefore, combining the theories of two giants has become a more knotty problem because before doing so, we have to answer the question "what is the evolutionary nexus among these pathogens at the cellular, subcellular, and molecular levels?" which, however, is beyond the scope of Darwin's theory. Humans, extant animals, and plants exist independently and freely on Earth. Darwin bound all extant macroorganisms and extinct macroorganisms together through his evolution theory, however, in Darwin's theory, the content for the role played by bacterial microorganisms was missed.

In the 1940s, the emergence of the Modern Synthesis, our modern understanding of how evolution works, was attributed to the efforts made by many experts in genetics, biomathematics, zoology, paleontology, and botany to combine Darwinian evolution theories with Mendelian genetics. [50,165-169] Once again, in the Modern Synthesis, we cannot find a suitable place for either Pasteur's bacterial pathogens or for pathogenic viruses, fungi, protists, and prion. Moreover, to date, accumulating evidence has indicated that bacteria, archaea, viruses, fungi, protists, and prion-like proteins exist as normal entities in a natural state, but this raises a new question: Can we put them into one theoretical system? Recently, when we find the deficiency in the Modern Synthesis and expect a theoretical revolution for the future Synthesis, [50,168,170-180] we have to identify first what is the essential difference in the research between Darwin and Pasteur in the 19th century, and ask ourselves: Today, as their followers, do we have enough theoretical recognition and evidence to unite Pasteur with Darwin and Mendel after one and half centuries? In fact, when Leeuwenhoek first found the coexistence of macroorganisms and microorganisms in the 17th century, nobody knew the nature of bacterial microorganisms. In the 19th century, Pasteur found disease-related bacteria, which was the first answer to the question "what is the relationship between macroorganisms and bacterial microorganisms?" which had arisen since Leeuwenhoek's time. However, Pasteur didn't realize that besides a pathogenic relation, there is also an evolutionary correlation between macroorganisms and bacterial microorganisms. He unintentionally uncovered a participant that involves in biological evolution, although its real face was merely partially described as being pathogenic at that time.

While history has revealed that "Darwin often discussed microorganismal classification, origins and experimentation in his correspondence,"[181] Darwin didn't become aware of what Pasteur found as an evolution-driving power that he was looking for. From the fimpological perspective, Darwin and Pasteur looked like two theoretically isolated interpreters for the symphony of evolution—one was in England and the other in France, and no chord could be found in their different theories and different understanding of life. The combination of them with Darwin's tree of life wasn't realized until in the late 1970s when bacterial evolutionary relationship with traditional biology was acknowledged for the first time.[5]

7. The second time combining Darwin with Pasteur

While we realize that deciphering the sonata of evolution in the 19th century was not the solo of Lamarck, Darwin and Wallace's evolution theories and Mendel's law of

biological heredity, and that Pasteur's Germ theory was also an indispensable melody, from which virusian, fungian, protistian, archaeaian, and prionian were derived in succession, one of the tasks we have to complete today is to theoretically unite Darwinian evolution theories with Pasteurian viruses, fungi, protists, and prions for the second time. Obviously, the presence of microorganism during embryo development indicates that the interaction between prokaryotic bacterial cells and eukaryotic host cells starts before birth, not during delivery or after birth. However, the elucidation of mechanisms and significance for the relationship between prokaryotes and eukaryotes will involve microbiology, microecology, and evolutiology.

In the newly proposed fimpological UPOEE model,[1,2] all evolutionary entities at different evolutionary levels, including molecular, subcellular, prokaryotic, and eukaryotic levels, have been assembled in one theoretical system,[1,2,50,116] and microorganisms such as bacteria, archaea, viruses and fungi are labeled "Evolutionary Background Entities (EBEs)" referring to those entities at the lower evolutionary levels of the entities at the higher evolutionary levels.[1-3,50,116,130,182,183] For example, the EBEs of eukaryotic multicellular macroorganisms, including humans, nonhuman animals, and plants, embrace not only eukaryotic and prokaryotic monocellular entities but also include subcellular entities such as viruses, phages, extracellular vesicles, and molecular entities including RNA, DNA, and other relevant organic and inorganic entities.[1,3,50,130,182-193] Moreover, in fimpology, humans, nonhuman animals, and plants are not only inhabitants of natural habitats but also are the 'niches' or 'habitats' of evolutionary micro-entities including bacteria, archaea, viruses/phages, fungi, and protists.[2-4,56,130,182,183,185,188,193-206] In addition, the interaction between an evolutionary entity and its environment is actually the interaction between the entity and its environmental evolutionary entities at the same and/or different evolutionary levels.[2,207-212] The fate of an evolutionary entity at a given evolutionary level reflects the synthetic consequence of evolvamity and/or evoclash dealing with this entity, which is determined by the complex interactions among evolutionary entities at all relevant evolutionary levels.[1-4,50,116,130,183,207,213]

The fimpological UPOEE model, from a theoretical perspective, cleared away some critical obstacles including those between macroorganisms and microorganisms, between abiotic entities and biotic entities, between physiological function and pathogenic role, between individuality and population, and between extant bio-species and fossils on the path to the future Synthesis.[1,2,50,116] Recently, studies provided evidence suggesting that bacteria-released lactones influence plant growth.[214-216] Brummel and colleagues revealed that the lifespan of Drosophila was affected by the bacteria they contacted in early adult life.[164] They found that the presence of bacteria during the first week of Drosophila adult life enhanced their lifespan, but later in life, the presence of bacteria reduced the lifespan of Drosophila.[164]

8. Concluding Remarks

During the past decades, evidence obtained using culture-independent molecular approaches has support the notion that bacterial colonization in fetuses occurs before

birth through contact with bacteria in amniotic fluid. This challenges the traditional assumption proposed by Tissier 115 years ago that human fetuses develop in a sterile environment. The presence of bacteria in amniotic fluid indicates that the interaction between prokaryotic bacterial cells and eukaryotic host cells begins before birth, not during delivery or after birth, which is beyond the scope of the pathogenic relationship between bacteria and their macroorganism hosts described by Pasteur in his Germ Theory and the span of evolutionary relationship between extant macroorganism species and extinct macroorganism species proposed by Darwin and other masters in their evolutionary theories. The UPOEE model proposed in 2013[1] arms to theoretically unite Darwin's evolution theories with Pasteur's viruses, fungi, protists, and molecular prions for the second time.

In this article, the following three novel concepts are proposed from the fimpological perspective: (1) the growth and development of a fertilized egg, an embryo, and a fetus is not an automatic solo process of host eukaryotic cell lineages, but the complex interactions that occur at different developmental stages between host eukaryotic cell lineages and their environmental microentities such as bacteria, fungi, viruses, and extracellular vesicles at the cellular, subcellular and molecular levels; (2) There are two stages of non-host derived bacterial colonization normally experienced by human embryos, fetuses, and infants. The first stage is the primary or prenatal colonization, which occurs during the embryonic or prenatal period and is mainly sourced from maternal bacteria. The second stage is the secondary or postnatal colonization, which occurs during and after birth, with the major source from non-maternal environmental bacteria, which was previously believed to be the only stage of bacterial colonization experienced by infants; and (3) I also hypothesize for the first time that human embryos and fetuses may release bacteria during normal gestation and that these host-derived bacteria may be the unrecognized non-maternal source of bacteria in the amniotic cavity.

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Reference

1. Yin S-d. The universal pattern of evolutionary entities and its circulatory ladder-like pyramid feature. The Journal of Theoretical Fimpology. 2013; 1(4): e-20111024-1-4-8. Available from: http://www.fimpology.com

2. Yin S-d. Entity, environment and their relationship in evolution: no antagonistic essence between neo-Darwinians and Lamarckians. The Journal of Theoretical Fimpology. 2014; 2(1): e-20090203-2-1-9. Available from: http://www.fimpology.com
3. Yin S-d. Bacteria, viruses, membrane-enclosed microentities, and fungi as the environmental evolutionary entities coexisting in human milk. The Journal of Theoretical Fimpology. Volume 2, Issue 2: e-20120718-2-2-11. Available from: http://www.fimpology.com
4. Yin S-d. Evolutionary background entities at the cellular and subcellular levels in the human body. The Journal of Theoretical Fimpology. 2015; 3(1): e-20050615-3-1-15. Available from: http://www.fimpology.com
5. McInerney JO, Cotton JA, Pisani D. The prokaryotic tree of life: past, present... and future? Trends Ecol Evol. 2008; 23(5): 276-81
6. Wylie KM, Truty RM, Sharpton TJ, Mihindukulasuriya KA, Zhou Y, Gao H, et al. Novel bacterial taxa in the human microbiome. PLoS One. 2012; 7(6): e35294
7. Fodor AA, Desantis TZ, Wylie KM, Badger JH, Ye Y, Hepburn T, et al. The "most wanted" taxa from the human microbiome for whole genome sequencing. PLoS One. 2012; 7(7): e41294
8. Li K, Bihan M, Yooseph S, Methe BA. Analyses of the microbial diversity across the human microbiome. PLoS One. 2012;7(6):e32118
9. Rea MC, O'Sullivan O, Shanahan F, O'Toole PW, Stanton C, Ross RP, et al. Clostridium difficile carriage in elderly subjects and associated changes in the intestinal microbiota. J Clin Microbiol. 2012; 50(3): 867-75
10. Claesson MJ, Cusack S, O'Sullivan O, Greene-Diniz R, de Weerd H, Flannery E, et al. Colloquium Paper: Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci USA. 2011; 108(Suppl1): 4586-91
11. Bogaert D, Keijser B, Huse S, Rossen J, Veenhoven R, van Gils E, et al. Variability and diversity of nasopharyngeal microbiota in children: a metagenomic analysis. PLoS One. 2011; 6(2): e17035
12. Rousseau C, Levenez F, Fouqueray C, Dore J, Collignon A, Lepage P. Clostridium difficile colonization in early infancy is accompanied by changes in intestinal microbiota composition. J Clin Microbiol. 2011; 49(3): 858-65
13. Monira S, Nakamura S, Gotoh K, Izutsu K, Watanabe H, Alam NH, et al. Gut microbiota of healthy and malnourished children in bangladesh. Front Microbiol. 2011; 2: 228
14. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010; 464 (7285): 59-65
15. Palmer C, Bik EM, Digiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007; 5(7): e177
16. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006; 118(2): 511-21
17. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444(7122): 1022-3
18. Mueller S, Saunier K, Hanisch C, Norin E, Alm L, Midtvedt T, et al. Differences in fecal microbiota in different European study populations in relation to age, gender, and country: a cross-sectional study. Appl Environ Microbiol. 2006; 72(2): 1027-33
19. Rodriguez JM, Murphy K, Stanton C, Ross RP, Kober OI, Juge N, et al. The composition of the gut microbiota throughout life, with an emphasis on early life. Microb Ecol Health Dis. 2015; 26: 26050
20. Gritz EC, Bhandari V. The human neonatal gut microbiome: a brief review. Front Pediatr. 2015; 3: 60
21. Baughman RP, Thorpe JE, Staneck J, Rashkin M, Frame PT. Use of the protected specimen brush in patients with endotracheal or tracheostomy tubes. Chest. 1987; 91(2): 233-6
22. Thorpe JE, Baughman RP, Frame PT, Wesseler TA, Staneck JL. Bronchoalveolar lavage for diagnosing acute bacterial pneumonia. J Infect Dis. 1987; 155(5): 855-61
23. Beck JM, Young VB, Huffnagle GB. The microbiome of the lung. Transl Res. 2012; 160(4): 258-66
24. Funkhouser LJ, Bordenstein SR. Mom knows best: the universality of maternal microbial transmission. PLoS Biol. 2013; 11(8): e1001631
25. Tissier H. Recherches sur la flore intestinale des nourrissons (at normal et pathologique). Paris: G. Carre and C. Naud.1900

26. Wassenaar TM, Panigrahi P. Is a foetus developing in a sterile environment? Lett Appl Microbiol. 2014; 59(6): 572-9
27. Payne MS, Bayatibojakhi S. Exploring preterm birth as a polymicrobial disease: an overview of the uterine microbiome. Front Immunol. 2014; 5: 595
28. Combs CA, Gravett M, Garite TJ, Hickok DE, Lapidus J, Porreco R, et al. Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. Am J Obstet Gynecol. 2014; 210(2): e1-15
29. Stout MJ, Conlon B, Landeau M, Lee I, Bower C, Zhao Q, et al. Identification of intracellular bacteria in the basal plate of the human placenta in term and preterm gestations. Am J Obstet Gynecol. 2013; 208(3): 226.e1-7
30. Fichorova RN, Onderdonk AB, Yamamoto H, Delaney ML, DuBois AM, Allred E, et al. Maternal microbe-specific modulation of inflammatory response in extremely low-gestational-age newborns. MBio. 2011; 2(1): e00280-e00310
31. Rautava S, Collado MC, Salminen S, Isolauri E. Probiotics modulate host-microbe interaction in the placenta and fetal gut: a randomized, double-blind, placebo-controlled trial. Neonatology. 2012; 102(3): 178-84
32. Leviton A, Allred EN, Kuban KC, Hecht JL, Onderdonk AB, et al. Microbiologic and histologic characteristics of the extremely preterm infant's placenta predict white matter damage and later cerebral palsy the ELGAN study. Pediatr Res. 2010; 67(1): 95-101.
33. Han YW, Shen T, Chung P, Buhimschi IA, Buhimschi CS. Uncultivated bacteria as etiologic agents of intra-amniotic inflammation leading to preterm birth. J Clin Microbiol. 2009; 47(1): 38-47
34. McElrath TF, Hecht JL, Dammann O, Boggess K, Onderdonk A, et al. Pregnancy disorders that lead to delivery before the 28th week of gestation: an epidemiologic approach to classification. Am J Epidemiol. 2008; 168(9): 980-9
35. Hecht JL, Onderdonk A, Delaney M, Allred EN, Kliman HJ, Zambrano E, et al. Characterization of chorioamnionitis in 2nd-trimester C-section placentas and correlation with microorganism recovery from subamniotic tissues. Pediatr Dev Pathol. 2008; 11(1): 15-22
36. Steel JH, Malatos S, Kennea N, Edwards AD, Miles L, Duggan P, et al. Bacteria and inflammatory cells in fetal membranes do not always cause preterm labor. Pediatr Res. 2005; 57(3): 404-11
37. Perni SC, Vardhana S, Korneeva I, Tuttle SL, Paraskevas LR, Chasen ST, et al. Mycoplasma hominis and Ureaplasma urealyticum in midtrimester amniotic fluid: association with amniotic fluid cytokine levels and pregnancy outcome. Am J Obstet Gynecol. 2004; 191(4): 1382-6
38. Bearfield C, Davenport ES, Sivapathasundaram V, Allaker RP. Possible association between amniotic fluid micro-organism infection and microflora in the mouth. BJOG. 2002; 109(5): 527-3339. Willson JR. The conquest of cesarean section-related infections: a progress report. Obstet Gynecol. 1988; 72(3 Pt 2):519-3240. Proctor LM. The Human Microbiome Project in 2011 and beyond. Cell Host Microbe. 2011; 10(4): 287-91
41. Robinson CJ, Bohannan BJM, Young VB. From structure to function: the ecology of host-associated microbial communities. Microbiol Mol Biol Rev. 2010; 74(3): 453-76
42. Hamady M, Knight R. Microbial community profiling for human microbiome projects: tools, techniques, and challenges. Genome Res. 2009; 19(7): 1141-52
43. Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, et al. The NIH Human Microbiome Project. Genome Res. 2009; 19(12): 2317-23
44. Romano-Keeler J, Weitkamp JH. Maternal influences on fetal microbial colonization and immune development. Pediatr Res. 2015; 77(1-2): 189-95
45. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Sci Transl Med. 2014; 6(237): 237ra65
46. Dickson RP, Erb-Downward JR, Freeman CM, Walker N, Scales BS, Beck JM, et al. Changes in the lung microbiome following lung transplantation include the emergence of two distinct pseudomonas species with distinct clinical associations. PLoS One. 2014; 9(5): e97214
47. Charlson ES, Bittingger K, Haas AR, Fitzgerald AS, Frank I, Yadav A, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. Am J Respir Crit Care Med. 2011; 184(8): 957-63

48. Erb-Downward JR, Thompson DL, Han MK, et al. Analysis of the lung microbiome in the "healthy" smoker and in COPD. PLoS One. 2011; 6(2): e16384
49. Jones HE, Harris KA, Azizia M, Bank L, Carpenter B, Hartley JC, et al. Differing prevalence and diversity of bacterial species in fetal membranes from very preterm and term labor. PLoS One. 2009; 4(12): e8205
50. Yin S-d. A fimpological view: The future synthesis of biology, ecology, and evolutiology. The Journal of Theoretical Fimpology. 2013; 1(3): e-20080225-1-3-5. Available from: http://www.fimpology.com
51. Tissier H. Recherches sur la flore intestinale des nourrissons (at normal et pathologique). Paris: G. Carre and C. Naud.1900
52. Gordon HA. The germ-free animal: its use in the study of "physiologic" effects of the normal microbial flora on the animal host. American Journal of Digestive Diseases 1960; 5(10): 841-67 (http://www.springerlink.com/content/f88452j814th553v/fulltext.pdf) (Accessed October 19, 2010)
53. Mundt JO, Hinkle NF. Bacteria within ovules and seeds. Appl Environ Microbiol. 1976; 32(5): 694-8
54. Fernbach MA. De l'absence des microbes dans les tissues vegetaus. Ann Inst Pasteur. 1888; 2: 567-70
55. Pirttila AM, Laukkanen H, Pospiech H, Myllyla R, Hohtola A. Detection of intracellular bacteria in the buds of Scotch pine (Pinus sylvestris L.) by in situ hybridization. Appl Environ Microbiol. 2000; 66(7): 3073-7
56. Yin S-d. The cellular and subcellular environmental entities confronted by spermatozoa and ova migrating along the reproductive tract of the human body. The Journal of Theoretical Fimpology. 2015; 3(3): e20050615-3-3-17. Available from: http://www.fimpology.com
57. DiGiulio DB, Romero R, Amogan HP, Kusanovic JP, Bik EM, Gotsch F, et al. Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: a molecular and culture-based investigation. PLoS One. 2008; 3(8): 33056
58. Jimenez E, Fernandez L, Marin ML, Martin R, Odriozola JM, Nueno-Palop C, et al. Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. Curr Microbiol. 2005; 51(4): 270-4
59. Martin R, Langa S, Reviriego C, Jimenez E, Martin ML, Olivares M, et al. The commensal microflora of human milk: new perspectives for food bacteriotherapy and probiotics. Trends Food Sci Technol. 2004; 15: 121-7
60. Nguyen DP, Gerber S, Hohlfeld P, Sandrine G, Witkin SS. Mycoplasma hominis in mid-trimester amniotic fluid: relation to pregnancy outcome. J Perinat Med. 2004; 32(4): 323-6
61. Mandar R, L ivukene K, Ehrenberg A, Smidt I, Raukas E, Kask V, et al. Amniotic fluid microflora in asymptomatic women at mid-gestation. Scand J Infect Dis. 2001; 33(1): 60-2
62. Keski-Nisula L, Kirkinen P, Katila ML, Ollikainen M, Saarikoski S. Cesarean delivery. Microbial colonization in amniotic fluid. J Reprod Med. 1997; 42(2): 91-8
63. Jacobsson B, Mattsby-Baltzer I, Hagberg H. Interleukin-6 and interleukin-8 in cervical and amniotic fluid: relationship to microbial invasion of the chorioamniotic membranes. BJOG. 2005; 112(6):719-24
64. Andrews WW, Hauth JC, Goldenberg RL, Gomez R, Romero R, Cassell GH. Amniotic fluid interleukin-6: correlation with upper genital tract microbial colonization and gestational age in women delivered after spontaneous labor versus indicated delivery. Am J Obstet Gynecol. 1995; 173(2): 606-12
65. Hillier SL, Witkin SS, Krohn MA, Watts DH, Kiviat NB, Eschenbach DA. The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstet Gynecol. 1993; 81(6): 941-8
66. Racicot K, Cardenas I, Wünsche V, Aldo P, Guller S, Means RE, et al. Viral infection of the pregnant cervix predisposes to ascending bacterial infection. J Immunol. 2013; 191(2): 934-41
67. Simhan HN, Caritis SN, Krohn MA, Hillier SL. The vaginal inflammatory milieu and the risk of early premature preterm rupture of membranes. Am J Obstet Gynecol. 2005; 192(1): 213-8
68. Goldenberg RL, Thompson C. The infectious origins of stillbirth. Am J Obstet Gynecol. 2003; 189(3): 861-73
69. Hitti J. Vaginal indicators of amniotic fluid infection in preterm labor. Obstet Gynecol. 2001; 97(2): 211-9
70. Peipert JF. Association of lower genital tract inflammation with objective evidence of endometritis. Infect Dis Obstet Gynecol. 2000; 8(2): 83-7

71. Rezeberga D, Lazdane G, Kroica J, Sokolova L, Donders GG. Placental histological inflammation and reproductive tract infections in a low risk pregnant population in Latvia. Acta Obstet Gynecol Scand. 2008; 87(3): 360-572. Ochiel DO, Fahey JV, Ghosh M, Haddad SN, Wira CR. Innate immunity in the female reproductive tract: role of sex hormones in regulating uterine epithelial cell protection against pathogens. Curr Womens Health Rev. 2008; 4(2): 102-17
73. Zervomanolakis I, Ott HW, Hadziomerovic D, Mattle V, Seeber BE, Virgolini I, et al. Physiology of upward transport in the human female genital tract. Ann N Y Acad Sci. 2007; 1101: 1-20
74. Bulletti C, DE Ziegler D, Setti PL, Cicinelli E, Polli V, Flamigni C. The patterns of uterine contractility in normal menstruating women: from physiology to pathology. Ann N Y Acad Sci. 2004; 1034: 64-83
75. Wildt L, Kissler S, Licht P, Becker W. Sperm transport in the human female genital tract and its modulation by oxytocin as assessed by hysterosalpingoscintigraphy, hysterotonography, electrohysterography and Doppler sonography. Hum Reprod Update. 1998; 4(5): 655-66
76. Leyendecker G, G.Kunz, Wildt L, Beil D, Deininger H. Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. Hum Reprod. 1996; 11(7): 1542-51
77. Spence MR, Blanco LJ, Patel J, Brockman MT. A comparative evaluation of vaginal, cervical and peritoneal flora in normal, healthy women: a preliminary report. Sex Transm Dis. 1982; 9(1): 37-40
78. Friberg J, Confino E, Suarez M, Gleicher N. Chlamydia trachomatis attached to spermatozoa recovered from the peritoneal cavity of patients with salpingitis. J Reprod Med. 1987; 32(2):120-2
79. Kunz G, Beil D, Deiniger H, Einspanier A, Mall G, Leyendecker G. The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. Adv Exp Med Biol. 1997; 424: 267-77
80. Parr EL, Parr MB. Secretory immunoglobulin binding to bacteria in the mouse uterus after mating. J Reprod Immunol. 1985; 8(1): 71-82
81. Kornman KS, Loesche WJ. The subgingival microbial flora during pregnancy. J Periodont Res. 1980; 15(2): 111-22
82. Fardini Y, Chung P, Dumm R, Joshi N, Han YW. Transmission of diverse oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection. Infect Immun. 2010; 78(4): 1789-96
83. Dasanayake AP, Li Y, Wiener H, Ruby JD, Lee MJ. Salivary Actinomyces naeslundii genospecies 2 and Lactobacillus casei levels predict pregnancy outcomes. J Periodontol. 2005; 76(2):171-7
84. Lopez NJ, Smith PC, Gutierrez J. Higher risk of preterm birth and low birth weight in women with periodontal disease. J Dent Res. 2002; 81(1): 58-63
85. Belanger M, Reyes L, von Deneen K, Reinhard MK, Progulske-Fox A, Brown MB. Colonization of maternal and fetal tissues by Porphyromonas gingivalis is strain-dependent in a rodent animal model. Am J Obstet Gynecol. 2008; 199(1): 86.e1-7
86. Jimenez E, Marin ML, Martin R, Odriozola JM, Olivares M, Xaus J, et al. Is meconium from healthy newborns actually sterile? Res Microbiol. 2008; 159(3): 187-93
87. Rescigno M, Urbano M, Valsazina B, Francoloni M, Rotta G, Bonasio R, et al. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. Nature Immunol. 2001; 2(4): 361-7
88. Weng SL, Chiu CM, Lin FM, Huang WC, Liang C, Yang T, et al. Bacterial communities in semen from men of infertile couples: metagenomic sequencing reveals relationships of seminal microbiota to semen quality. PLoS One. 2014; 9(10): e110152
89. Hou D, Zhou X, Zhong X, Settles ML, Herring J, Wang L, et al. Microbiota of the seminal fluid from healthy and infertile men. Fertil Steril. 2013;100(5): 1261-9
90. Kiessling AA, Desmarais BM, Yin HZ, Loverde J, Eyre RC. Detection and identification of bacterial DNA in semen. Fertil Steril. 2008; 90(5): 1744-56
91. Gervasi MT, Romero R, Bracalente G, Chaiworapongsa T, Erez O, Dong Z, et al. Viral invasion of the amniotic cavity (VIAC) in the midtrimester of pregnancy. J Matern Fetal Neonatal Med. 2012; 25(10): 2002-13

92. Morioka I, Sonoyama A, Tairaku S, Ebina Y, Nagamata S, Morizane M, et al. Awareness of and knowledge about mother-to-child infections in Japanese pregnant women. Congenit Anom (Kyoto). 2014; 54(1): 35-40
93. Kristina M. Waldorf A, McAdams RM. Influence of infection during pregnancy on fetal development. Reproduction. 2013; 146(5): R151-62
94. Paquet C, Yudin MH. Toxoplasmosis in pregnancy: prevention, screening, and treatment. J Obstet Gynaecol Can. 2013; 35(1): 78-9
95. Hau n L, Kwan N, Hollier LM. Viral infections in pregnancy. Minerva Ginecol. 2007; 59(2): 159-74
96. McClure EM, Goldenberg RL. Infection and stillbirth. Semin Fetal Neonatal Med. 2009; 14(4): 182-9
97. Younes AS, Csire M, Kapusinszky B, Szomor K, Takacs M, Berencsi G. Heterogeneous pathways of maternal-fetal transmission of human viruses. Pathol Oncol Res. 2009; 15(3): 451-6598. Syridou G, Spanakis N, Konstantinidou A, Piperaki ET, Kafetzis D, Patsouris E, et al. Detection of cytomegalovirus, parvovirus B19 and herpes simplex viruses in cases of intrauterine fetal death: association with pathological findings. J Med Virol. 2008; 80(10): 1776-182
99. Petersson K, Norbeck O, Westgren M, Broliden K. Detection of parvovirus B19, cytomegalovirus and enterovirus infections in cases of intrauterine fetal death. J Perinat Med. 2004; 32(6): 516-21
100. Zheng XY, Zhang T, Wang YF, Xu C, Chen G, Xin RL, et al. Intrauterine infections and birth defects. Biomed Environ Sci. 2004; 17(4): 476-91
101. Nelson J, Leong JA, Levy JA. Normal human placentas contain RNA-directed DNA polymerase activity like that in viruses. Proc Natl Acad Sci USA. 1978; 75(12): 6263-7
102. Naresh A, Simhan H. Absence of viruses in amniotic fluid of women with PPROM: a case series. J Reprod Immunol. 2012; 96(1-2): 79-83
103. Adams LL, Gungor S, Turan S, Kopelman JN, Harman CR, Baschat AA. When are amniotic fluid viral PCR studies indicated in prenatal diagnosis? Prenat Diagn. 2012; 32(1): 88-93
104. Miller JL, Harman C, Weiner C, Baschat AA. Perinatal outcomes after second trimester detection of amniotic fluid viral genome in asymptomatic patients. J Perinat Med. 2009; 37(2): 140-3
105. Biri A, Bozdayi G, Cicfti B, Dinc B, Yucel A, Rota S. The detection of CMV in amniotic fluid and cervicovaginal smear samples by real-time PCR assay in prenatal diagnosis. Arch Gynecol Obstet. 2006; 273(5): 261-6
106. Reddy UM, Baschat AA, Zlatnik MG, Towbin JA, Harman CR, Weiner CP. Detection of viral deoxyribonucleic acid in amniotic fluid: association with fetal malformation and pregnancy abnormalities. Fetal Diagn Ther. 2005; 20(3): 203-7
107. Baschat AA, Towbin J, Bowles NE, Harman CR, Weiner CP. Prevalence of viral DNA in amniotic fluid of low-risk pregnancies in the second trimester. J Matern Fetal Neonatal Med. 2003; 13(6): 381-4
108. Younes AS, Csire M, Palyi B, Mikala G, Valyi-Nagy I, Cseh I, et al. Endotoxins do not influence transplacental transmission of lymphotropic human herpesviruses and human papillomaviruses into amniotic fluid taken from healthy mothers before parturition in Hungary. Acta Microbiol Immunol Hung. 2007; 54(3): 279-303
109. Kaspersen MD, Hollsberg P. Seminal shedding of human herpesviruses. Virol J. 2013; 10: 226
110. Meckes DG Jr, Raab-Traub N. Microvesicles and viral infection. J Virol. 2011; 85(24): 12844-54
111. Zhu H, Fan GC. Extracellular/circulating microRNAs and their potential role in cardiovascular disease. Am J Cardiovasc Dis. 2011; 1(2): 138-49
112. Thery C. Exosomes: secreted vesicles and intercellular communications. F1000 Biol Rep. 2011; 3: 15
113. Oliveira DL, Nakayasu ES, Joffe LS, Guimaraes 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
114. Mause SF, Weber C. Microparticles: Protagonists of a novel communication network for intercellular information exchange. Circ Res. 2010; 107(9):1047-57
115. Anand PK. Exosomal membrane molecules are potent immune response modulators. Commun Integr Biol. 2010; 3(5): 405-8
116. Yin S-d. Natural selection is the interaction among evolutionary entities and operates at all evolutionary levels. The Journal of Theoretical Fimpology. 2014; 2(1): e-20071024-2-1-10. Available from: www.fimpology.com

117. Taylor DD, Akyol S, Gercel-Taylor C. Pregnancy-associated exosomes and their modulation of T cell signaling. J Immunol. 2006; 176(3): 1534-42
118. Keller S, Rupp C, Stoeck A, Runz S, Fogel M, Lugert S, et al. CD24 is a marker of exosomes secreted into urine and amniotic fluid. Kidney Int. 2007; 72(9): 1095-102
119. Asea A, Jean-Pierre C, Kaur P, Rao P, Linhares IM, Skupski D, et al. Heat shock protein-containing exosomes in mid-trimester amniotic fluids. J Reprod Immunol. 2008; 79(1): 12-7
120. Keller S, Ridinger J, Rupp AK, Janssen JW, Altevogt P. Body fluid derived exosomes as a novel template for clinical diagnostics. J Transl Med. 2011; 9: 86
121. Bretz NP, Ridinger J, Rupp AK, Rimbach K, Keller S, Rupp C, et al. Body fluid exosomes promote secretion of inflammatory cytokines in monocytic cells via TLR signaling. J Biol Chem. 2013; 288(51): 36691-702
122. Yanez-Mo M, Siljander PR, Andreu Z, Zavec AB, Borras FE, Buzas EI, et al. Biological properties of extracellular vesicles and their physiological functions. J Extracell Vesicles. 2015; 4: 27066
123. Ng YH, Rome S, Jalabert A, Forterre A, Singh H, Hincks CL, et al. Endometrial exosomes/microvesicles in the uterine microenvironment: a new paradigm for embryo-endometrial cross talk at implantation. PLoS One. 2013; 8(3): e58502
124. Saadeldin IM, Oh HJ, Lee BC. Embryonic-maternal cross-talk via exosomes: potential implications. Stem Cells Cloning. 2015; 8: 103-7
125. Rosenbluth EM, Shelton DN, Wells LM, Sparks AE, Van Voorhis BJ. Human embryos secrete microRNAs into culture media - a potential biomarker for implantation. Fertil Steril. 2014; 101(5): 1493-500
126. Olaya-Abril A, Prados-Rosales R, McConnell MJ, Martin-Pena R, Gonzalez-Reyes JA, Jimenez-Munguia I, et al. Characterization of protective extracellular membrane-derived vesicles produced by Streptococcus pneumoniae. J Proteomics. 2014; 106: 46-60
127. McFall-Ngai MJ. Unseen forces: the influence of bacteria on animal development. Dev Biol. 2002; 242(1): 1-14
128. Tebben J, Tapiolas DM, Motti CA, Abrego D, Negri AP, Blackall LL, et al. Induction of larval metamorphosis of the coral Acropora millepora by tetrabromopyrrole Isolated from a Pseudoalteromonas Bacterium. PLoS One. 2011; 6(4): e19082
129. Huang Y, Callahan S, Hadfield MG. Recruitment in the sea: bacterial genes required for inducing larval settlement in a polychaete worm. Sci Rep. 2012; 2: 228
130. Yin S-d. Evolutionary background entities at the cellular and subcellular levels in bodies of invertebrate animals. The Journal of Theoretical Fimpology. 2014; 2(4): e-20081017-2-4-14. Available from: http://www.fimpology.com
131. Reid G, Brigidi P, Burton JP, Contractor N, Duncan S, Fargier E, et al. Microbes central to human reproduction. Am J Reprod Immunol. 2015; 73(1): 1-11
132. Williams SC. Gnotobiotics. Proc Natl Acad Sci USA. 2014; 111(5): 1661
133. Uribe A, Alam M, Midtvedt T, Smedfors B, Theodorsson E. Endogenous prostaglandins and microflora modulate DNA synthesis and neuroendocrine peptides in the rat gastrointestinal tract. Scand J Gastroenterol. 1997; 32(7): 691-9
134. Sonnenburg JL, Xu J, Leip DD, Chen CH, Westover BP, Weatherford J, et al. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. Science. 2005; 307(5717): 1955-9
135. Rawls JF, Mahowald MA, Ley RE, Gordon JI. Reciprocal gut microbiota transplants from zebrafish and mice to germ-free recipients reveal host habitat selection. Cell. 2006; 127(2): 423-33
136. Hapfelmeier S, Lawson MA, Slack E, et al. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. Science. 2010; 328(5986): 1705-9
137. Goodman AL1, Kallstrom G, Faith JJ, Reyes A, Moore A, Dantas G, et al. Extensive personal human gut microbiota culture collections characterized and manipulated in gnotobiotic mice. Proc Natl Acad Sci USA. 2011; 108(15): 6252-7
138. Lamouse-Smith ES, Tzeng A, Starnbach MN. The intestinal flora is required to support antibody responses to systemic immunization in infant and germ free mice. PLoS One. 2011; 6(11): e27662
139. Willing BP, Van Kessel AG. Intestinal microbiota differentially affect brush border enzyme activity and gene expression in the neonatal gnotobiotic pig. J Anim Physiol Anim Nutr (Berl). 2009; 93(5): 586-95

140. Bouskra D, Brezillon C, Berard M, Werts C, Varona R, Boneca IG, et al. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature. 2008; 456(7221): 507-10
141. Meurens F, Berri M, Siggers RH, Willing BP, Salmon H, Van Kessel AG, et al. Commensal bacteria and expression of two major intestinal chemokines, TECK/CCL25 and MEC/CCL28, and their receptors. PLoS One. 2007; 2(7): e677
142. Haverson K, Rehakova Z, Sinkora J, Sver L, Bailey M. Immune development in jejunal mucosa after colonization with selected commensal gut bacteria: A study in germ-free pigs. Vet Immunol Immunopathol. 2007; 119(3-4): 243-53
143. Loynachan AT, Pettigrew JE, Wiseman BS, Kunkle RA, Harris DL. Evaluation of a diet free of animal protein in germfree swine. Xenotransplantation. 2005; 12(2):149-55
144. Cebra JJ, Periwal SB, Lee G, Lee F, Shroff KE. Development and maintenance of the gut-associated lymphoid tissue (GALT): The roles of enteric bacteria and viruses. Dev Immunol. 1998; 6(1-2):13-8
145. Alexander TJ, Lysons RJ, Elliott LM, Wellstead PD. Techniques for rearing gnotobiotic lambs. Lab Anim. 1973; 7(3): 239-54
146. Alexander TJ, Lysons RJ. Observations on rearing gnotobiotic lambs. Br Vet J. 1971; 127(8): 349-57
147. Lysons RJ, Alexander TJ, Wellstead PD, Hobson PN, Mann SO, Stewart CS. Defined bacterial populations in the rumens of gnotobiotic lambs. J Gen Microbiol. 1976; 94(2): 257-69
148. Trust TJ. Sterility of salmonid roe and practicality of hatching gnotobiotic salmonid fish. Appl Microbiol. 1974; 28(3): 340-1
149. Rawls JF, Samuel BS, Gordon JI. Gnotobiotic zebrafish reveal evolutionarily conserved responses to the gut microbiota. Proc Natl Acad Sci USA. 2004; 101(13): 4596-601
150. Rekecki A, Gunasekara RA, Dierckens K, Laureau S, Boon N, Favoreel H, et al. Bacterial host interaction of GFP-labelled Vibrio anguillarum HI-610 with gnotobiotic sea bass, Dicentrarchus labrax (L.), larvae. J Fish Dis. 2012 Feb 13. doi: 10.1111/j.1365-2761.2011.01342.x.
151. Forberg T, Vestrum RI, Arukwe A, Vadstein O. Bacterial composition and activity determines host gene-expression responses in gnotobiotic Atlantic cod (Gadus morhua) larvae. Vet Microbiol. 2012; 157(3-4): 420-7152. Velagapudi VR, Hezaveh R, Reigstad CS, Gopalacharyulu P, Yetukuri L, Islam S, et al. The gut microbiota modulates host energy and lipid metabolism in mice. J Lipid Res. 2010; 51(5): 1101-12
153. Schwarzer M, Repa A, Daniel C, Schabussova I, Hrncir T, Pot B, et al. Neonatal colonization of mice with Lactobacillus plantarum producing the aeroallergen Bet v 1 biases towards Th1 and T-regulatory responses upon systemic sensitization. Allergy. 2010; 66(3): 368-75
154. Ding S, Chi MM, Scull BP, Rigby R, Schwerbrock NM, Magness S, et al. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. PLoS One. 2010; 5(8). pii: e12191
155. Rabot S, Membrez M, Bruneau A, Gerard P, Harach T, Moser M, et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. FASEB J. 2010; 24(12): 4948-59
156. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med. 2009; 1(6): 6ra14
157. Mahowald MA, Rey FE, Seedorf H, Turnbaugh PJ, Fulton RS, Wollam A, et al. Characterizing a model human gut microbiota composed of members of its two dominant bacterial phyla. Proc Natl Acad Sci USA. 2009; 106(14): 5859-64
158. Pang X, Hua X, Yang Q, Ding D, Che C, Cui L, et al. Inter-species transplantation of gut microbiota from human to pigs. ISME J. 2007; 1(2): 156-62
159. Rawls JF, Buck SS, Gordon JI. Gnotobiotic zebrafish reveal evolutionarily conserved responses to the gut microbiota. Proc Natl Acad Sci USA. 2004; 101(13): 4596-601
160. Wilson KH, Sheagren JN, Freter R, Weatherbee L, Lyerly D. Gnotobiotic models for study of the microbial ecology of Clostridium difficile and Escherichia coli. J Infect Dis. 1986; 153(3): 547-51
161. Pollard M. Applications of germ-free animals to problems in comparative medicine. Adv Vet Sci. 1967; 11: 139-57

162. Pallai R, Hynes RK, Verma B, Nelson LM. Phytohormone production and colonization of canola (Brassica napus L.) roots by Pseudomonas fluorescens 6-8 under gnotobiotic conditions. Can J Microbiol. 2012; 58(2): 170-8
163. Simons M, van der Bij AJ, Brand I, de Weger LA, Wijffelman CA, Lugtenberg BJ. Gnotobiotic system for studying rhizosphere colonization by plant growth-promoting Pseudomonas bacteria. Mol Plant Microbe Interact. 1996; 9(7): 600-7
164. Brummel T, Ching A, Seroude L, Simon AF, Benzer S. Drosophila lifespan enhancement by exogenous bacteria. Proc Natl Acad Sci USA. 2004; 101(35): 12974-9
165. Mayr, Ernst. The growth of biological thought: diversity, evolution, and inheritance. Belknap Press. Pp: 566-570. USA. 1982
166. 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
167. 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
168. Pigliucci M. An extended synthesis for evolutionary biology. Ann N Y Acad Sci. 2009; 1168: 218-28
169. Koonin EV, Wolf YI. Evolution of microbes and viruses: a paradigm shift in evolutionary biology? Front Cell Infect Microbiol. 2012; 2: 119
170. Pigliucci M. Do we need an extended evolutionary synthesis? Evolution. 2007; 61(12): 2743-9
171. Rose MR, Oakley TH. The new biology: beyond the Modern Synthesis. Biol Direct. 2007; 2: 30
172. Carroll SB. Evo-devo and expanding evolutionary synthesis. A genetic theory of morphological evolution. Cell. 2008; 134(1): 25-36
173. 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
174. Koonin EV. Darwinian evolution in the light of genomics. Nucleic Acids Res. 2009; 37(4): 1011-34
175. Boto L. Horizontal gene transfer in evolution: facts and challenges. Proc R Soc B. 2010; 277(1683): 819-27
176. Koonin EV. Does the central dogma still stand? Biol Direct. 2012; 7: 27
177. Salvucci E. Selfishness, warfare, and economics; or integration, cooperation, and biology. Front Cell Infect Microbiol. 2012; 2: 54
178. 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): 1054-6
179. Noble D. Physiology is rocking the foundations of evolutionary biology. Exp Physiol. 2013; 98(8): 1235-43
180. Baluska F, Witzany G. At the dawn of a new revolution in life sciences. World J Biol Chem. 2013; 4(2): 13-5
181. O'Malley MA. What did Darwin say about microbes, and how did microbiology respond? Trends Microbiol. 2009; 17(8): 341-7
182. Yin S-d. Bacteria, viruses, membrane-enclosed microentities and fungi as the environmental evolutionary entities coexisting in non-human mammalian milk. The Journal of Theoretical Fimpology. 2014; 2(2): e-20120719-2-2-12. Available from: http://www.fimpology.com
183. Yin S-d. Evolutionary background entities at the cellular and subcellular levels in bodies of nonhuman vertebrate animals. The Journal of Theoretical Fimpology. 2014; 2(3): e-20081017-2-3-13. Available from: http://www.fimpology.com
184. Johnston-Monje D, Raizada MN. Conservation and diversity of seed associated endophytes in Zea across boundaries of evolution, ethnography and ecology. PLoS ONE 2011; 6(6): e20396
185. Lucero ME, Unc A, Cooke P, Dowd S, Sun S. Endophyte microbiome diversity in micropropagated Atriplex canescens and Atriplex torreyi var griffithsii. PLoS One. 2011; 6(3): e17693
186. Taghavi S, Garafola C, Monchy S, Newman L, Hoffman A, Weyens N, et al. Genome survey and characterization of endophytic bacteria exhibiting a beneficial effect on growth and development of poplar trees. Appl Environ Microbiol. 2009; 75(3): 748-57
187. Zachow C, Tilcher R, Berg G. Sugar beet-associated bacterial and fungal communities show a high indigenous antagonistic potential against plant pathogens. Microb Ecol. 2008; 55(1): 119-29

188. Pirttila AM, Pospiech H, Laukkanen H, Myllyla R, Hohtola A. Seasonal variations in location and population structure of endophytes in buds of Scots pine. Tree Physiol. 2005; 25(3): 289-97
189. Barea JM, Pozo MJ, Azcon R, Azcon-Aguilar C. Microbial co-operation in the rhizosphere. J Exp Bot. 2005; 56(417): 1761-78
190. Ganley RJ, Brunsfeld SJ, Newcombe G. A community of unknown, endophytic fungi in western white pine. Proc Natl Acad Sci USA. 2004; 101(27): 10107-12
191. Reiter B, Pfeifer U, Schwab H, Sessitsch A. Response of endophytic bacterial communities in potato plants to infection with Erwinia carotovora subsp. atroseptica. Appl Environ Microbiol. 2002; 68(5): 2261-8
192. Yang C, Crowley DE, Menge JA. 16S rDNA fingerprinting of rhizosphere bacterial communities associated with healthy and Phytophthora infected avocado roots. FEMS Microbiol Ecol. 2001; 35(2): 129-36193. Hallmann J, Quadt-Hallmann A, Mahaffee WF, Kloepper JW. Bacterial endophytes in agricultural crops. Can J Microbiol. 1997; 43(10): 895-914
194. Tervet IW, Hollis JP. Bacteria in the storage organs of healthy plants. Phytopathology. 1948; 38(12): 960-7
195. Sanford GB. The occurrence of bacteria in normal potato plants and legumes. Sci Agric. 1948; 28: 21-5
196. Araujo WL, Maccheroni Jr.W, Aguilar-Vildoso CI, Barroso PAV, Saridakis HO, Azevedo JL. Variability and interactions between endophytic bacteria and fungi isolated from leaf tissues of citrus rootstocks. Can J Microbiol. 2001; 47(3): 229-36
197. Lodewyckx C, Vangronsveld J, Porteous F, Moore ER, Taghavi S, Mezgeay M, et al. Endophytic bacteria and their potential applications. Crit Rev Plant Sci. 2002; 21(6): 583-606
198. Arnold AE, Mejía LC, Kyllo D, Rojas EI, Maynard Z, Robbins N, et al., Fungal endophytes limit pathogen damage in a tropical tree. Proc Natl Acad Sci USA. 2003; 100(26):15649-54
199. Rosenblueth M, Martinez Romero E. Rhizobium etli maize populations and their competitiveness for root colonization. Arch Microbiol. 2004; 181(5): 337-44
200. Cankar K, Kraigher H, Ravnikar M, Rupnik M. Bacterial endophytes from seeds of Norway spruce (Picea abies L. Karst). FEMS Microbiol Lett. 2005; 244 (2): 341-5
201. Reiter B, Sessitsch A. Bacterial endophytes of the wildflower Crocus albiflorus analyzed by characterization of isolates and by a cultivation-independent approach. Can J Microbiol. 2006: 52(2): 140-9
202. Castillo UF, Browne L, Strobel G, Hess WM, Ezra S, Pacheco G, et al. Biologically active endophytic Streptomycetes from Nothofagus spp. and other plants in Patagonia. Microb Ecol. 2007; 53(1): 12-9
203. Dutta D, Gachhui R. Nitrogen-fixing and cellulose-producing Gluconacetobacter kombuchae sp. nov., isolated from Kombucha tea. Int J Syst Evol Microbiol. 2007; 57(Pt 2): 353 -7
204. Kaga H, Mano H, Tanaka F, Watanabe A, Kaneko S, Morisaki H. Rice seeds as sources of endophytic bacteria. Microbes and Environments. 2009; 24(2):154-62
205. Compant S, Clement C, Sessitsch A. Plant growth-promoting bacteria in the rhizo- and endosphere of plants: Their role, colonization, mechanisms involved and prospects for utilization. Soil Biology and Biochemistry. 2010; 42(5): 669-78
206. Rouws LF, Meneses CH, Guedes HV, Vidal MS, Baldani JI, Schwab S. Monitoring the colonization of sugarcane and rice plants by the endophytic diazotrophic bacterium Gluconacetobacter diazotrophicus marked with gfp and gusA reporter genes. Lett Appl Microbiol. 2010; 51(3): 325-30
207. Mulvey HE, Chang A, Adler J, Del Tatto M, Perez K, Quesenberry PJ, et al. Extracellular vesicle-mediated phenotype switching in malignant and non-malignant colon cells. BMC Cancer. 2015; 15: 571
208. Dustin ML. What counts in the immunological synapse? Mol Cell. 2014; 54(2): 255-62
209. Harding CV, Heuser JE, Stahl PD. Exosomes: Looking back three decades and into the future. J Cell Biol. 2013; 200(4): 367-71
210. Gyorgy B, Szabo TG, Pasztoi M, Pal Z, Misjak P, Aradi B, et al. Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles. Cell Mol Life Sci. 2011; 68(16): 2667-88
211. Hristov M, Erl W, Linder S, Weber PC. Apoptotic bodies from endothelial cells enhance the number and initiate the differentiation of human endothelial progenitor cells in vitro. Blood. 2004; 104(9): 2761-6
212. Bergsmedh A, Szeles A, Henriksson M, Bratt A, Folkman MJ, Spetz AL, et al. Horizontal transfer of oncogenes by uptake of apoptotic bodies. Proc Natl Acad Sci USA. 2001; 98(11): 6407-11

213. Schooling SR, Beveridge TJ. Membrane vesicles: an overlooked component of the matrices of biofilms. J Bacteriol. 2006; 188(16): 5945-57
214. Klein I, von Rad U, Durner J. Homoserine lactones: do plants really listen to bacterial talk? Plant Signal Behav. 2009; 4(1): 50-1
215. Liu F, Bian Z, Jia Z, Zhao Q, Song S. The GCR1 and GPA1 participate in promotion of Arabidopsis primary root elongation induced by N-acyl-homoserine lactones, the bacterial quorum-sensing signals. Mol Plant Microbe Interact. 2012; 25(5): 677-83
216. Singh RP, Baghel RS, Reddy CR, Jha B. Effect of quorum sensing signals produced by seaweed-associated bacteria on carpospore liberation from Gracilaria dura. Front Plant Sci. 2015; 6: 117
217. http://www.answersingenesis.org/creation/v14/i1/pasteur.asp (Accessed 2008-7-31)