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Understanding the complexity of the immune system during pregnancy

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Abstract

Progress in our understanding of the role of the maternal immune system during healthy pregnancy will help us better understand the role of the immune system in adverse pregnancy outcomes. In this review we discuss our present understanding of the "immunity of pregnancy" in the context of the response to cervical and placental infections and how these responses affect both the mother and the fetus. We discuss novel and challenging concepts that help explain the immunological aspects of pregnancy and how the mother and fetus respond to infection.

Keywords

pregnancy; trophoblast; immune regulation; macrophages

Introduction

The field of Reproductive Immunology has experienced vast progress over the last 60 years since Peter Medawar's classic essay proposing the potential mechanisms for tolerance of the semi-allogeneic fetus in placental mammals. In our original review[1], this progress was defined and the role of immune cells and cytokines during pregnancy were described in the context of historic paradigms and our present understanding. For example, the model of "immune suppression" during pregnancy was long accepted, but now we recognize that while the presence of the placenta changes and adapts the immune system to pregnancy, it is not suppressed and pregnant women are very much capable of having robust immune responses when mother and/or fetus are at risk. Furthermore, this idea was accompanied by the belief that pregnancy was "Th2 dominant" as yet another means of quenching the immune retaliation against the developing fetus. Indeed, cytokines such as IL-10 and TGF beta are present during the second and part of the third trimester, but a large part of the first trimester and approaching the end of pregnancy are very much pro-inflammatory[2, 3]. This progress in our understanding has helped us better understand the role of the immune system in healthy pregnancies and has created an opportunity to discover the role of the immune system in adverse pregnancy outcomes. In this update we will review our present

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understanding of the “immunity of pregnancy” in the context of the response to cervical and placental infections, and how these responses can affect both the mother and the fetus.

The immunology of pregnancy: old and new paradigms

Maternal mortality and preterm birth are rising problems not only in developing countries, but also in the US[4]. Although there is little question that infection plays a major role on the etiology of preterm birth and maternal mortality, various treatments to reduce the preterm birth rate, usually with antibiotics, have given disappointing or mixed results[5, 6]. This is the result of our poor understanding of the immunologic status of pregnancy and the contribution of the placental-fetal unit to the immune response[7]. The old concept that pregnancy is associated with immune suppression has created a myth of pregnancy as a state of immunological weakness and therefore of increased susceptibility to infectious diseases[8]. Today, there is increasing evidence suggesting that this concept is incorrect and the immune system during pregnancy is functional and highly active[1]. We suggest that, while there may be an active mechanism preventing a maternal immune response against paternal antigens, the trophoblast and the maternal immune system have established a cooperative status. Furthermore, we propose placental-immune cell interactions create a pregnancy-supportive immune environment while still being fully capable of defending the mother and fetus against pathogens[2, 9–11] (Fig. 1).

The placenta is tightly regulated immune organ

Pregnant women represent an immunologically unique population; the presence of the fetus and placenta alters maternal immunity and physiology to sustain pregnancy, while in some pathological conditions, the placental response can be detrimental to mother and child. External factors such the decidual immune cells and intrinsic regulators such as TLRs and IFNs play roles maintaining placental function throughout gestation[12]. The importance of these mechanisms for normal pregnancy is illustrated by the resulting pathologies when they are lost or dysregulated.

Within the decidua there are unique subsets of immune cell populations that actively contribute to the tolerance and function of the placenta. The largest population of immune cells found in the decidua are the uterine natural killer (uNK) cells[13]. It is becoming increasingly clear that this cell type plays an important role in species with invasive placentation. In humans these cells represent approximately 70% of the total leukocyte population and are characterized by the surface markers CD56bright CD16−[14]. In normal pregnant women there is evidence that these cells are critical for the development of the placenta by regulating spiral artery formation and controling the invasion of trophoblast into the endometrium, probably by secreting pregnancy-promoting cytokines[14]. Interestingly, these cells are highly cytotoxic when activated in other tissues and the circulation; therefore, the factors produced at the implantation site are critical to maintaining the pro-pregnancy phenotype of these cells. One of such factors involved in promoting pregnancy is IL-10[15, 16]. Although the mechanism is not completely defined, there is evidence that it is a major regulator of uNK cytotoxic activity. In mice lacking IL-10, very low doses of LPS induce an inflammatory response and uNK activation, resulting in fetal demise[15]. Interestingly, in

some cases of unexplained spontaneous abortions it was found that there were lower concentrations of this cytokine[17, 18], further supporting the possibility that the IL-10-uNK cell balance controls excessive inflammation and promotes healthy pregnancies.

Macrophages are the predominant subset of human leukocytes antigen presenting cells (APC) in the human decidua and comprise about 20–25% of the total decidua leukocytes[19]. In general, decidua macrophages present a phenotype related to tissue renewal and repair, loosely termed M2[20], characterized by enhanced expression of scavenger receptors, mannose receptors, secretion of IL-1 receptor antagonist and reduction of IL-12 expression[21]. Accumulative evidence suggests macrophages are critical for the normal development of pregnancy. They are present in the uterus and the ovaries and are implicated in a wide range of gestational processes including implantation, ovarian function, placental development and cervical ripening[2223, 24]. For example, the loss of these cells results in infertility due to failure to implant and loss of steroidogenesis within the corpus luteum[22]. Furthermore, increases in macrophage numbers within the decidua are associated with pregnancy complications such as preterm labor[25].

Recently we demonstrated that trophoblast secreted factors can induce peripheral blood monocytes differentiation into macrophages with a unique phenotype that resemble those found in pregnant decidual samples[26]. Similarly, placental secreted factors enhance the population of iTreg[27]. All these data strongly support the notion that the placenta plays an active role regulating the differentiation and function of maternal immune cells in order to support the pregnancy and protect the fetus.

While these data show the placenta regulates the differentiation and function of maternal immune cells it is not clear what factors intrinsic to the placenta assure appropriate communication with the maternal environment. We, and others, have demonstrated that the trophoblast, just like an innate immune cell, expresses Pattern Recognition Receptors (PRRs) that function as “sensors” of the surrounding environment[28–31]. Through these sensors, the trophoblast can recognize the presence of bacteria, viruses, dying cells and damaged tissue. Upon recognition, the trophoblast will often secrete a specific set of cytokines that, in turn, will act upon the immune cells within the decidua (*i.e.*, macrophages, T regulatory cells, NK cells) “educating” them to work together in support of the growing fetus[32].

Another potential intrinsic regulator of placental function is Type I interferon. Interferons are potent anti-viral proteins that are targeted by a number of viruses, such as influenza and members of the herpes virus family, as a mechanism to evade immune recognition and cellular targeting[33]. Interestingly, IFN also has important immunomodulatory functions: After binding its receptor, a signaling cascade is activated resulting in the activation of not only antiviral proteins but inhibitory proteins such as SOCS1 and 3[34, 35]. These act at the level of signal transduction of multiple inflammatory pathways and result in suppression of the immune response[36–38]. This function is demonstrated quite eloquently in studies with IFN receptor knockout mice (IFNAR-/-) demonstrating that without functional IFN animals experience severe inflammatory responses to microbial challenges compared to wild-type controls[35]. Interestingly, placental extracts containing high concentrations of “trophoblast

interferon" were used historically to treat inflammation, while purified IFN is currently used to treat patients with MS[39, 40]. We propose that placenta IFN may play an important role as modulator of the maternal immune system. A further understanding of both intrinsic and extrinsic regulation of the placenta will help us determine how placental function is affected by infection and/or inflammation.

Bacterial Infections and Pregnancy

Intrauterine infection caused by bacteria and the consequent production of pro-inflammatory cytokines plays a central role in the mechanism of preterm labor. Most microbes reach the uterus by ascending the female reproductive tract when there is inadequate protection by the cervix and mucosa of the reproductive tract[41]. Another route of infection is via maternal circulation and indeed it has been found that bacteria such as *Fusobacterium nucleatum*, a microbe involved in peridontal infections[42], can be detected in the amnion, and can lead to inflammation and pregnancy complications. Once pathogenic bacteria reach the decidua, a proinflammatory response is induced via activation of pattern recognition receptors and cytokines can then negatively affect pregnancy outcome (by inducing preterm birth) and/or disrupt fetal development. For example, the proinflammatory cytokine, IL-1, has been associated with women who experience preterm labor; it is not only expressed by the human decidua in response to bacterial endotoxin, but it induces prostaglandin production from the decidua and can stimulate myometrial contractions[43]. Another proinflammatory cytokine, TNF-alpha[44, 45], has also been found to be elevated in the amnion of preterm women, and it is highly upregulated by bacteria and their products in women and animal models[43]. Indeed, TNF-alpha may also contribute to pregnancy complications by inducing prostaglandin expression and myometrial contractions, but may also cause premature cervical ripening via upregulation of matrix metalloproteinases[46].

Interestingly, for years the uterus and amniotic cavity were considered sterile, however this concept has been challenged by new findings using fluorescent *in situ* hybridization with DNA probes specific for conserved regions of bacterial DNA that have detected bacteria in the fetal membranes of up to 70% of women undergoing elective cesarean sections at term[47–49]. Furthermore, extensive sequencing studies have identified a "placental microbiome" present in normal healthy pregnancies[50]. These findings suggest that presence of bacteria alone are not pathological and a second "hit" is required to affect this normal interaction. Indeed, we proposed that when a woman is infected with another pathogen, such as a virus, the placenta becomes hypersensitive to bacterial infection, and thus together, induce an inflammatory response, which results in preterm birth[1].

Preterm-Labor as a Polymicrobial Disease

There is growing compelling evidence that many infections of humans and animals are caused by more than one microorganism[51, 52]. Although the mixed microbial nature of these diseases has been recognized since the early 1920s[53], only more recently we have begun to understand the molecular and cellular mechanisms involved in this process. Polymicrobial diseases can be caused by the synergistic or sequential action of infections agents from either the same or different kingdoms, genera, species, strains or by different phenotypic

variant of a single specie[52]. To better understand the potential implications of multi-microbial infections during pregnancy we developed an animal model of polymicrobial disease that leads to preterm birth[54, 55]. The model consists of a viral infection of the placenta and decidua leading to increased sensitivity to bacterial products, which then triggers a pro-inflammatory "cytokine storm" and preterm birth[54, 55]. We use the murine gammaherpesvirus 68 (Murid herpesvirus 4 (NC_001826.2); MHV68), a gammaherpesvirus of rodents that shares significant genomic co-linearity with two human pathogens, Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV)[56]. As with these two viruses, the effect of MHV-68 in pregnancy has long been unknown. Maternal infection with MHV-68 had no effect on pregnancy outcome, including litter size, weight or gestational age at delivery[54, 55], however, it had a significant effect on the response to microbial products such as LPS. Although, high doses of LPS administered to pregnant mice have been shown to trigger pre-term birth; low doses have no detrimental or a mild effect on pregnancy outcome[17, 57]. When we infect pregnant C57BL/6 mice with MHV68 on day E8.5 followed by LPS injection (20ug/kg) on day E15.5 we observed preterm delivery in 100% of the mice in less than 24 hours. Similar dose of LPS in control mice (did not receive virus) had a mild effect on pregnancy outcome. The preterm birth observed with the combination of virus and LPS was characterized by a cytokine storm consisting of high levels of IL-6, IL-8, IL-1β; pro-inflammatory cytokines associated with parturition. Based on these findings, we proposed a double hit hypothesis where a viral infection at the implantation site predisposes the placenta and decidua (maternal immune cells) to bacterial products leading to preterm labor.

Viral infections and pregnancy

Limited epidemiological studies have demonstrated an association between viral infections and preterm birth and/or fetal congenital anomalies[58], however it is well known that pregnant women are more severely affected by infections with some viruses including influenza A virus, hepatitis E virus (HEV) and herpes simplex virus (HSV)[59], compared to non-pregnant counterparts. In order to elucidate the effect of viral infection during pregnancy we developed an animal model of sub-clinical viral infection[54, 60]. We demonstrated that while placental viral infection, alone, did not result in preterm birth, it did cause developmental abnormalities in the fetal brain and lungs[54, 55]. Interestingly, the murine herpesvirus used in this model is from a family of viruses that are the most common cause of viral-related perinatal neurologic injury in the USA[61]. Pathology in these cases generally occurred due to a primary infection of the mother during the first trimester or infection of the infant during delivery. However even in the absence of placental transmission, the fetus could be adversely affected by the maternal response to the infection[62].

A viral infection in the placenta that triggers a mild inflammatory response will not terminate the pregnancy but might be able to activate the immune system, not only from the mother but from the fetus as well. This activation may have several consequences: First, it may promote an inflammatory response in the fetus, even though there is no viral transmission. This condition is termed Fetal Inflammatory Response Syndrome (FIRS) and is characterized by an absence of cultivable microorganisms, but a placental infection with

very high concentrations of inflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF-α[63–65]. These cytokines have been shown to affect the CNS and the circulatory system[65, 66], and can cause fetal morphologic abnormalities in animal models, including ventriculomegaly and hemorrhage. Beyond morphological effects on the fetal brain, the presence of FIRS has been associated with increased risk for diagnosis of autism, schizophrenia, neurosensorial deficits and psychosis later in life[67–69]. The second consequence of placental viral infection is the potential for sensitization to bacterial co-infection.

Infection of the lower reproductive tract during pregnancy

As we indicated above, bacterial infections are thought to gain access to gestational tissues through one of three major routes: by ascending into the uterus from the lower tract; by descending into the uterus from the peritoneal cavity; or via the maternal circulation[70]. However, growing evidence suggests bacteria are a normal component of the pregnant and non-pregnant uterus[60]. Indeed, we have shown that in mice, E-coli delivered in the vagina is able to reach the upper RT in 24 hours and is detectable up to two weeks[60]. That is not the case in the pregnant FRT, where E-coli is mainly found at the vagina and it does not reach the uterus, placenta or fetus. We posit that contrary to the non-pregnant FRT, where bacteria is a normal component and is constantly migrating through the upper RT; the pregnant uterus is less receptive to bacteria coming from the vagina by enhancing the control at the level of the cervix.

There is growing interest to better understand the normal flora of the female reproductive tract (FRT), the mechanisms controlling pathogenic bacteria and how those populations relate to intrauterine infection and preterm labor. Bacterial infections that ascend from the lower FRT are the most common route of uterine infection, and it is not known why some women suffer such infections that threaten pregnancies and fetal survival. Consequently, there is a need to determine the factors that predispose some patients to an adverse outcome following exposure to bacterial.

In a healthy pregnancy, the uterus and growing fetus are protected from ascending infection by the cervix[71, 7273]. The cervix has a unique role in the FRT in that it actively controls and limits microbial access by the production of mucus, inflammatory cytokines and anti-microbial peptides (AMP)[7473]. In non-pregnant women, the cervical mucus is a viscous fluid in the endocervical canal; however after conception the endocervical canal develops a structure called the cervical mucus plug, which is an anatomical and immunological barrier against ascending infection[75]. Indeed, analysis of the composition and antimicrobial activity of cervical mucus plug revealed the presence of AMPs with potent anti-microbial activity[76]. Also expressed in the cervical epithelia are the pattern recognition receptors such as Toll like receptors (TLRs) capable of sensing the presence of microorganisms and eliciting an innate immune response characterized by the production of cytokines and AMPs[12, 7778, 79]. Collectively, the cervix plays a key role in the protection against ascending intraamniotic infection. If the mucus plug is expelled or cervical length is short, the risk of ascending uterine infection increases (Fig 2).

Viral infection of the lower reproductive tract

Viral infections of the lower genital tract are relatively common (e.g. papilloma virus, herpes virus, HIV, etc.), yet there is a paucity of knowledge about the effect of such localized infections on mucosal immunity of the lower genital tract during pregnancy[80]. In humans, the most common viral infection of the cervix is human papillomavirus (HPV), and a handful of studies have shown that HPV infection of the placenta is associated with adverse pregnancy outcomes[81, 82]. Even more recently, HPV infection of *the cervix* was related to placental abnormalities and preterm birth[83]. Furthermore, Caserta and associates (2007) found that two beta herpesviruses HHV-6 and HHV-7, were detectable in cervix samples from pregnant women, although delivery status was not reported[84], while CMV detection in the vagina was shown to predispose women to adverse pregnancy outcomes[85].

Using a mouse model of herpes virus infection (MHV68) we found important differences between the pregnant and not pregnant cervix in terms of sensitivity to infection[60]. Interestingly, we found that only the pregnant cervix was infected by MHV68. This susceptibility was associated with molecular changes in the cervix brought on by the sex hormones estrogen and progesterone. Furthermore, MHV68 infection of the cervix decreased TLR and antimicrobial Defensin mRNA expression while significantly reducing cervical capacity to control the movement of bacteria into the upper reproductive tract. These data suggest that viral infection can affect the capacity of both the lower and upper tract to regulate inflammation. Furthermore, although the virus typically does not reach the fetus, its presence can increase inflammation and affect fetal health and development.

How does infection affect the developing fetus and future offspring?

“The stage must be set before the play begins” is a perfect analogy for the relationship between the placenta and the developing fetus. A “genetically healthy fetus” will only become healthy offspring with a well-developed placenta that is provided with the proper nutrients and devoid of environmental challenges including, but certainly not limited to, infection and inflammation. The influence of the *in utero* environment on the developing fetus has been a topic of study for several decades. The notion of developmental plasticity, or the ability of environmental factors to influence fetal development, was first realized by David Barker and his associates in the 1980s[86]. They performed pivotal epidemiological studies on a population of women in England and discovered that there was a correlation between low birth weight and coronary heart disease later in life[86]. These observations brought attention to the vulnerability of the fetus in utero, and have since led to multitudes of epidemiological studies, and more recently several clinical and animal trials, all seeking to understand this phenomenon.

Epidemiological studies first showed a correlation between infection during pregnancy, either bacterial or viral in nature, and neurodevelopmental disorders in offspring. Maternal inflammation has been linked to development of schizophrenia, autism, psychosis[61, 66] and related disorders in adult offspring. Furthermore, it was proposed that infection led to an induction of pro-inflammatory cytokines, disrupting or altering brain development in the fetus[87]. Since that time, prospective cohort studies have further defined the role of maternal

cytokines in development of the fetal brain and central nervous system. For example, Brown and colleagues demonstrated that schizophrenia was associated with elevated concentrations of maternal IL-8 and serological evidence of influenza during pregnancy[88]. Buka and associates (2001) showed that maternal TNF-alpha concentrations during late pregnancy were correlated with development of psychosis in adult offspring[61]. Furthermore, TNF-alpha was elevated in the cerebrospinal fluid of autistic children[89]. In addition, neuroinflammation, as determined by increased concentrations of MCP-1 in the brain and CSF, and immunocytochemical evidence of microglia activation, were discovered in the brain of autism patients of all ages[90].

Numerous animal studies have been performed by several groups to better understand the mechanism of maternal infection resulting in aberrant neuronal development and psychological abnormalities in offspring. Animal models, including rodents, rabbits and sheep have been injected with TLR ligands to determine if the inflammation downstream of TLR signaling had effects on development and offspring behavior. Both LPS (ligand for TLR4) and Poly (I:C) (ligand for TLR3) treatment during pregnancy lead to defects in prepulse inhibition (PPI), social interactions and learning in offspring[66]. Upon further evaluation, these animals exhibited brain inflammation and altered microglia, suggesting that TLRs induced a response that caused deviations in the brains of animals that develop behavioral problems later in life. Similar observations were made when animals were infected with influenza, and indeed, poly (I:C) or virus treated animals had very similar cerebellar pathology as found in human cases of autism[66, 67]. Furthermore, using the rodent model of maternal immune activation, a very elegant study described, at least in part, the mechanism of virus-induced IL-6 effects on brain development[91]. In that study, it was shown that a single injection of IL-6 had very similar effects on PPI and latent inhibition in offspring compared to poly (I:C) injection, and moreover, neutralizing IL-6 antibody injections in conjunction with poly (I:C) prevented behavioral defects and the aberrant gene expression in the brains of offspring. Our own studies using MHV-68 infection showed that infection of the placenta and subsequent inflammation has detrimental effects on fetal brain anatomy characterized by changes on the vascularity leading to hydrocephalus, defined as an increase in the subaracnoid space, in the brains of all fetuses from infected mothers[54]. Studies like these are important for improving our understanding of how inflammation leads to debilitating neurological disorders in humans.

Conclusion

There is growing evidence that the type of response initiated by the placenta might determine the immunologic response of the mother and consequently, the pregnancy outcome. In the past, we have considered the placenta and decidua to be non-active immunological organs, depending only on the action of the maternal immune system. It is now clear the placenta and decidua represent important immune modulators that affect the global response of the mother to microbial infections (Fig. 3). Understanding the cellular and molecular aspects of this interaction is relevant for making decisions associated with treatment and prevention during infections and pandemics.

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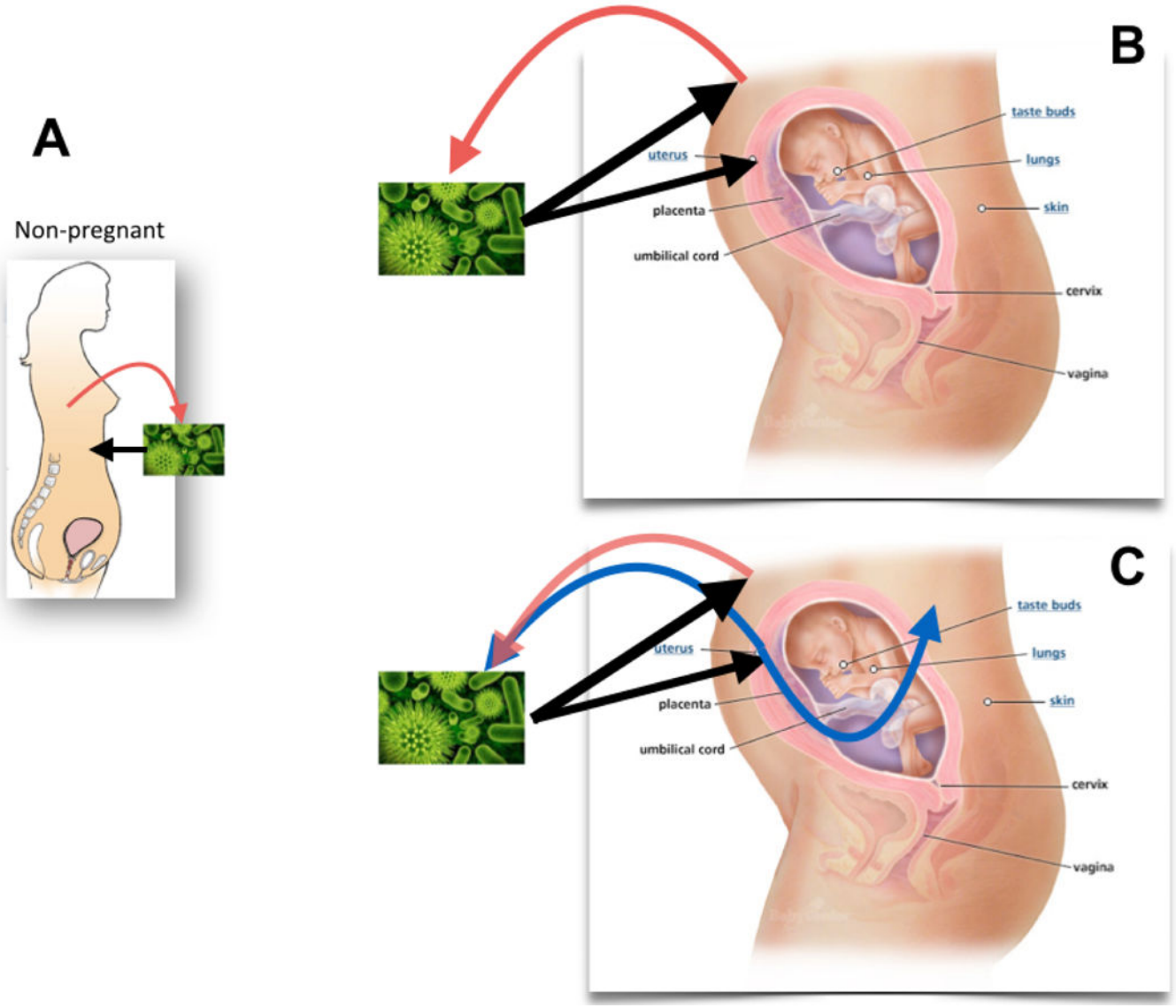

Figure 1.

The placenta as an immune regulatory organ. Contrary to non pregnant women (A); the presence of the placenta during pregnancy modifies the immunologic response of the mother to microorganisms. The old model (B) conceives the maternal immune system as the major player in response to the fetus and microorganisms (red arrow). Fetal responses (fetus and placenta) are considered limited. The new integrational model takes in consideration the fetal-placental immune response and the maternal immune system as integrated.

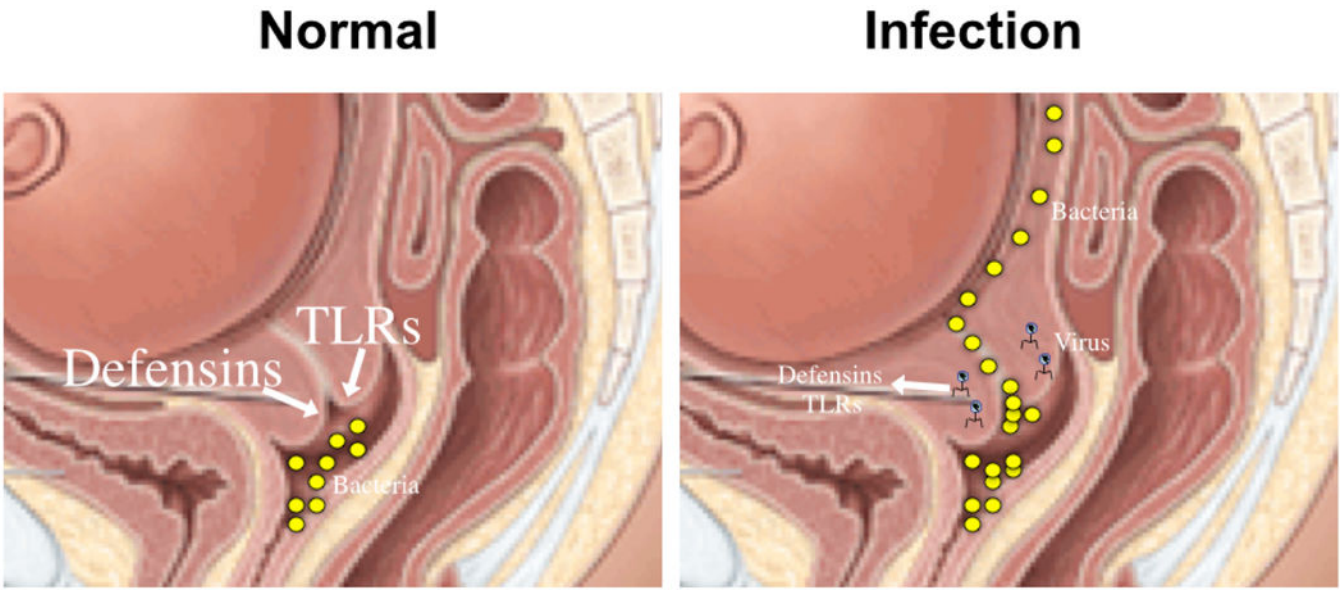

Figure 2.

Role of the cervix controlling bacterial migration to the upper reproductive tract. A viral infection of the cervix alters the expression and function of TLRs and Defensins, therefore altering the protective role of the cervix.

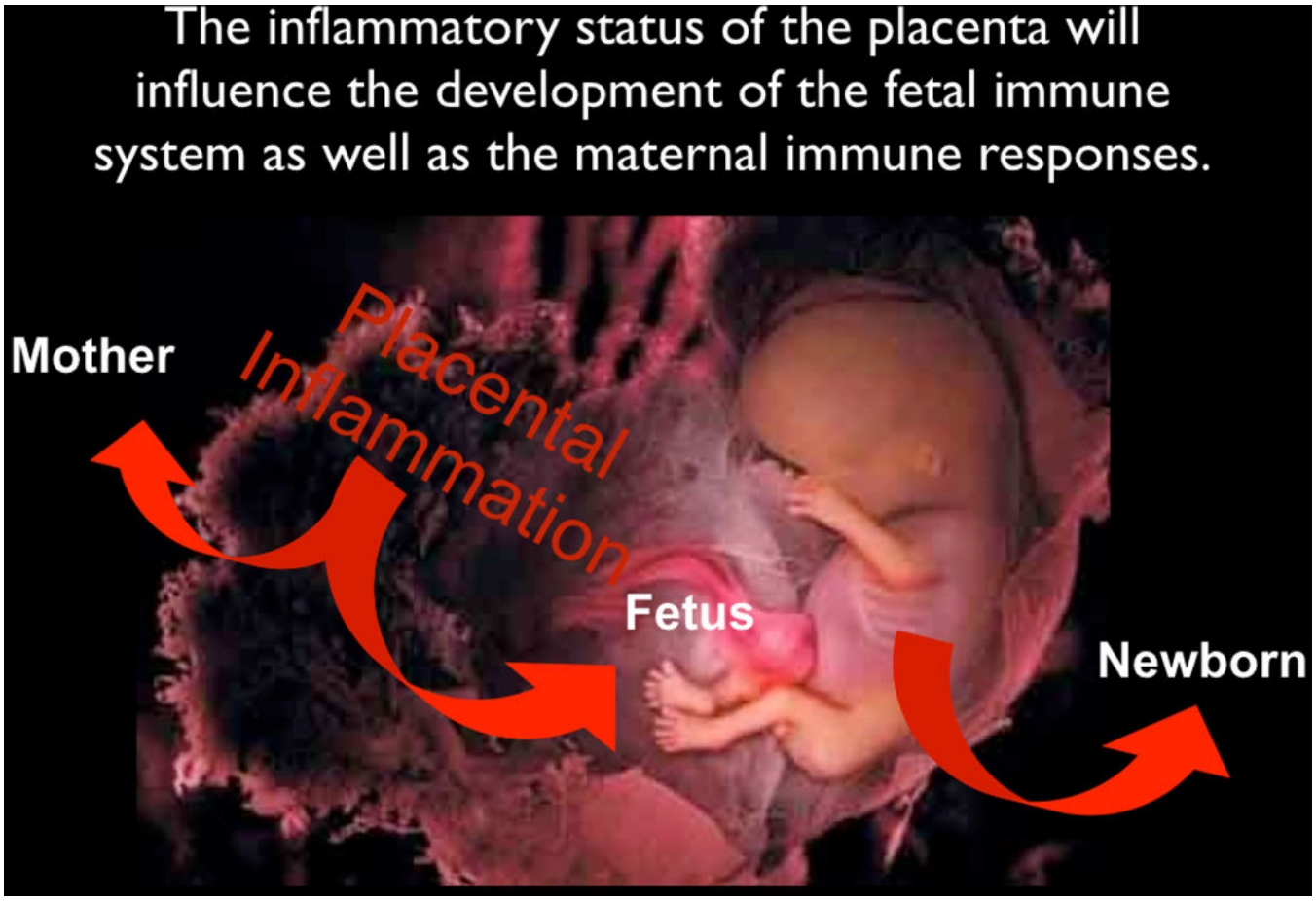

Figure 3.

Role of the placenta as a modulator of fetal and maternal responses. Inflammation at the placenta has a bi-directional effect. Activates the maternal immune system as well as the fetus by creating an inflammatory environment. The inflammatory response may also influence the development of the fetal immune system with important consequences during post-natal age.