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Editorial

Feto-Marenal Interactions – Undisputable Evidence for the Concept of Neuroimmune Biology

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Neuroimmune Biology (NIB) was conceived in 2000. At that time it was predicted that neuroimmune mechanisms play a major regulatory role in Biology. Hence the term, Neuroimmune Biology was introduced [1]. Now it is apparent that in feto-maternal interactions, which represent Reproduction Biology, the Neuroimmune Supersystem plays a fundamental role. Reproduction Biology is a perfect example for how Neuroimmune mechanisms regulate bodily functions.

With the development of transplantation immunology it has been realized that the fetus is a semiallogeneic allograft as the father's transplantation antigens are expressed in fetal tissues. According to the rules of transplantation the semiallogeneic fetus should have been rejected but fetuses survive as a rule. Pregnancy was an exception to Transplantation Immunology. Medawar predicted that neuroendocrine and immune regulatory mechanisms should be involved in the protection of the fetus [2].

First immunological tolerance has been tested as a survival mechanism for the fetus, but it could not be proven. Next the Th1-Th2 switch was examined as the possible mechanism but it was not the case either. Finally it became gradually clear that the immune system plays a very active role during gestation. It helps actively growth and development of the fetus with growth factors, cytokines and possible even classical hormones [3]. The immune system is capable of producing cytokines, chemokines and also classical hormones, which is delivered into target areas, such as the fetus [4].

Some years ago the noted Canadian scientist, Tom Wegman declared that "*the fetus is bathed in cytokines*". However, the amniotic fluid contains the most prolactin in the body and is also very rich in placental lactogenic hormones [5] and steroid hormones and other mediators [6]. Clearly the amniotic fluid contains numerous important biological regulators. So, the above statement should sound like this: "*the fetus is bathed in hormones, cytokines, chemokines and neuropeptides etc.*", pretty well everything what is significant in Biological regulation. These mediators act on the skin and also internally as the fetus consumes amniotic fluid continuously.

Theoretically animal growth is regulated by hormones that provide the animal tissues with *competence for growth*. Such hormones are growth hormone, prolactin and placental lactogens, also type I (gamma c) cytokines. The next stage is *progression.* Insulin like growth factor (IGF-I) and some cytokines serve as progression factors [7]. Numerous other mediators regulate differentiation and function.

A likely source of most of these mediators is the placenta as it transforms into an endocrine organ with the aim of protecting the fetus against maternal influences and interests [5, 6].

The mothers adaptive immune system recognizes the fetus and produces antibodies. The immune system must be activated in order for successful pregnancy to

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take place. Anti-sperm antibodies are present in more than 10% of women with unexplained infertility. Seminal plasma contains paternal antigens, transforming growth factor – beta and induces tolerance in females to paternal antigens of the fetus [8].

Natural killer (NK) cells were required for successful pregnancy. NK cells are involved in the transformation of the local vessels. NK cells are activated by Il-12, IL-18, NK tripod, and by *tumour necrosis factor-like*, *weak inducer of apoptosis* (TWEAK) in mice and human [3]. Uterine natural killer (uNK) cells will ultimately represent up to 50%–70% of the cellular content of the basal decidual stroma. By producing the chemokines CXCL8 and CXCL10, decidual NK cells regulate trophoblast invasion [8]. These cells regulate local angiogenesis, control the development of a special functional arterial system and the spiral arterioles. During early human pregnancy extravillous cytotrophoblasts invade these vessels and replace the endothelial cells [9]. Decidual NK cells secrete angiogenic factors [10] and induce vascular growth in the decidua [11].

Decidual NK cells fulfill dual tasks. During normal conditions they contribute to creating a favourable environment for placentation, but at the same time they are equipped with cytotoxic potential to fight intrauterine infections [8]. NK cell deficient mice [12] have an abnormally small placenta and low birth weight fetuses [13]. uNK cells of women predisposed to miscarriage may have a higher activating potential and both inhibitory and activating killer immune receptors (KIRs) on uNK cells are important for the maintenance of pregnancy [14].

Progesterone (P) plays a role in uterine homing of NK cells by promoting NK cell interactions with the endothelium [14], and by progesterone-induced specific endometrial production of chemokines [15, 16]. Progesterone is one of the factors to control trophoblast invasiveness either directly [20] or via progesterone induced blocking factor (PIBF) – by reducing the secretion of MMP9 from trophoblasts. High levels of glucocorticoids inhibit pituitary luteinizing hormone and ovarian estrogen and progesterone secretion [8].

In the peri-implantation period both Th1 and Th2 type cytokines are expressed locally in a stage-specific manner [17] and certain Th1 cytokines (e.g., LIF, IL-11 and IFN-γ) seem to be crucial for implantation of the mouse blastocyst [18]. A mild local inflammatory reaction is required for loosening the endometrial tissue, thus promoting implantation, however, in later stages of pregnancy the dominance of Th1 cytokines seems to be detrimental (8).

Recently regulatory T cells (Tregs) emerged, which recognize signals of the embryo. Newly emerged factors are follicular fluid granulocyte-macrophage colony stimulating factor (FF-GCSF) and sHLA-G [3].

Several factors including hormones, growth factors, cytokines, chemokines, adhesion molecules, extracellular matrix components, and matrix-degrading enzymes are involved in creating the appropriate environment for implantation. Progesterone regulated genes are crucial for the establishment and maintenance of pregnancy. The initial implantation steps are characterised by rather extensive use of inflammatory molecules. Complement related pathways are involved in the regulation of angiogenesis as well as in expression of adhesion molecules, matrix metalloproteinase (MMP) and serine proteases. The invading trophoblast anchors the embryo and also establishes an immunological interface between the mother and the fetus. The placenta formed from the decidua and outer layers of the embryo, connects the developing fetus to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's blood supply [8].

The long pentraxin 3 (PTX3) and the decoy receptor for inflammatory chemokines D6, are involved in regulating inflammation at the maternal-foetal interface [19].

In extreme cases of infection (e.g *Brucellosis*) when the fetus can no longer be protected, it is aborted in order to control the infectious agent. Here the adaptive immune system is also involved [21]. Regulating, protecting the fetus, or, if things are terribly wrong, sacrifice the fetus for the prospect of clearing the infection and saving the mother and maintain the possibility of recovery and to continue reproduction.

Survival of the *corpus luteum*, which makes conception possible, is regulated by prolactin (PRL) activated phgocytic cells, which is an innate immune (INIM) mechanism [22]. As a rule, *the fetus relies on innate immunity* for development and protection [23].

The placenta is a self regulating unit, which produces various hormone, cytokines chemokines, virtually all the biological regulators that the fetus will need. By this action the placenta functions as a unit independent of the mother's neurendocrine system, and defends the interest of the fetus against the interest of the mother [5, 6].

It seems that the immune cells, that come from the maternal immune system, such as (u) NK cells, adapt to their new function and work to nourish and defend the fetus and not the mother. During fetal life the

adaptive immune system is immature, so *the fetus must rely on innate immune mechanisms* for nourishment and for defense [23]. The invasion of maternal cytotoxic cells into the embryo is normally prevented by the trophoblast [24], which could be overruled by severe injury or infectious disease, causing abortion [25].

Reproduction involves the generation of offspring by animals and man. The entire complexity of this process depends on an intact and fully functional immune system. Thus Neroimmune Supersystem (NISS) serves as a fundamental regulator of reproduction. The Central Nervous System (CNS) and hormones were known for a long time to regulate reproduction. But now it is sure that the immune system is part of this process. The immune system regulates *growth and development* of the fetus, *which is Biology.* Defending the fetus is *Immunology* and *Pathology*. It seems that the Immune system is executing the orders of the neuroendocrine regulatory mediators as well as those delivered by the internal regulatory network of Immunity.

Apparently it is enough to antagonize pregnancy by inhibiting an immunosuppressing hormone, progesterone, using a contraceptive pill (RU486). Pregnancy is interrupted, the fetus is rejected by the immune system, which goes out of control due to the antagonization of a key immunosuppressive hormone. mRNA profiling was done in the periimplantation uterus using oligonucleotide microarrays to analyze changes in mRNA levels in response to RU 486. A variety of novel progesterone receptor (PR)-regulated molecules were identified, such as growth factors, protease inhibitors, metabolic enzymes, peptide hormones, transcription factors, immune response molecules, cytoskeletal proteins, and cell adhesion molecules, that are potential mediators of P action in the peri-implantation mouse uterus [26].

So, not only the Immune System, but the Neurimmune Supersytem, including the CNS, Endocrine system, and the numerous regulatory circuits [27], that in this case affect normal development of the fetus, are involved.

The fetus is not innervated. This limits the influence of the CNS on fetal regulation. It is possible, however, that mediators that are released into the serum, such as catecholamines, dopamine etc. would affect fetal development. Suppressor-regulatory T cells (Tsr), which recently gained recognition as involved with pregnancy [3] is an innate immune cell, which is regulated by glucocorticoids and catecholamines [27].

Recent observations revealed that during parturition and shortly afterwards the bodily functions of animals and babies are imprinted for life. Healthy mothers will have healthy babies with normal imprinting and sick mothers will have sick babies who will suffer from diseases all their life [28]. Thus NISS does not only affect directly mothers and babies, it has a long term effect, affecting an entire generation, affecting the maintenance of the species!! As a part of this system, the Immune system has to do with everything in the body. It produces and delivers to the target tissue hormones, cytokines and chemokines, even neuropeptides, with greater capacity than produced in the Nuroendocrine System [4]. It protects from infection and noxious insults. INIM is of special importance in this job. And it is never lost, always ready to serve the host [29].

The NISS is the ultimate regulatory system in Health and Disease and from conception till death [29]. We come a long way from the concept of the immune system being an intelligent and self sufficient system, which protects the body. Now it is certain that the immune system is deeply imbedded in physiological and pathological mechanisms and carries the ability to decide the fate of the organism for life. As an executing system it may nourish and protect but also can destroy, even the entire organism, if necessary.

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