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Decidual Stromal Cells as regulators of T Cell Access to the Maternal-Fetal Interface

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Abstract

A recent study in the journal Science offer insights into the mechanism behind feto-maternal tolerance, as evidenced by changes in the immunological environment of the uterus and decidua, they also provide a rich area of research for the understanding of the regulation of the immune system in other complicated medical conditions, including cancer, and pregnancies affected by infection or autoimmunity.

Establishment and maintenance of proper maternal-fetal interface is essential for the success of pregnancy. A critical aspect in the establishment of a proper maternal-fetal interaction is the regulation of the maternal immune system present at the implantation site. Our understanding of this interaction has significantly increased since the original observation by Sir Peter Medawar, over fiftyyears ago proposing the theory of the fetus as a semi-allograft that is not rejected by the maternal immune system[1, 2]. The presence of a high number of innate immune cells (macrophages, dendritic cells, Natural Killer cells) was presented as evidence for the recognition of the maternal immune system to the paternal antigens present in the trophoblast[3].

We know, today, that the innate immune system is present at the implantation site as a supportive element for the process of implantation, trophoblast invasion and spiral arteries transformation[4-7]. There is strong supporting evidence that the early presence of innate immune cells is not related to antigens from the father, but rather helps tissue renewal and establishment of the pregnancy [8, 9]. That is not the case for the regulation of the adaptive immune system, T and B cells. Many of the studies associated with the uterine regulation of T cells have focused on characterizing the presence and the role of Treg[10, 11]. However the function of Treg could not explain the control of T cell distribution in the pregnant uterus. New findings by Nancy, et al,[12]may provide some insights into this process.

The June 2012 issue of Science published an article entitled “Chemokine Gene Silencing in Decidual Stromal Cells Limits T Cell Access to the Maternal-Fetal Interface” by Nancy, et al. [12]. The authors presented data to support their hypothesis that decreased chemoattraction of T cells to the decidua occurs in order to support fetomaternal tolerance. They used a mouse model to study the effects of pre-pregnancy antigen exposure with subsequent re-exposure during pregnancy on the inflammatory cascade.

C57BL/6 female non-pregnant mice were immunized with soluble OVA prior to mating with a male mouse hemizygous for Act-mOVA transgene. Then, on E5.5, the pregnant mice

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were rechallenged with both OVA and the combination of CD40 antibodies+poly(I:C). Using a variety of immunostaining techniques the authors were able to show a significant lack of decidual response to the inflammatory stimulus as evidenced by a decreased level of CD3+ Tcell infiltration in the decidua compared to the myometrium overlying the implantation site and both the myometrium and endometrium of the interimplantation sites. Parallel to these findings the levels of key Th1/Tc1-attracting chemokines were decreased in the decidua compared to the other sites. Specifically, gene expression of *Cxcl9* and *Ccl5* were not increased in the decidua as they were in the myometrium. (*Cxcl10* expression was only minimally increased in the decidua, but not above the basal level of that seen in the myometrium.)

These expression differences were then shown functionally with transwell migration assays. Interestingly, this differential expression appeared to be occurring at the level of the individual gene regulation and not as a result of an inefficient inflammatory response of the cell. To support this finding, chromatin immunoprecipitation assays showed that the expression of the chemoattractants increased in non-pregnant endometrial stromal cells as well as in the myometrium and interimplantation sites of pregnant uteri but not in the decidua. This suggested a change in gene expression during the cellular transformation of endometrial stromal cells to decidual stromal cells. Ex vivo investigation of the promoter region of *Cxcl9* and *Cxcl10* revealed elevated levels of the repressive histone mark H3K27me3 in decidual versus myometrial stromal cells, which was confirmed in vivo. Furthermore, in response to inflammation, myometrial stromal cells showed upregulation of the marker of active gene transcriptionH4Ac in the promotion of chemoattract genes *Cxcl9/10*, whereas decidual stromal cells did not.

These findings provide a new interpretation of the regulation of the maternal immune system by the pregnant uterus. Contrary to previous studies focused on mechanisms by the placenta (trophoblast cells) inducing either cell death of T cells (e.g. Fas-FasL hypothesis [13]) or deletion of T cells, this study suggests an active role of the decidua controlling the migration of maternal T cells through the implantation site.

The fact that the inhibition of chemokine production in the decidua is associated with methylation of these genes suggests that epigenetic regulatorscontrol the capacity of the decidua to attract T cells. Although this study does not provide an answer to this question, it begs the question as to what the source is and what the factors are, that are controlling the expression of chemokines by decidual cells. A potential source could be the trophoblast (Figure 1A). We and others have shown that trophoblasts secrete cytokines that regulate the function and differention of decidual immune cells. It is plausible that the same factors could induce epigenetic changes in stromal decidual cells, consequently inhibiting their capacity to produce chemokines responsible for T cell recruitment. However; in pathologic conditions, such as infection, the inhibitory status can be broken and the same stromal decidual cells would become actively involved in the recruitment and activation of T cells to the implantation site [14]. These changes may have detrimental consequences for pregnancy.

In conclusion, not only do these findings offer insight into the mechanism behind feto-maternal tolerance, as evidenced by changes in the immunological environment of the uterus and decidua, they also provide a rich area of research for understanding the regulation of the immune system in other complicated medical conditions, including cancer, and pregnancies affected by infection or autoimmunity.

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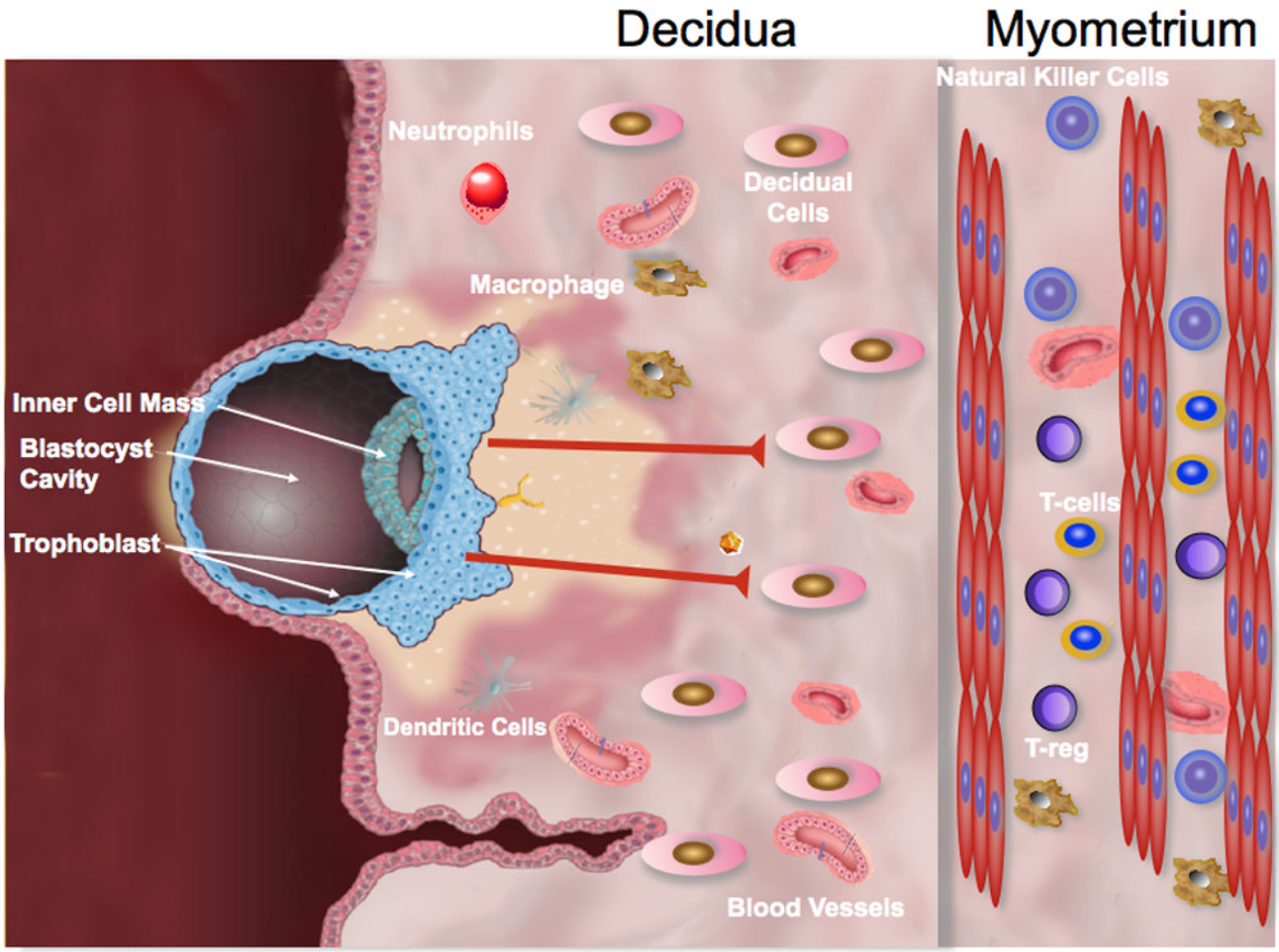

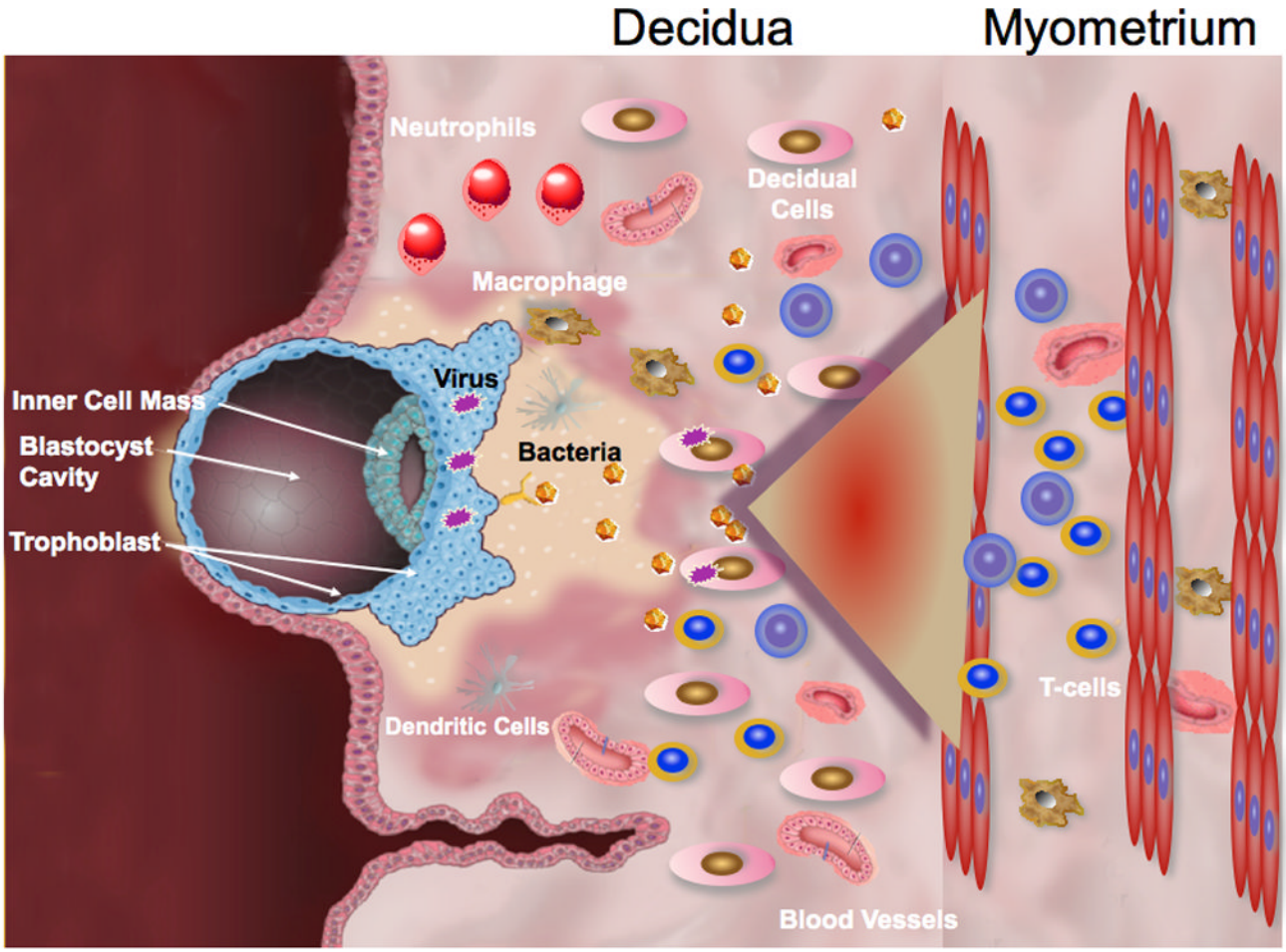

Figure 1. Model of molecular interaction between the trophoblast and decidua

A. Decidual cells are unable to attract T cells to the endometrium as result of lack of chemokine production. Consequently, the implantation site is free of adaptive immune cells. Trophoblast cells may constitute the source of regulatory factors preventing chemokine production by stromal decidua cells.

B. Viral or bacterial infection inhibit the regulatory factors allowing decidual cells to produce chemokines, enhancing the migration of T cells and NK cells towards the decidua