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EDITORIAL

Lessons from Immune Escape Mechanisms of Embryo Development in Uterus

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The development of semi-allogenic embryo in uterus during pregnancy is an immunological paradox, the immune tolerance in the fetomaternal interface is naturally established to prevent the embryo rejection. Solid tumors exist as a "new life" develop years, employ local or distant body nutrients to adapt, grow and metastasize to different organs of host. The development of embryo and tumor shares numerous similarities across the immune landscape and microenvironmental factors. Lessons from embryo development can increase our understanding on tumorigenesis and its components that could potentially transform anticancer therapeutic interventions.

Embryo implantation is occurring in a precisely controlled "window" period. In response to implanting embryo, the surrounding endometrium undergoes cellular transformation, a process known as decidualization, to accommodate embryonic growth and invasion [1]. The uterus decidua as well as the upcoming developed placenta are physical barriers between the mother and the fetus, play key roles in promoting the anti-inflammatory environment necessary for embryo development and pregnancy progression.

Distinct factors, including genetical, biological and immunological, work corporately in guiding fetus prevention during pregnancy [2]. Here we mainly illustrate major mechanisms of allogenic embryo escape the mother's immune systems.

lack of expression of classic HLA-I molecules

Healthy placental trophoblast cells are lack of paternal MHC class II or Ia molecules, which normally present

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antigens to the cytotoxic T lymphocytes. However, class Ib non-polymorphic molecules, such as HLA-G, HLA-E and HLA-F, are highly expressed on tropoblasts, and play roles in inhibiting the proliferation and cytotoxic of T lymphocytes and NK cells [3]. This point was believed to be one explanation of why embryo escape the immunosurveillance of the mother. However, this view has been questioned recently since the rate of pregnancy was not affected by transgenic expression of parental MHC molecules in several studies, suggesting that the lack of MHC class is dispensable in maintaining the fetomaternal tolerance [4].

Activation of a type Th2 regulatory lymphocyte response

The T helper type 1 (Th1)-Th2 theory defines that Th1 cells-derived cytokines, such as IFN-γ, predominantly promote cell-mediated immunity, whereas cytokines produced by Th2 cells, such as IL-4, induce humoral immunity and the production of immunoglobulin antibodies. Pregnancy was proposed as a Th2 phenomenon, and a shift from Th1 to Th2 is essential for a successful pregnancy. However, this Th1-Th2 paradigm has been challenged since IFN-γ that is detrimental to human pregnancy facilitates uterine vascular modification, decidualization and uNK cells differentiation in mice [5]. With the evidences of more subtypes on differentiation of CD4+ T helper cells, The Th1/Th2/Th17 and regulatory T cells (Tregs) paradigm during pregnancy has been proposed and drawn extensive attention of immunologists [6].

Production of immunosuppressive cytokines

The uterus could produce multiple cytokines, such as IL-4, IL-10, IL-5, PGE2 and M-CSF, to induce Th2 response for successfully pregnancy. On another hand, T cell attracting chemokines in decidua were epigenetically silenced, which lead to the effector T cells fail to infiltrate into the decidua in response to fetal challenge [7]. Besides, DC cells were entrapped by decidua and thus minimizing the activation of naïve T cells that responsible for fetal rejection during early pregnancy at the fetomaternal interface [8]. NK cells in placenta present different CD56+ cells secreting IL-8 and IL-6 to reduce vascular resistance [9]. It has been reported that the number of NKs significantly reduced in pregnancy and their capability to produce IFNγ is also dampened. Placental Tregs modulate active T cells using a series of repressive reactions including expropriation of IL-2 as well as increased release cytokines and other molecules [10].

In general, precise modulations of immune system maintain successful pregnancy till parturition, while uncontrolled immune suppression preserves the tumor for an indefinite period. A comprehensive study of immunoregulatory mechanisms of embryo development during pregnancy could provide fresh ideas on how to overcome tumor immune evasion and inspire more durable approaches to arrest cancer progression.

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