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Review

Popular myths in reproductive immunology☆

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ABSTRACT

According to Mark Twain, "It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so." Four items believed by reproductive immunologists are analyzed. (1) In a semiallogeneic (outbred) mating, maternofetal tolerance is required to prevent immune rejection manifesting as infertility, recurrent pregnancy loss, preeclampsia and fetal growth restriction. (2) Regulation of natural killer (NK) cells at the fetomaternal interface by interaction with fetal trophoblast paternal class I MHC is obligatory for pregnancy success. (3) Failure of angiogenesis triggered by complement activation is a key mechanism in pregnancy pathology. (4) Randomized controlled (double-blind) clinical trials and systematic reviews exemplified by the Cochrane database provide reliable evidence on which to base treatment and promulgate guidelines. Those who heed not the lessons of history are doomed to repeat the same mistakes in the future. History shows that we do this and expect a different outcome.

1. The myth of maternofetal tolerance

Tolerance is phenomenology defined by the absence of rejection and the presence of the peaceful coexistence of two putatively incompatible organisms. Classical immunological tolerance is a systemic change in the immune system. However, the pregnant mother is not immunologically tolerant of her intrauterine embryo. In semi-allogeneic matings in rodents as reported by Woodruff (1958), the pregnant mother can reject fetal tissue transplanted to an extrauterine site, and yet the remaining intrauterine embryos survive unaffected within their cocoon of fetal trophoblasts until parturition. If the pregnant mother was "immunologically tolerant," she could potentially be attacked by immunocompetent fetal T cells crossing the placental trophoblast into her circulation, and if the fetal immune system was tolerant and unable to reject maternal cells, then maternal cells crossing into the fetus would be unrestrained in their ability to attack fetal tissue. This exchange is illustrated in Fig. 1. Further, stem cell transplants from the immunologically tolerant offspring to the mother would not cause graft versus host

Abbreviations: MBL, mannan binding lectin; KIR, killer immunoglobulin-like receptors; RIF, recurrent implantation failure; RM, recurrent miscarriage; PE, preeclampsia; FGR, fetal growth retardation; CTL, cytotoxic T lymphocyte; LIT, lymphocyte immunotherapy; MHC, major histocompatibility complex antigen; miH, minor histocompatibility antigen; Tregs, regulator T cells; APC, antigen presenting cell; DC, dendritic cells (a type of APC); mAb, monoclonal antibody.

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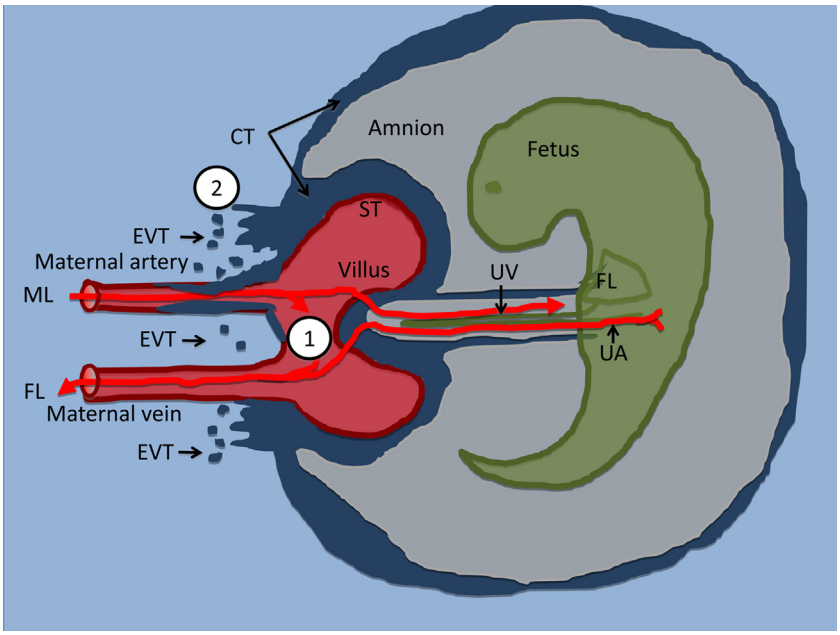

Fig. 1. Schematic diagram of the interface of the mother with the mature placental–fetal unit. Potential conflict/confrontation arises from the bidirectional transplacental traffic of immunocompetent maternal and fetal T cells (①). A second site of potential conflict/confrontation is at the interface of extravillous trophoblasts (EVT) expressing paternal class I MHC antigen(s) with maternal decidua (②): at this point in pregnancy, endovascular trophoblast plugging is minimal (Clark, 2014). In humans, the trophoblasts lining the outer surface of the villus (syncytiotrophoblasts, ST) line the proximal segment of the maternal veins, whereas cytotrophoblasts (CT) that invade the decidua (EVT) also invade arterial walls and form endovascular plugs. For homologies with the mouse and rat, see Clark (2014). Maternal lymphoid cells (ML) enter via the maternal artery, cross the trophoblasts lining a villus, and travel in the umbilical vein (UV) to the fetal liver (FL). Fetal lymphoid cells (FL) enter the villus via the umbilical artery (UA), cross the trophoblast into the maternal blood and exit into the mother's systemic circulation via the maternal vein.

disease (GvHD), and immunologically tolerant maternal cells transplanted to the offspring would not cause GvHD. Both expectations are contradicted by the data (Craven and Ward, 1999; Stern et al., 2008). As the antigens on semi-allogeneic maternal cells entering the developing fetus generate fetal Tregs that limit fetal T cell rejection responses against maternal cells and render offspring 'tolerant' of non-inherited maternal MHC antigens (Mold et al., 1988), the mother has some protection against aggression from fetal T cells entering her circulation. As activated Treg cells act nonspecifically, fetal Tregs may also suppress potentially aggressive invading maternal T cells (Clark and Chaouat, 2012; Martin et al., 2013). Lack of GvHD in mother and/or fetus may also be explained simply by the quantitative limiting of transplacental cell traffic by trophoblast (Fig. 1, site ①) to less than that required to cause GvHD (maternal and fetal microchimerism notwithstanding).

Based on the above, semiallogeneic fetal trophoblast must be considered a key target (Fig. 1 site ②) if maternal adaptive and innate rejection mechanisms are to explain recurrent implantation failure (RIF) or recurrent miscarriages (RM). The uterine decidua is not an immunologically privileged site; allografts are rejected promptly if the mother is alloimmunized, and allografts at non-uterine sites are recognized and rejected in unprimed females (reviewed in Clark, 1991). By contrast, pregnant mothers, whether human or murine, do not reject gestating semi-allogeneic or completely allogeneic (foreign) embryos, even if pre-immunized against the alloantigens of the father (Wegmann et al., 1979). Further, a pregnant female can make an immune response to the foreign MHC and minor non-MHC antigens of her fetus, but anti-MHC antibodies are not harmful, unlike antibodies to blood group antigens such as Rh, which can cross trophoblast and attach to the baby's Rh-positive erythrocytes, and sensitized maternal T cells do not cause pathological conditions either (Lissauer et al., 2012). A potential caveat is the lack of antibodies to the type of paternal MHC alloantigens and paternal minor histocompatibility antigens (miH) that may be expressed on trophoblasts. But maternal T cells can be sensitized, resulting in effector and memory effector T cells with regulatory functions (Tregs) and such cells can act locally and systemically (Rowe et al., 2012; Samstein et al., 2012). A local accumulation of Tregs can create an illusion of tolerance, similar to what happens when antigenic tumors resist rejection in immune hosts (Wick et al., 1997).

During normal pregnancy, there are some systemic alterations of maternal immune and inflammatory responses: infectious agents such as Leishmania etc. can thrive in pregnant hosts where rejection would normally occur, and when the infection is being effectively attacked, as shown by a mouse model, embryo resorptions occur (Krishnan et al., 1996a, 1996b). Further, there may also be systemic enhancement of the growth of paternal tumor cells induced by paternal antigens in seminal plasma (Robertson et al., 2009), and in the artifactual situation where a female mouse has a monomorphic MHC-specific T cell receptor (TcR) on maternal T cells, recognizing a single