**The role of fetomaternal MHC class II histoincompatibility in regulating tolerance of the semi-allogenic fetus**

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**Problem:** Viviparous pregnancy represents a physiological state in which the maternal immune system must tolerate a semi-allogenic fetus expressing “non-self” antigens derived from the paternal genome. While a critical role for paternal antigen-specific regulatory T (Treg) cells in regulating fetal tolerance is now well established, roles for specific classes of paternal antigens in regulating Treg cells are not defined.

**Methods of Study:** Literature review

**Results:** Studies in animals and humans support a role for MHC class II allele disparity (histoincompatibility) between mother and fetus in preventing fetal rejection that can cause abortion, fetal growth restriction, and preeclampsia. Although MHC class II molecules are not present on the surface of trophoblasts and likely do not serve as targets for maternal anti-fetal rejection, they are present on sperm, in seminal fluid, and intracellularly in trophoblasts where they are likely released into maternal circulation within exosomes. Paternal class II antigens are therefore subject to indirect presentation by maternal tolerogenic antigen-presenting cells to generate paternal class II-specific Treg cells. MHC class II disparity promotes tolerance of allografts at other immune-privileged sites including liver and cornea, and expression of donor class II antigens through tolerogenic routes promotes acceptance of allografts at non-immune-privileged sites. MHC class II, but not MHC class I, alloantigens are capable of triggering linked suppression of the full complement of alloantigens present in an allograft, including minor H antigens (mHAgs) which are present on trophoblasts and represent likely targets of anti-fetal alloresponses. Evidence for MHC class II-induced linked suppression during human pregnancy comes from studies showing that fetomaternal MHC class II histocompatibility regulates amelioration of maternal autoimmunity.

**Conclusions:** We propose a model whereby allogenic paternal MHC class II antigens trigger linked suppression of fetal mHAgs and a lack of fetomaternal class II disparity facilitates effector immune responses to mHAgs mediating fetal rejection.