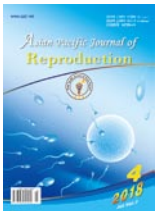

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Functions of follicular and marginal zone B cells in pregnancy

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Dear Editor,

Pregnancy is a physiological condition when immune cells face a dual crisis, as on one hand, the body needs to essentially tolerate semi-allogenic fetus possessing antigens from maternal and paternal sides, while on the other hand the maternal as well as the fetal body must not be adversely affected by infections. This delicate balance between immune tolerance and responses is regulated by an orchestra of immune cells. Various immune regulations by B cells are lately being explored. These include the production of asymmetric antibodies, induced by pregnancy factors, providing protection against maternally derived antipaternal symmetric antibodies at the feto-maternal interface[1] to protect the fetus from immune attack by destructive maternal natural killer cells as well as cytotoxic lymphocytes[2]. Moreover, the regulatory B cells can inhibit pro-inflammatory responses triggered by T cells and pro inflammatory mediators during pregnancy, by secreting interleukin-10, a potent anti-inflammatory cytokine[3]. Interleukin-10, secreted by B cells, also suppresses activities of the dendritic cells and keeps them in an immature state as mature dendritic cells would induce T cells which are detrimental to pregnancy sustenance[4].

B cells are the pioneer cells in humoral immunity, being released from the bone marrow and attaining ultimate maturation while they encounter antigen in the secondary lymphoid organs, producing plasma cells and memory cells. In spleen and lymph nodes, the pro B cells develop either into follicular (FO) B cells or marginal zone (MZ) B cells[5]. Once encountering an antigen, FO B cells get activated by T cells and differentiate into high-affinity immunoglobulin G (IgG)-producing plasma cells as well as memory B cells[6,7], providing specific immune defence lasting for about 5 days. On the contrary, the MZ B cells can be more quickly activated without any requirement of T cell signals owing to their pre-activated phenotype and strategic localization in the marginal sinus area of lymph node and spleen. The MZ B cells differentiate into short-life plasma cells generating low-affinity antibodies[8], mainly IgM and IgA natural antibodies, which regulate the first wave of an infection. Pregnancy may be maintained by the inhibition of the highly specific FO B cells to restrict rejection of the semi-allogenic fetus by maternal immune responses, and expansion of MZ cells in normal pregnancy to compensate the reduced number of FO B cells in combating infections.

In a recent study, female CBAJ mice which were crossed either with DBA/2J male mice had immune-mediated pregnancy disturbances[9], while the CBAJ mice mated with BALB/c male mice showed normal pregnancy outcome. It supported the notion of overall reduced B cell lymphopoiesis in pregnancy irrespective of the pregnancy outcome as all the pregnant mice whether with normal pregnancy or with pregnancy disturbances showed significant reduction in total number of pro and pre B cells, as compared to nonpregnant control mice. But in spite of significant diminution of FO B cells in normal and disturbed pregnancy compared to nonpregnant ones, an expansion of MZ B cells was pronounced only in the pregnant mice with normal pregnancy outcome. In addition, higher IgM in the serum of normal pregnant mice compared to disturbed pregnant group as well as nonpregnant mice, confirm that in normal pregnancy, the immune suppression

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mediated by inhibited T cell-dependent FO B cell differentiation (producing highly specific IgG) to ameliorate maternal immune tolerance to the fetus, is compensated by the non-specific antibodies (IgM/IgA) producing short-lived plasma cells by the T cell-independent MZ cell differentiation, to protect maternal health against infections. The reductions in the level of B cell-activating factor in both normal and disturbed pregnancy cases suggest that there are other factors apart from B cell-activating factor which control the dynamics of MZ B cells during gravidity. Moreover, it is known that exposure to semen at mating in mice triggers immune responses that are characterized by lymphocyte activation and B cell proliferation in draining lymph nodes[10] and the number of B cells in the uterine-draining lymph nodes significantly increases in pregnancy regardless of the outcome of the pregnancy.

Thus, FO B and MZ B cell populations are minutely regulated during pregnancy to balance immune tolerance and responsiveness in mediating restoration of fetal development and combating pathogens respectively (Figure 1). The concise presentation of this concept will aid future research aiming to mitigate the undesirable outcome of immune-mediated pregnancy disturbances owing to reduction in FO B cell population, with the help of strategies to induce MZ B cell expansion to compensate the immune suppression and aiding better protection against pathogen mediated abortions in different stages of pregnancy.

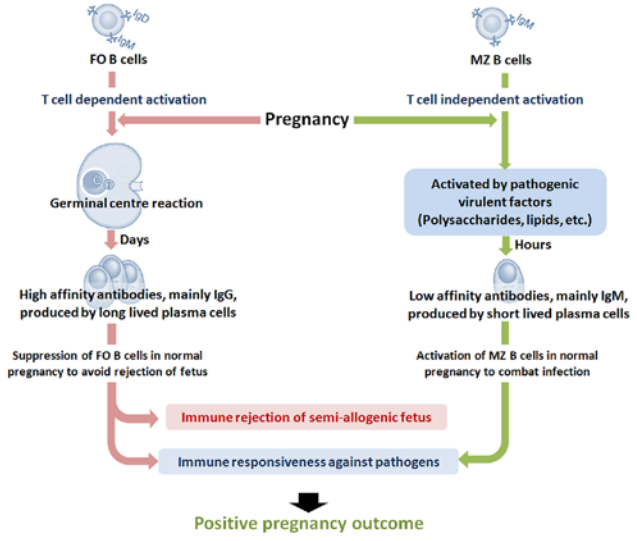

Figure 1. Suppression of FO B cells and expansion of MZ B cells in maintenance of pregnancy.
Red and green coloured arrows indicate activation and inhibition respectively.

Conflict of interest statement

The authors declare that they have no conflict of interest.

References

[1] Roussev RG, Dons'koi BV, Stamatkin C, Ramu S, Chernyshov VP, Coulam CB, et al. Preimplantation factor inhibits circulating natural killer cell cytotoxicity and reduces CD69 expression: Implications for recurrent pregnancy loss therapy. *Reprod Biomed Online* 2013; **26**(1): 79-87.

[2] Dubinsky V, Junovich G, Gentile T, Gutiérrez G. IL-6 as a regulatory factor of the humoral response during pregnancy. *Am J Reprod Immunol* 2008; **60**(3): 197-203.

[3] Iwata Y, Matsushita T, Horikawa M, Dilillo DJ, Yanaba K, Venturi GM, et al. Characterization of a rare IL-10-competent B-cell subset in humans that parallels mouse regulatory B10 cells. *Blood* 2011; **117**: 530-541.

[4] Schumacher A, Wafula PO, Teles A, El-Mousleh T, Linzke N, Zenclussen ML, et al. Blockage of heme oxygenase-1 abrogates the protective effect of regulatory T cells on murine pregnancy and promotes the maturation of dendritic cells. *PloS One* 2012; **7**: e42301.

[5] Muzzio DO, Ziegler KB, Ehrhardt J, Zygmunt M, Jensen F. Marginal zone B cells emerge as a critical component of pregnancy well-being. *Reproduction* 2016; **151**: 29-37.

[6] Allman D, Pillai S. Peripheral B cell subsets. *Curr Opin Immunol* 2008; **20**: 149-157.

[7] Chu H, Awasthi A, White GC 2nd, Chrzanowska-Wodnicka M, Malarkannan S. Rap1b regulates B cell development, homing, and T cell-dependent humoral immunity. *J Immunol* 2008; **181**: 3373-3383.

[8] Cerutti A, Cols M, Puga I. Marginal zone B cells: Virtues of innate-like antibody-producing lymphocytes. *Nat Rev Immunol* 2013; **13**: 118-132.

[9] Clark DA, Chaput A, Tutton D. Active suppression of host-vs-graft reaction in pregnant mice. VII. Spontaneous abortion of allogeneic CBA/J × DBA/2 fetuses in the uterus of CBA/J mice correlates with deficient non-T suppressor cell activity. *J Immunol* 1986; **136**: 1668-1675.

[10]Glynn DJ, Heng K, Russell DL, Sharkey DJ, Robertson SA, Anand-Ivell R, Ivell R. Male seminal relaxin contributes to induction of the post-mating cytokine response in the female mouse uterus. *Front Physiol* 2017; **8**: 422.