IL-33/ST2 axis affects the polarization and efferocytosis of decidual macrophages in early pregnancy

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Introduction:
It has been fully elucidated that decidual macrophages (dMφs) are the most important professional APCs at the maternal-fetal interface in the first trimester. Numerous researchers have found that M1/M2 imbalance can lead to the pathological pregnancy, such as pre-eclampsia (PE), spontaneous abortions, or unexplained recurrent spontaneous abortions (RSA). During uncomplicated normal pregnancies, M2 macrophages are the predominant subtype, while increased numbers of M1 macrophages are found during pathological pregnancy, which secrete damaging pro-inflammatory factors.

In the process of extravillous trophoblast cells invading the uterine stroma, most decidual stromal cells (DSCs) rapidly undergo apoptosis and begin to accumulate as uncleared apoptotic cells. Defective removal of dying cell causes the secondary necrosis of apoptotic cells, which subsequently triggers the immune response to self-antigens, resulting in systemic autoimmune diseases. We hypothesized that the phagocytic clearance of dying cells (efferocytosis), particularly by macrophages and other immune phagocytes as well as M1/M2 balance may engender profound effects on pregnancy, physiologically or pathologically.

As a member of the IL-1 family, interleukin (IL)-33 is widely expressed in the nucleus of a variety of cells under normal physiological conditions. Upon mechanical injury and/or tissue damage, IL-33 expression increases, and it is released as an “alarmin” to activate both the innate and adaptive immune system through binding to the ST2/IL-1 receptor accessory protein complex. Membrane-bound ST2 (ST2 or ST2L) is the functional component for IL-33 signaling, while the soluble, secreted form ST2 (sST2) acts as a decoy receptor for IL-33 to inhibit the IL-33/ST2 signaling pathway and the following biological responses. Considering our previous findings that the IL-33/ST2 signaling pathway may be a crucial modulatory mechanism of maintaining maternal-fetal tolerance during the first trimester. Here, we sought to investigate the pattern of IL-33 and ST2 expression in dMφs at the maternal-fetal interface and to analyze the regulatory effects of sST2 on the differentiation and efferocytosis activity of dMφs during the first trimester.

Materials/Patients and methods:
The phenotype characteristics of dMφs from both normal pregnant women and RSA patients were determined by real-time polymerase chain reaction (RT-PCR). Then, the efferocytosis and expression of IL-33 and its receptor (ST2) in dMφs were analyzed by flow cytometry (FCM). Finally, the effects of sST2, a decoy receptor for IL-33 that inhibits the IL-33/ST2 signaling pathway, on the polarization and efferocytosis of dMφs and human macrophage cell line U937 were investigated.

Results:
Compared with normal pregnancy, dMφs from RSA patients presented a M1 phenotype and expressed low levels of IL-33, while highly expressing ST2. However, dMφs from RSA patients possessed a more powerful efferocytosis ability to clear the apoptotic DSCs compared with dMφs from normal pregnancy patients. Treatment with recombinant human sST2, led to the up-regulation of M1 bias and efferocytosis ability of both normal dMφs and U937.

Conclusion:
This study indicates that IL-33 secreted by dMφs promotes M2 bias at the fetomaternal interface, and as a result, RSA might attribute to the disturbance of IL-33/ST2 axis and the enhancement of efferocytosis of dMφs.

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