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Comment on "Human Pregnancy Up-regulates Tim-3 in Innate Immune Cells for Systemic Immunity"

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Comment on “Human Pregnancy Up-regulates Tim-3 in Innate Immune Cells for Systemic Immunity”

We read with interest the article by Zhao et al. (1), which provides encouraging data on the role of Tim-3 in systemic immunity. It lends support to our view that TIM-3 could be a potential therapeutic target for systemic lupus erythematosus (SLE) (2).

To date, the etiology and pathogenetic mechanisms of SLE have not been clearly elucidated. It is well known that SLE occurs much more frequently in women, with a 9–10:1 female/male ratio, especially during the childbearing years, and commonly relapses or flares in the early trimester of pregnancy or after parturition. However, the exact explanation for the striking predilection of SLE for pregnant women remains unclear. Recently, association of TIM-3 polymorphisms with susceptibility to several autoimmune diseases has been identified (3, 4). In addition, Wang et al. (5) have explored the role of TIM-3 in SLE patients and have found increased expression of TIM-3 and galactin-9 in PBMCs from SLE patients. This evidence suggested that TIM-3 may be implicated in the pathogenesis of SLE, but what role it plays in SLE is unknown. Zhao et al. first correlated TIM-3 with pregnancy; they found that during pregnancy, TIM-3 is strikingly upregulated in the peripheral blood of pregnant women, mostly by monocytes, but not by T or B cells. Moreover, their clinical data show that an abnormal TIM-3 expression level might be connected with pregnancy loss (1).

Collectively, we conclude that the susceptibility to SLE of pregnant women may be related to the upregulation of TIM-3. This may partly explain why pregnant women are often affected with SLE. The development of therapeutic agents targeting TIM-3 could result in important new innovative therapies for the treatment of SLE and other autoimmune diseases.

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Response to Comment on “Human Pregnancy Up-regulates Tim-3 in Innate Immune Cells for Systemic Immunity”

The function of Tim-3 as an inhibitory receptor in T cell immune regulation has been well documented to date (1, 2). However, the positive immunoregulatory function of Tim-3 has also been implicated by studies (3). Recently, we constructed a CHO cell line expressing full-length Tim-3, designated as Tim-3-CHO, which highly expressed Tim-3. We cultured bone marrow-derived immature DCs in the presence of prefixed Tim-3-CHO, and found that DCs were induced and became mature by upregulating CD80, CD86, and MHC class II. This process could be prevented by the addition of Tim-3 Ab. Moreover, we found that Tim-3 stimulation enhanced the presentation of tumor Ag by DCs. Thus, Tim-3 seems to have a positive role in immunoregulation.

Systemic lupus erythematosus (SLE), one of the most common autoimmune disorders, affects numerous organ systems. Although most patients with SLE lead full, active, and healthy lives, the induction of disease activity (flares) might be catastrophic. It is well known that pregnancy may increase the frequency of SLE flares (4). However, the underlying mechanism still remains elusive. In our recent work (5) we showed that Tim-3 is upregulated in innate immune cells during pregnancy, and the increased Tim-3 is involved in the maintenance of systemic immunity. This study not only further reinforces the concept of Tim-3 as a positive immune regulator but also implies that the upregulation of Tim-3 expression could facilitate SLE flares during the pregnancy of SLE patients. We agreed with the comment “TIM-3 may be implicated in the pathogenesis of SLE and TIM-3 could be a potential therapeutic target for systemic lupus erythematosus” by Dr. Pan et al. Actually, our unpublished data showed that Tim-3 is more highly expressed in SLE pregnant women, compared with normal counterparts. Therefore, Tim-3 in pregnancy may protect the body from infection, and has a potential to trigger autoimmune response.

We also tested other clinical settings besides pregnancy. Interestingly, we found that Tim-3 is quickly upregulated in innate immune cells during infection. This may be explained

by the observation that Tim-3 stimulation promotes the phagocytosis of pathogens. On the basis of these findings and previous studies, we propose that Tim-3 crucially regulates immune responses at different phases: Tim-3 acts as a positive regulator by enhancing DC maturation, Ag presentation, and pathogen clearance at the innate stage; but as a negative regulator by limiting excessive T cell responses and avoiding autoimmunity at the adaptive stage.

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