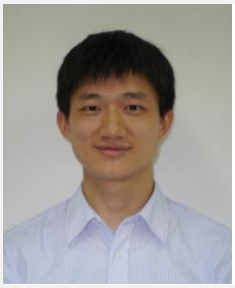
ImmunoTools *special* Award 2014



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Participation of Treg in embryo implantation, modulation by HCG

According to the report of Centers for Disease Control and Prevention (CDC), Untied States, about 10% of women (6.1 million) in the US between 15 and 44 years have difficulty in getting pregnant or staying pregnant, while the rate in France was up to 14.1% (Thonneau et al., 1991). Assisted reproduction, particularly in-vitro fertilization (IVF) technology could help them in getting healthy offspring. However, many women are still unable to conceive despite of multiple IVF-ET treatment cycles (Malizia et al., 2013). Failure could be caused by different factors, including age, follicles reservation, endometrial thickness, embryo quality, and some “unexplained”. Increasing data have demonstrated that so-called “unexplained” implantation failures to a large extent due to immunological dysfunction (Cha et al., 2012). Regulatory T cells (Treg), a subset of T lymphocytes that is essential for self-tolerance and tissue homeostasis, have been suggested to play a major role in play a major role in maternal-fetal tolerance establishment (Leavy, 2012). In human, Treg ratios in peripheral blood of fertile women change dynamically in different time point of the menstrual cycle (Arruvito et al., 2007), and expand systemically and locally during pregnancy (Mjosberg et al., 2009). Additionally, a specific subset or entire Tregs ratio of the infertile patients before IVF treatment was positively correlated with pregnancy rate (Schlossberger et al., 2013; Zhou et al., 2012). Furthermore, the proportion of decidua Treg was significantly reduced in patients with spontaneous abortion compared to those with induced abortions (Sasaki et al., 2004).

To maximize the implantation rate, many efforts have been practically performed and optimized, including intrauterine infusion of human chorionic gonadotrophin (HCG) (Licht et al., 2007; Mansour et al., 2011). HCG, a hormone produced by trophoblast and syncytiotrophoblast, plays a crucial role in human pregnancy for the development

of local maternal immune tolerance. Moreover, HCG has a strong immunomodulatory and chemotactic effect on lymphocytes (Nakayama et al., 2002). Recently, Schumacher et al. found that HCG has the ability to recruit Tregs to fetal–maternal interface and augment the suppressive capacity of Tregs during early human and mice pregnancy (Schumacher et al., 2009; Schumacher et al., 2013). However, many issues on the mechanism of human Treg participating in embryo implantation and how Treg regulate by HCG still need to be addressed. In this project, we hypothesize Tregs promote embryo implantation by creating a specific cytokines profile, and HCG is essential for the regulatory process of Tregs. To achieve consolidated findings, we isolate human Tregs, and use heterologous implantation models (*in vitro)* and Foxp3DTR knock-in mice (*in vivo)* to mimic conditions as physiological as possible, to investigate the involvement of Tregs and HCG in embryo implantation and the consequences if block their interactions. In the *in vitro* model, HCG receptor in Treg cells will be targeted knockdown or antagonist and will be rescued, and migration of Tregs and invasion of blastocyts will be evaluated. In addition, cytokines related to Treg function and embryo implantation will be assessed, including LIF, TGF-β,IL-6, IL-8, IL-10, IP-10, IL-23, TSLP, human IFN-gamma, TNF-α, PGE2, IL-15 etc. The aim of this study is to get a more profound and direct evidences of Tregs participate in mammal embryo implantation and how HCG regulates this process. The ELISA-sets provided by **ImmunoTools** would be greatly helpful for me to analyze the profile of cytokines after HCG receptor knockdown or angonnist of Tregs and therefore strongly support my project.

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