11

The Special Implication of Sex Hormones on Dendritic Cells During Pregnancy

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1. Introduction

Pregnancy bears a great challenge to the immune system: simultaneously, immune cells have to protect the reproductive tract against imminent infections, while the developing conceptus has to be tolerated. To face this problem, a distinct composition of immune cells has to be present in the decidualized endometrium (Gomez-Lopez, Guilbert *et al.*, 2010). The predominant subsets amongst those represent uterine natural killer cells (uNK cells) and cells of the monocyte/macrophage lineage like monocytes, macrophages and dendritic cells (DC) (Loke and King, 1995). Among the latter ones, DC as antigen-presenting cells (APC) are forming an important subgroup (Steinman, 2003).

DC represent a highly adaptive cell type, which can either be transformed into an immunostimulatory phenotype after exposure to inflammatory or infectious signals or into a tolerogenic phenotype preventing T cell activation when located in an adequate anti-inflammatory microenvironment. Establishing contact with invading microorganisms or cells, DC acquire their antigens and process them into antigenic peptides in the context of MHC class I and class II molecules as ligands for antigen-specific T cell receptors. This action is accompanied by migration of DC to secondary lymphoid organs. Here, the processed antigens are presented together with co-stimulatory molecules like CD40, CD80 and CD86 as well as CD83 and MHC molecules (Inaba, Metlay *et al.*, 1990;Steinman, 2003) to select and activate naive T cells (Sallusto and Lanzavecchia, 1999).

Apart from antigens, DC differentiation and maturation is considerably influenced by cytokines, hormones and other soluble factors. Lacking infectious/danger- signals or localiezed in a distinct anti-inflammatory micromilieu (e.g. TGF beta, IL-10), a specific phenotype of DC is generated which prevents T cell activation and which is supposed to protect the semi-allogenic fetus (Rutella, Bonanno *et al.*, 2006).

In human endometrium only a small number of fully matured DC are detected (Rieger, Honig *et al.*, 2004). Thereby, the amount of mature, CD83+ DC is generally low in both pregnant and non-pregnant endometrium with a slight peak in late secretory phase endometrium. During pregnancy, a distinct DC subtype expressing CD14, CD68, HLA-DR and DC-SIGN is found in increased levels in decidua (Bonifaz, Bonnyay *et al.*, 2002;Kammerer, Eggert *et al.*, 2003). These DC, presumably an intertype between immature DC (iDC) and macrophages, are supposed to represent a "pro-fetal" tolerogenic population which is able to induce a TH2 pre-dominant state (Miyazaki, Tsuda *et al.*, 2003) and to suppress the activation of T cells (Kammerer, Eggert *et al.*, 2003).

There is evidence that female sex hormones contribute to the modulation of decidual immune cells into tolerogenic subtypes (for review see: (Kyurkchiev, Ivanova-Todorova *et al.*, 2010) and especially can impact on DC (Segerer, Muller *et al.*, 2009). Thereby, the "micromilieu" determines if the captured antigens are presented in a tolerogenic or immune activating way resulting also in different phenotypes of DC. In the following, we will highlight the impact of the characteristic pregnancy hormones on DC and their potent implication on the development of a tolerogenic subtype of DC.

2. hCG

Human chorionic gonadotropin (hCG) is a heterodimeric hormone of the glycoprotein hormone family and is composed by two subunits linked in a non-covalent way. While the alpha subunit does not differ from the other glycoprotein hormones, the beta subunit of hCG represents the biggest one of the glycoprotein hormones holding a large glycosylated domain which refers to its high stability. hCG represents the very early hormonal factor of pregnancy already produced by the trophoblast layer of the blastocyst before implantation (Bonduelle, Dodd *et al.*, 1988;Lopata and Hay, 1989) and after implantation by the syncytiotrophoblast in increasing amounts (Hoshina, Boothby *et al.*, 1985). The production of hCG reaches a peak between the 10^{th} and 11^{th} week of gestation and thereafter declines to a lower but constant level throughout pregnancy. Preventing luteolysis of the corpus luteum and stimulating the production of progesterone (Keay, Vatish *et al.*, 2004), hCG represents the essential factor to protect and to promote early pregnancy. Despite of these direct effects, hCG can also act as a paracrine factor modulating the proliferation of myometrial smooth muscle cells (Horiuchi, Nikaido *et al.*, 2000;Kornyei, Lei *et al.*, 1993) and increasing endometrial angiogenesis (Berndt, Blacher *et al.*, 2009).

There is also evidence that hCG contributes to maternal tolerance of the developing conceptus by influencing the surrounding immune cells. Thus, experiments on uNK cells revealed that hCG acts as a regulator of uNK cell proliferation (Kane, Kelly *et al.*, 2009). Despite of this direct effect on uNK cell proliferation, hCG can facilitate the adequate establishment and maintenance of pregnancy by inducing the secretion factors which promote angiogeneis by uNK cells and thus could even support placentation (Lash, Schiessl *et al.*, 2006).

Investigations on DC demonstrated hCG receptors to be constitutively expressed by these cells which allows a direct activation of DC via hCG (Yoshimura, Inaba *et al.*, 2003). Experiments on mouse DC revealed that hCG acts in an immunregulatory way by increasing the production of immunosuppressive factors like Interleukin-10 (IL-10) by DC and by reducing antigen-specific T-cell proliferation (Wan, Versnel *et al.*, 2008). In humans, hCG was also able to significantly decrease T-cell stimulatory capacity of DC (Huck, Steck *et al.*, 2005). In contrast, the phenotype of hCG-treated DC ressembeled that of matured DC expressing co-stimulatory molecules like CD 40, CD83 and CD 86 (Segerer, Muller *et al.*, 2009). Thus, hCG seems to be able to induce a tolerogenic subtype of DC even though co-stimulatory molecules of the mature subtype were expressed.

3. Estrogen

Estrogen receptors (ER) alpha and beta (ER α/β) are widely expressed in human endometrium but also in most immune cells (Lindzey, Wetsel *et al.*, 1998). Thereby, they are localized in different cellular compartments. The cytoplasmatic and membrane associated

receptors confer to specific intracellular signaling pathways promoting genomic and non-genomic effects. Gene transcription and regulation is also mediated by nuclear ER acting as transcription factors and thus regulating long-term effects (Tamrazi, Carlson *et al.*, 2002;Biswas, Singh *et al.*, 2005). Recently, another estrogen receptor, GPR30, which represents an intracellular transmembrane G protein-coupled receptor was detected (Revankar, Cimino *et al.*, 2005). This receptor is proposed to initiate rapid non-genomic signaling effects and was found to be expressed in human endometrium throughout menstrual cycle and in early pregnancy decidua (Kolkova, Noskova *et al.*, 2010).
B and T lymphocytes were detected to be specific targets of estradiol (Peeva and Zouali, 2005;Nalbandian, Paharkova-Vatchkova *et al.*, 2005;Nalbandian and Kovats, 2005;Smithson, Couse *et al.*, 1998). Thereby, estrogen was able to modulate B lymphopoiesis and the production of immunoglobulins (Ig) where effects were mediated via ERα (Erlandsson, Jonsson *et al.*, 2003). T cell function was found to be modulated by estradiol changing the cytokine profile (Karpuzoglu and Zouali, 2011;Pernis, 2007;Salem, 2004).
Regarding DC, estradiol effects were mediated via ERα and β, both of which are expressed in DC. So far, the intracellular G-protein receptor GPR 30 has not been described in DC. Even though estradiol promotes the differentiation of DC (Paharkova-Vatchkova, Maldonado *et al.*, 2004;Segerer, Muller *et al.*, 2009) towards an immunostimulatory phenotype, expressing co-stimulatory molecules like CD40, CD83 and CD86, T-cell priming was significantly impaired in the presence of estradiol (Segerer, Muller *et al.*, 2009). In addition, investigations of the effects of E2 on murine spleen CD11c-positive dendritic cells revealed an increased stimulatory capacity of DCs and an elevated expression of the anti-inflammatory cytokines like IL-10 (Yang, Hu *et al.*, 2006).
In autoimmune diseases, estrogens seem to have conflicting effects on immune cells. While a reduction of disease activity was seen during pregnancy in multiple sclerosis, it was reported that systemic lupus erythematodes (SLE) could frequently flare up during pregnancy and remit with menopause (Petri, Howard *et al.*, 1991).
It could be speculated, that the effect of estrogen on DC participates in the flare up of SLE during pregnancy: DC generated from monocytes which were isolated from patients suffering from SLE exhibited a matured, pro-inflammatory phenotype, expressing co-stimulatory molecules. In addition, these SLE-DC were very effective in activating T-cells (Ding, Mehta *et al.*, 2006). Perhaps, estrogen could even accelerate the maturation-process of SLE-DC and thus promote disease during ongoing pregnancy.

4. Progesterone

During the menstrual cycle, progesterone is produced by granulosa cells and the corpus luteum (Bachelot and Binart, 2005). In pregnancy, the corpus luteum is rescued 4-5 weeks after implantation. At that time, placental progesterone production becames sufficient to maintain pregnancy (Csapo and Pulkkinen, 1978). Several studies revealed that progesterone acts in an immunosuppressive way (Stites and Siiteri, 1983;Miyaura and Iwata, 2002b). Analysing the effects of progesterone on T lymphocytes, a direct and indirect inhibition of TH1 cell development was detected (Miyaura and Iwata, 2002a). DC cultured under the influence of progesterone changed their phenotype into an immunostimulatory maturated phenotype expressing co-stimulatory molecules (Ivanova, Kyurkchiev *et al.*, 2005;Segerer, Muller *et al.*, 2009). In contrast to effects seen for hCG and estradiol, the capacity of DC to stimulate T-cell proliferation was not significantly altered (Segerer, Muller *et al.*, 2009). However, progesterone had profound effects on rat mDC by suppressing the

production of pro-inflammatory cytokines like tumor necrosis factor alpha (TNFα) and interleukin 1beta (IL-1β) as well as by inhibiting the DC-stimulated proliferation of T-cells (Butts, Shukair *et al.*, 2007). Thus, even though the expression of co-stimulatory molecules and T-cell stimulatory capacity was not affected progesterone seems to modulate immune responses by changing the cytokine secretion prolife.

5. Activin A and inhibin A

Activin A represents a distinct growth factor and member of the TGF beta superfamily (Chang, Brown *et al.*, 2002) which is composed by two activin β_A subunits. Its counterpart inhibin A is formed by a dimer consisting of an activin β subunit and a structurally different α subunit (Phillips, Jones *et al.*, 2005). Initially, the function of these glycoprotein hormones was defined as feedback factors regulating the release of the follicle-stimulating hormone (FSH) (Tong, Wallace *et al.*, 2003). Later, it was observed that activin A and inhibin A are endowed by diverse functions acting as cytokines in an autocrine or paracrine manner, too. Thus, activin A was detected to be involved in inflammatory responses (Jones, de Kretser *et al.*, 2004) and acting as a chemoattractant for monocytes (Eramaa, Hurme *et al.*, 1992;Shao, Frigon, Jr. *et al.*, 1992).

During pregnancy, activin A and inhibin A are locally produced by human placenta, decidua and fetal membranes resulting in serum levels in the low ng/ml range peaking at 10 weeks of gestation (Lockwood, Ledger *et al.*, 1997). Both glycoprotein hormones seem to have some impact on implantation and early embryo development (Birdsall, Ledger *et al.*, 1997;Muttukrishna, Jauniaux *et al.*, 2004;Jones, Salamonsen *et al.*, 2002). Furthermore, they have been found to be useful diagnostic markers for pregnancy success. While decreasing activin A levels indicated both an ongoing miscarriage or ectopic pregnancy (Florio, Severi *et al.*, 2007), decreasing inhibin A levels were used as a specific marker to reveal preclinical abortions (Muttukrishna, Jauniaux *et al.*, 2004;Prakash, Laird *et al.*, 2005).

Previous studies revealed that activin A is able to modulate immune responses via type I and II activin receptors on DC (Robson, Phillips *et al.*, 2008). Even though the expression of co-stimulatory molecules was not significantly affected neither by activin A nor inhibin A, both glycoprotein hormones were able to decrease the T-cell stimulatory capacity of DC. Thus, we propose that activin A and inhibin A are distinct modulating factors that could promote the generation of tolerance-inducing DC by affecting their T-cell stimulatory capacity (Segerer, Muller *et al.*, 2008) .

	DC phenotype	**T-cell stimulatory capacity**	**cytokines**
hCG	immunostimulatory (CD40 ↑, CD83 ↑, CD86 ↑)	↓	IL-10 ↑
estrogen	immunostimulatory (CD40 ↑, CD83 ↑, CD86 ↑)	↓	IL-10 ↑
progesterone	immunostimulatory (CD40 ↑, CD83 ↑, CD86 ↑)	↓ (in rats) → (in humans)	TNF-α ↓, IL-1 β ↓ (in rats)
activin A and inhibin A	immunostimulatory (CD40 ↑, CD83 ↑, CD86 ↑)	↓	no significant effects

Table 1.

6. Summary

During pregnancy, the levels of the glycoprotein hormones activin A and inhibin A as well as female sex hormones (hCG, estradiol, progesterone) are substantially elevated in parallel with increased occurrence of cells of the monocyte/macrophage lineage like DC in the decidua. In vitro experiments revealed that all of them can induce a tolerogenic subtype of DC even though effects were found on different levels (reduction of the expression of co-stimulatory molecules, reduction of T-cell stimulation, tolerogenic cytokine-profile). Thus, this distinct mixture of hormonal factors seems to be indispensable to support the development of tolerance-inducing DC which could play a key role in the acceptance of the fetus.

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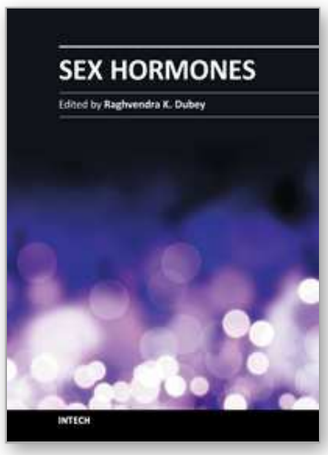

Sex Hormones

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Sex Hormones not only regulate reproductive function, but they also play a prominent role in the biology and physiology of several organs/tissues and in the pathophysiology of several diseases. During the last two decades, the information on the mechanisms of action of sex hormones, such as estrogens and androgens, has rapidly evolved from the conventional nuclear receptor dependent mechanisms to include additional non-nuclear, non-genomic and receptor-independent mechanisms. This highlights the need to update the current knowledge on sex hormones and their mode of action. Increasing evidence that exogenous/epigenetic factors can influence sex hormone production and action highlights the need to update our knowledge on the mechanisms involved. This book provides a systematic and updated overview of the male/female sex-hormones and their impact in the biology and physiology of various organs. Additionally, the book discusses their positive and negative association with the pathophysiology of various diseases (e.g. osteoporosis, cardiovascular-disease, hypogonadism, reproduction, cancer) and their therapeutic potential.

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