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Antigen presenting cells costimulatory signaling during pre-implantation pregnancy*

Sygnały kostymulacyjne wysyłane przez komórki prezentujące antigen w przedimplantacyjnym okresie ciąży

Anna Sławek, Tomasz Maj, Anna Chełmonska-Soyta

Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Laboratory of Reproductive Immunology, Wrocław

Summary

Success of pregnancy depends on many factors. Three phenomena inducing immune tolerance against semi-allogeneic conceptus may play a crucial role in the pre-implantation period of pregnancy: influence of sex hormones in sex cycle, presence of oocyte or embryo and the presence of semen in the female reproductive tract. On the other hand dendritic cells are the most effective antigen-presenting cells in regulation of immune phenomena and also are considered as potent participants in inducing immune tolerance in the pregnancy. They communicate with T cells in cell contact-dependent manner or via cytokines. During cell-cell contacts, costimulatory molecules play a key role and their expression is often dependent on cytokines milieu. Both costimulatory molecules and cytokines influence generation of T regulatory cells. Interactions of these molecules are closely related. In this paper we would like to pay attention to the importance of antigen presenting cells costimulatory potency in immune regulation during a pre-implantation period of pregnancy.

Key words: **costimulatory molecules • antigen presenting cells • preimplantation pregnancy**

Streszczenie

Prawidłowy rozwój ciąży zależy od wielu współdziałających ze sobą czynników. Jednym z najważniejszych jest ustalenie stanu tolerancji immunologicznej wobec antygenów semiallogenicznego płodu. W przedimplantacyjnym okresie ciąży zmieniające się środowisko hormonalne zależne od cyklu jajnikowego, obecność nasienia w układzie rozrodczym, obecność oocytu i w końcu zarodka bezpośrednio i pośrednio oddziałują na komórki układu odpornościowego uczestniczące w powstawaniu tolerancji. W fazie indukcji odpowiedzi tolerogennej najważniejszą rolę odgrywają komórki (APC) prezentujące antygen limfocytom dziewiczym. Wśród nich komórki dendrytyczne stanowią populację o najskuteczniejszej prezentacji ze względu na silne odziaływania kostymulacyjne. Komórki te komunikując się bezpośrednio z limfocytami T (kontakt komórka-komórka) wysyłają sygnały kostymulacyjne, dzięki obecności tzw. cząsteczek kostymulacyjnych. Skutkiem prezentacji antygenu przez komórki APC w sprzyjającym środowisku cytokinowym jest indukcja limfocytów T o charakterze regulatorowym. Takie limfocyty odgrywają dominującą rolę w nabywaniu tolerancji obwodowej towarzyszącej ciąży. W artykule przedstawiono uwarunkowania zmiennego potencjału kostymulacyjnego komórek prezentujących antygen w okresie przedimplantacyjnego rozwoju ciąży.

Słowa kluczowe: **cząsteczki kostymulacyjne • komórki prezentujące antygen • ciąża**

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Author's address: Prof. Anna Chełmonska-Soyta, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Laboratory of Reproductive Immunology, R. Weigla Str. 12, 53-114 Wrocław, Poland; e-mail: soyta@iitd.pan.wroc.pl

Abbreviations: **Ag** – antigen; **APC** – antigen presenting cell; **BMDCs** – bone marrow derived dendritic cells; **CFSE** – carboxyfluorescein succinimidyl ester; **CTLA-4** – cytotoxic T-lymphocyte antygen-4; **DC** – dendritic cells; **ER**α – receptor α; **G-CSF** – granulocyte – colony stimulating factor; **GM-CSF** – granulocyte- macrophage – colony stimulating factor; **hCG** –human chorionic gonadotropin; **HLA** – human leukocyte antigen; **HSP** – heat shock protein; **ICOS-1** – inducible costimulatory molecule 1; **IDO** – indoleamine 2,3-dioxygenase (*IDO*; EC 1.13.11.42); **ICAM** – intracellular adhesion molecule; **IFN** – interferon; **IL** – interleukin; **iNKT** –invariant NKT cell; **LFA-1** – lymphocyte functional antigen-1; **LPS** – lipopolisaccharide; **LN** – lymph node; **MHC** – major histocompatibility complex; **PD-1** – programmed death-1 antigen; **ROR** – related orphan receptor; **TGF-**β – transforming growth factor beta; **Th** – T helper lymphocyte; **Tregs** – regulatory T lymphocytes; **URSA** – unexplained recurrent spontaneous abortion.

Pre-implantation period of pregnancy as possible time of priming lymphocytes to develop of immune tolerance

Implantation, a key process in an establishment of intimate contact between mother and fetus is a kind of paradox from an immunological point of view. On the one hand we can see a maternal organism, which has to fight infectious diseases, both locally in an uterus and peripherally, in other tissues. A female immune system should recognize each non-self antigens, especially proteins, and such action is a key point of immune response. On the other hand, molecules characteristic for sperm, zygotes and embryos are foreign for maternal immune system, since they are allogenic or semiallogenic in their antigenic constituency. In 1953 Peter Medawar asked the key question in reproductive immunology: why immune system does not reject fetal cells and which immune mechanisms are active for induction of immune tolerance against fetal cells [72]? After nearly 60 years the question is still topical, while some answers are known.

Thus, the pregnancy is an example of natural dilemma how to favor tolerance in face of continuous foreign antigens threaten. A lot of local and systemic events accompanied the process of pregnancy development, however a preimplatation period of pregnancy is critical for its maintenance. Recent data explain some of these crucial phenomena such as: pregnancy recognition or molecular interactions between uterus epithelium and embryo. However, it seems that the pre-implantation period of pregnancy is also important for priming the mother's immune system to recognize the antigenically foreign conceptus and to development of immune tolerance mechanisms indispensable for its acceptance. It is the period of coexistence of many phenomena at the same time, which together can initiate fetal-specific maternal immune tolerance.

Hormonal environment

The first of such mentioned above phenomena is an estrous cycle-dependent regulation of a mother immune system. In the female reproductive tract, estrogens and progesterone are the main hormones influencing immune cells function. The number and distribution of immune cells vary in a tissue-specific manner with the stage of the estrous cycle [49]. In the mice during estrus and diestrus-I, when an estrogen level in the uterus is the highest, the abudance of uterine macrophages with the expression of F4/80$^+$ antigen (one of the surface markers of rodent macrophages) is also the highest. In contrast, in diestrus-II, when the estrogen level decreases and the progesterone level increases, mature, major histocompatibility complex II (MHC II)-positive macrophages are found in small numbers [25,41]. Female rat steroid hormones regulate antigen presentation in the thymus: at estrus and proestrus the presentation is more efficient than at diestrus, when estradiol level is low [90,118]. Production of pro-inflammatory molecules in uterine leukocytes is also regulated by sex hormones [42]. Moreover, estrogen enhanced the Foxp3 transcription factor expression, the most important regulatory T cells marker [88]. Dalal et al. [22] showed that risk of infection in each phase of estrous cycle is different. Mice were more susceptible to *Neisseria gonorrhoeae* infection in an estrus. It is worth noting that influence of estrous cycle does not only limit to the reproductive tract, where though there it is the strongest. Maximal changes both at the local and systemic level precede ovulation that leads conclusion that modulation of immune response in the estrous cycle can be preparation of mother's organism for the acceptance of embryo.

Cytokine environment

If the estrous cycle runs properly, the most important effect is an ovulation. Thus, the second signal of forthcoming pregnancy is the presence of ovulated oocyte in the lumen of reproductive tract. An ovulation is connected with disengagement of follicular fluid, which just like semen, is rich source of bioactive factors, like cytokines and growth factors: IL-2, IL-4, IL-7, IL-8, IL-10, IL-13, IL12/IL-23, IL-18, G-CSF, IFN-gamma [16,83,111]. Follicular fluid induces the

expression of IL-10 gene in lymphocytes. Moreover, in supernatants of lymphocytes incubated with the culture medium of sperms + oocytes, the concentration of IL-10 was significantly higher than in the lymphocytes incubated with follicular fluid alone. This result indicates the possibility of Th1/Th2 balance regulation shortly after fertilization [52].

Influence of semen

Obviously, the stage of estrous cycle and the presence of oocyte do not determine the beginning of pregnancy. However, if a fertile semen is present in female reproductive tract the pregnancy is expected in a few hours. Therefore, the third factor, which can indirectly signaling incoming pregnancy is presence of a semen in a female reproductive tract during peri-ovulatory period. Seminal plasma is a rich source of cytokines [14,64,74,78], hormones [81] and another bioactive substances, like prostaglandins [14]. Besides this, the presence of the semen itself stimulates the uterine mucous membrane to produce cytokines, like IL-1, TGF-β or GM-CSF [79,92]. The bioactive factors present in a seminal plasma and their influence on the female reproductive tract tissues evoke multidirectional effects. Spermatozoa and seminal plasma induce a number of immune phenomena, especially the influx of macrophages, dendritic cells and granulocytes into the uteri of ewes, pigs and mice [47,71,80,101]. The number of endometrial macrophages increases considerably by two- to threefold after mating [9,24]. Moreover seminal fluid regulates the cytokines secretion and antigen presentation [91]. The influence of a semen on female immune response is visible several hours after an insemination. For example, one-time intravaginal application of bioactive TGF-β 3 can enhance success of pregnancy in an established abortion prone CBA x DBA/2 mouse model. The result could be explained by a local recruitment of CD4+8+Foxp3+ cells [18]. In our own experiments we observed an elevation of ERα level shortly after mating in splenic, but not in uterine macrophages. This observation probably indicates also an early systemic response to paternal antigens [87].

Therefore, we can speculate, that the permissiveness for paternal/fetal antigens in female immune system is created very early after or even before fertilization. It seems to be reasonable from evolutionary point of view: a successful pregnancy and birth of the offsprings are the key points in the way of species survival and cheating of maternal immune system can be worth of its price. We can assume, that (1) estrous stage of sex cycle ensures, that an uterus has a proper morphology and physiological properties needed for embryo implantation; (2) estrous stage means the presence of oocyte(s); (3) the presence of fertile semen in connection with two previous factors leads to pregnancy. Thus, simultaneous presence of these three factors can prepare maternal immune system for forthcoming pregnancy, even before fertilization. In this place the question of Sir Paul Medawar is still up-to-date: which mechanisms take part in setting up maternal-fetal immune tolerance? To answer this question we have to look closer at the biology of antigen presenting cells.

Antigen delivery, presentation and recognition: a key process leading to immune tolerance

Antigen presenting cells (APCs) are the functionally different cell subsets, sharing one basic property: they can endocyte foreign antigens, from their environment, digest them to small fragments (a few aminoacids oligopeptides in a case of proteins) and expose these oligopeptides on the cell surface as a complex with major histocompatibility complex (MHC) class II proteins. Dendritic cells (DC) are a heterogeneous group of APCs, which are located in different tissues of an individual and they are known as the most potent APCs. During homeostasis DCs are tissue-resident cells. They efficiently absorb antigens present in their environment by pinocytosis or endocytosis and the way of antigen internalization influences the effect of antigen presentation [11,48]. Tissue dendritic cells after picking-up antigens migrate to local lymph nodes where they acquired the state of maturity and expressed an array of costimulatory molecules. Mature dendritic cells are capable of effective antigen presentation to lymphocytes. Interdigitating DCs are capable to prime naive T cells. Other subsets of APCs, like monocytes/macrophages or B cells substantially are not capable to priming T cells [7].

"Danger model" and pregnancy

Danger model of Poly Matzinger assumes that effectively protective immune response is developed when the non-self signal is associated with danger signal. Classical view of "danger" signal was concentrated on the presence of microbial (like lipopolysacharide (LPS), CpG-rich sequences etc.), viral (like ssDNA) or fungal antigens (like zymosan), however contemporary comprehension is extended. In some cases specific invaders proteins and other compounds are not immunogenic. Some parasites are immunologically similar to individual's own antigens and in such situations DCs can sense the danger through receptors for heat shock proteins (HSP) released from stressed host cells [28,29,121]. Moreover, mediators secreted by other (non-immune) cells in the tissue after infection or tissue damage are able to stimulate DCs as well [67,95]. Danger model of immune response seems to fit well to the pregnancy: on the one hand we can see non-self (paternal) antigens, cytokines and other bioactive substances present in seminal plasma, on the other hand implantation of growing trophoblast harms uterine tissue. As a result of activation, DCs and other APCs express higher level of MHC class II and co-stimulatory molecules (see next section), then they migrate to the nearest lymph node (LN) or another peripheral lymphoid organ and stimulate lymphocytes recognizing the antigens internalized in the tissue at the time of danger signal appearance [7]. Indeed, uterine DCs migrate to local lymph nodes even in the steady-state conditions, since $CD11c^{+}CFSE^{bright}$ cells appeared in LN after 28 hours after CFSE injection into uterine lumen.. These DCs are immature (iDCs), with low expression of costimulatory molecules. Localized in peripheral tissues they may migrate constitutively to secondary lymphoid organs under steady-state conditions inducing anergic, apoptotic, or T reg cells [105]. However, in transgenic mouse model using OVA expression in a uterus and OVA-specific T cells Erlebacher et al., [27] demonstrated, that migratory DCs were also capable to elicit immune response. Such mature DCs (mDCs) express high levels of MHC class II and costimulatory molecules, including CD40, CD80 (B7-1), CD83 and CD86 (B7-2), on their surface. Nonetheless, in comparison with the uterus, the CD11c+ population in the uterine draining nodes express higher levels of both MHC class II and CD80 [8].

Three interactive signals: DC-T cell interaction

Three general signals are involved in DC-T cell cross-talk: the first is MHC – TCR signal, the second signal is mediated by costimulatory molecules (especially B7-family members with their ligands like CD28 and CTLA-4) and the third by cytokines [60]. It is worth noting, that Ag-specific CD4+ and CD8+ T cell activation can occur after coitus in response to male seminal fluid Ags, via Ag cross--presentation in female APCs [73]. Pooley et al. [89] indicate, that the CD8+ DCs, but not CD8- DCs, are specialized for *in vivo* cross-presentation of exogenous soluble Ags via the class I MHC presentation pathway.

In fact, the effect of antigen presentation is dependent on the properties of APC and other cells bound to these cells. For example, it is well known, that low-level expression of costimulatory molecules is connected with tolerogenic properties of DCs, while high expression of these molecules results in inflammatory response. On the other hand, cytokines in environment of APC can modify the properties of these cells. After exposition of DCs to IL-10 the cells gain the ability to induce Foxp3+ Tregs [40]. At any time every single APC is tied with several different immune cells. The cells communicate not only with APC, but with other cells in such complex as well and in this way they create a microenvironment determining the outcome of antigen presentation. For instance, iNKT cells have ability to trigger tolerogenic phenotype of DCs [13] and Tregs, after interaction with DCs can not only down-regulate the level of CD80 and CD86 on APC, but also out-compete naïve T cells, blocking their maturation and differentation [82]. Therefore, the result of antigen presentation is dependent on different cell-dependent and cell independent signals and APCs are a central point, orchestrating all of these phenomena. In these interactions especially in context of pregnancy the role of cytokines is considerably well-studied, on the other hand the role of costimulatory molecules, is still enigmatic.

The participation of dendritic cells and costimulatory molecules in tolerance induction

In general expression of costimulatory molecules on APC may be constitutive or regulated by external factors like hormones [50,77] and cytokines [10,53,103]. For example, the expression of MHC II and CD40, stimulatory capacity and intracellular levels of IL-6 and IL-10 is increased, while the expression of CD54 and IL-12, endocytosis and nuclear level of NF-kappaB P65 of murine spleen CD11c-positive dendritic cells decreased after progesterone treatment [120]. On the other hand, the progesterone treatment of mature bone marrow-derivied dendritic cells (BMDCs) in rat caused down-regulation of costimulatory molecules CD80 and MHC II expression [12]. Another data considering the influence of sex hormones on the maturation and function of human dendritic cells indicate, that unlike human chorionic gonadotropin (hCG), which inhibited HLA-DR expression, progesterone and estradiol (E2) did not prevent the upregulation of surface markers characteristic for mature DCs, such as CD40, CD83, and CD86. Moreover, hCG and E2 inhibit the T-cell stimulatory capacity of DCs, which may help in preventing an allogenic T-cell response against the embryo [102].

CD40 and CD40L (CD154) belong to the TNF family ligands and receptors, that also includes OX40L, OX40 (CD134), 4-1BBL, 4-1BB (CD137), TRANCE (RANK), TRANCE (RANK-L), CD27, CD27L (CD70), CD30L (CD153), CD30 [65]. Originally B lymphocytes were described as a source of CD40. However, subsequent data indicated, that many cells also could express CD40, for example: monocytes/macrophages, dendritic (Langerhans) cells, epithelial cells and fibroblasts. Similarly, CD40L previously described on the activated CD4+ T lymphocytes, occurs also on monocytes/macrophages, dendritic cells, epithelial cells, mast cells, natural killer (NK) cells and platelets [36,98]. At the amino acid level, human and murine CD40 share 62% overall sequence similarity [6]. Expression of CD40 and CD40L depends on the presence of cytokines. Shurin et al. [103] show, that IL-10 inhibits CD40 expression on DCs and DC precursors and suppress their maturation and function. On the other hand, IL-1, IL-12, TNF-α, GM-CSF, IFN-γ enhance the expression of CD40 and its ligand. The CD40-CD154 interactions can influence T cell priming, T cell-mediated effector functions; they can also upregulate costimulatory molecules and activate macrophages, NK cells and endothelia [36,98,99]. The CD40 activation improves the antigen presentation capacity by B cells [63]. Darmochwal-Kolarz et al. [23] showed, that in pregnancy the expression of the CD40L on peripheral CD4+ T lymphocytes and the concentration of soluble CD40L were significantly lower than in non-pregnant women.

B7 family members play a critical role in maintaining fetal tolerance [86]. This family contains the most important molecules for APCs-T cells interactions i.e.: CD80 (B7-1)/CD86 (B7-2) on APCs cooperating with CD28 or CTLA-4 on naïve and activated T cells respectively, which together can induce tolerance or immunity [21]. These molecules play a critical role in the initiation of T-cell response. The CD28 and CD86 are constitutively expressed molecules, whereas CD80 and CTLA-4 are inducible upon activation. On murine activated DCs, the surface expression of CD86 is 10 times greater than that of CD80. Engagement of CD28 on naïve T cells by either CD80 or CD86 ligands on APCs provides a potent costimulatory signal for T cells activated through their T cell receptor, which results in an induction of IL-2 transcription and a CD25 expression [1,15,44]. Kelleher and Knight [53] showed, that IL-12 increased CD80 expression in bone marrow-derived dendritic cells. On the other hand, recombinant IL-10 decreased CD86 expression at the human DCs purified from peripheral blood of healthy volunteers [10]. The lack of CD80 expression at the maternal-fetal interface in human was found by Petroff et al. [85]. However, this authors indicate, that CD86 is expressed by both maternal and some fetal macrophages. Restricted expression of CD80 and CD86 could inhibit maternal rejection of fetuses in abortion-prone model of mice. The blocking antibodies administration caused an increase of T regulatory cells frequency and skewing toward a Th2 response. Bachy et al. [5] also show, that dendritic cell system in pregnancy favors Th2 response. On the other hand it is well known that blocking CD80/CD86 costimulation inhibits autoimmune disease progression in a variety of animal models [30,55,59,62].

Both CD80 and CD86 are able to bind CD28 and CTLA-4 molecules. Very often their function as molecules delivering the second signal to naïve lymphocytes is jointly considered.

However, despite their homology they differ in structure, mode of interaction with ligands and in effector function of a transmission of activating and inhibitory signals in co-stimulated lymphocytes. CTLA-4 binds with a higher affinity to CD80 and CD86 than CD28 and downregulates the immune response [113]. CTLA-4 displays an important role in indoleamine-pyrole 2,3-dioxygenase (IDO) synthesis, an enzyme which promotes tolerance in murine pregnancy [37,75]. Moreover, recent data show, that regulatory T cells contribute to peripheral tolerance by keeping the DCs in an immature state and CTLA-4 is necessary for control of DCs by regulatory T cells [97].

Another B7 family members: PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC) bind to the programmed cell death 1 (PD-1, CD-279) receptor on T cells and strongly inhibit CD4 T cells activation, thus they may also contribute to the maintenance of peripheral immune tolerance [100]. PD-L1 is constitutively expressed on mouse APCs (DCs, macrophages and B cells) and T cells. The expression of PD-L1 on cells surface was demonstrated on some endothelial cells as well as in tissues of placenta, testes and eye [26,51]. Tamura and colleagues [108] indicate, that this costimulatory molecule is capable of enhancing T cell proliferation and IFN-γ, IL-10 and GM-CSF production. On the other hand, another studies show that interaction of PD-L1 or PD-L2 with PD-1 inhibits T cell proliferation and cytokine production by phosphorylation of immunoreceptor tyrosine-based switch motifs and blockade of T cell receptor signalling [21,31,33]. PD-L1 is highly expressed in human placenta [85] and its expression increases after IFN-γ or EGF treatment [84]. Cytokines IL-2, IL-7, IL-15, IL-21 up-regulate both PD-1 and its ligands both *in vitro* and *in vivo*, whereas proinflammatory (IL-1β, TNF-α, IL-6, IL-8), immunosuppressive (TGF-β, IL-10), and immunoregulatory (IL-4, IFN-γ, IL-18) cytokines had no significant effect [57]. Polanczyk et al. [88] demonstrate, that both estrogen and pregnancy, enhanced PD-1 expression in several types of APCs.

Another member of B7 family – inducible costimulator ligand (**ICOS-L**) (also known as B7h, B7-RP1, GL50, LICOS, B7-H2) is expressed on most types of APC, subset of T cells, and also on endothelial cells [19,54]. Stimulation of ICOS on human T cells preferentially promotes IL-10 production, although production of IL-4, IL-5, IFN-γ, TNF-α, GM-CSF is also increased [43]. ICOS can stimulate both Th1 and Th2 cytokine production, but may have a preferential role in the generation of Th2 cells [70].

Suciu-Foca et al. [106] using cDNA microarray showed that expression of costimulatory molecules: CD40, CD80, CD86, OX40L, CD54 (ICAM-1 –intracellular adhesion molecule-1) and CD58 is down-regulated on tolerogenic DC. Interactions of ICAM-1 and ICAM-2 with LFA-1 (CD11a/CD18) are important for Th1/Th2 balance. Thus, blocking these interactions shifted Th1 immune response to a Th2 response (15- to 40-fold increase of Th2 cytokines production) [96]. Moreover, IL-10 decreases ICAM-1 expression on monocytes [116]. Maturation state of DCs might be a control point for the induction of tolerance through modifications of the activation state of T cells. iDCs are prone to induce regulatory T cells and promote tolerance, whereas mDCs stimulate effector T cells. Tolerogenic DCs are characterized by low MHC II, CD80 and CD86 expression. They also produce reduced level of IL-12. Molecules: IL-10, PD-L1 and IDO, which are expressed by DCs, may by connected signals to generate regulatory Tregs [68,93,100]. Immunosuppression, which is induced by iDCs, is mediated by both TGF-β- and IL-10-positive CD4+ regulatory T cells [20].

Interactions of costimulatory molecules and cytokines in Treg generation

In context of pregnancy, it was belived that during gestation a polarization of immune response towards Th2-mediated phenomena was critical for fetal tolerance [115]. However, this opinion is currently under discussion [17]. The importance of Th1/Th2 balance is diminished after accurate description of further Th cells subpopulations: Treg cells and Th17 cells. Tregs have a unique ability to antigen-specific and non-specific dampening of immune response and are characterized by expression of CD25 molecule, Foxp3 transcription factor, and secretion of immunoregulatory cytokines TGF-β and IL-10 [32,114,117]. The presence of Tregs during gestation is one of the key points to acquire active tolerogenic immune response against fetal alloantigens [3,110]. Th17 cells are defined as CD4+ T cells expressing ROR-γt transcription factor and producing IL-17 [45]. Th17 cells seems to be harmful to the maintenance of pregnancy, at least in humans. Liu et al. [66] showed, that the proportion of Th17 cells and IL-17A concentration was both significantly higher in patients with unexplained recurrent spontaneous abortion (URSA) than in normal early pregnancy and non-pregnant patients. Moreover, the ratio of Th17 to Treg was also significantly higher in URSA group than in the other two. There are evidences, that development of Th17 and induced Treg cells during immune response is mutually exclusive [58] and Th17/Treg system is similar to the Th1/Th2 balance. All above mentioned T cell subset can convert into another subset. Conversion between Th1/Th2 cells is well documented. Treg cells in inflammatory environment or converted to a population showing mixed properties of Th1 and Treg cells [122].

The induction and maintenance of tolerance is regulated by CD3+CD4+CD25+Foxp3+ regulatory T (Treg) cells, Th3 cells, Tr1 cells, regulatory NK cells and a tryptophan-catabolizing enzyme IDO [4,94,109]. Th3 cells are characterized as cells, which produce immunosuppressive cytokine TGF-β, whereas Tr1 cells produce IL-10. Recently, it has been clarified that there are also a regulatory NK cells: NK3 producing TGF-β, NKr1 producing IL-10 and NKreg also producing TGF-β [94]. However, recent reports suggest, that Treg cells play essential roles in alloantigen tolerance [2]. There are three mechanisms, by which this cells induce tolerance. In the first mechanism, cell-to-cell interaction-dependent membrane-bound TGF-β1 [76], Lag-3 [39] and galectin-1 [35] are involved. These cell-to-cell interactions inhibit T cells proliferation and NK cells activity. The second mechanism is when the cytokines such as TGF-β and IL-10 are produced by CD4+CD25+ Treg cells and inhibit T cell activation. The third mechanism depends on interactions CTLA-4 expressed on Treg cells with B7 complex on DCs and macrophages. These interactions induce interferon (IFN)-γ production and this cytokine, in turn, enhances the IDO expression

on DCs or macrophages [37]. Thus, by catabolizing tryptophan, T cell activity is suppressed [75].The generating of Treg depends on costimulatory molecules expression. Wakkach et al. [112] demonstrate, that CD2-CD58 interaction induces the differentiation of regulatory T cells secreting high level of IL-10 (Tr1 cells). CD28/CTLA-4 interactions with their B7-ligands are also very important. The blocking of CD80 and CD86 causes increasing Treg function [46]. The expression of costimulatory molecules is regulated by cytokines, for example IL-10 down-regulates CD80 [116] and CD86 [104] on APCs. The changes of costimulatory molecules expression are completed by changes in cytokines secretion, especially these regulating Th1/Th2 balance and Treg generation. The main cytokine, which is responsible for Treg generation, is TGF-β. A subset of DCs, CD11c+CD205+, is specialized to induce Treg in a TGF-β-dependent manner [119]. This cytokine, also present in semen, causes increase the level of two important Treg markers: Foxp3 [34] and CD25 [56]. Moreover, another cytokines play important roles in Treg generation and Th1/Th2 balance regulation, for example IL-10 [5,112] or IL-4, which determines the shape of immune response [38]. The effect of cytokines have a pleiotropic character, since these proteins can both directly influence the lymphocytes activity and can regulate APCs function, for example by regulation of costimulatory molecules expression presented higher up.

Conclusions

In early pregnancy maternal immune system faces to foreign paternal antigens. Still there is not confirmed where and how their recognition is achieved, however costimulation potency of antigen presenting cells is changed under the influence of sex hormone, cytokines and mating act (Fig. 1). Therefore it may by assumed that proper costimulation of naïve T cells may participate in favorable state of immune tolerance during pregnancy.

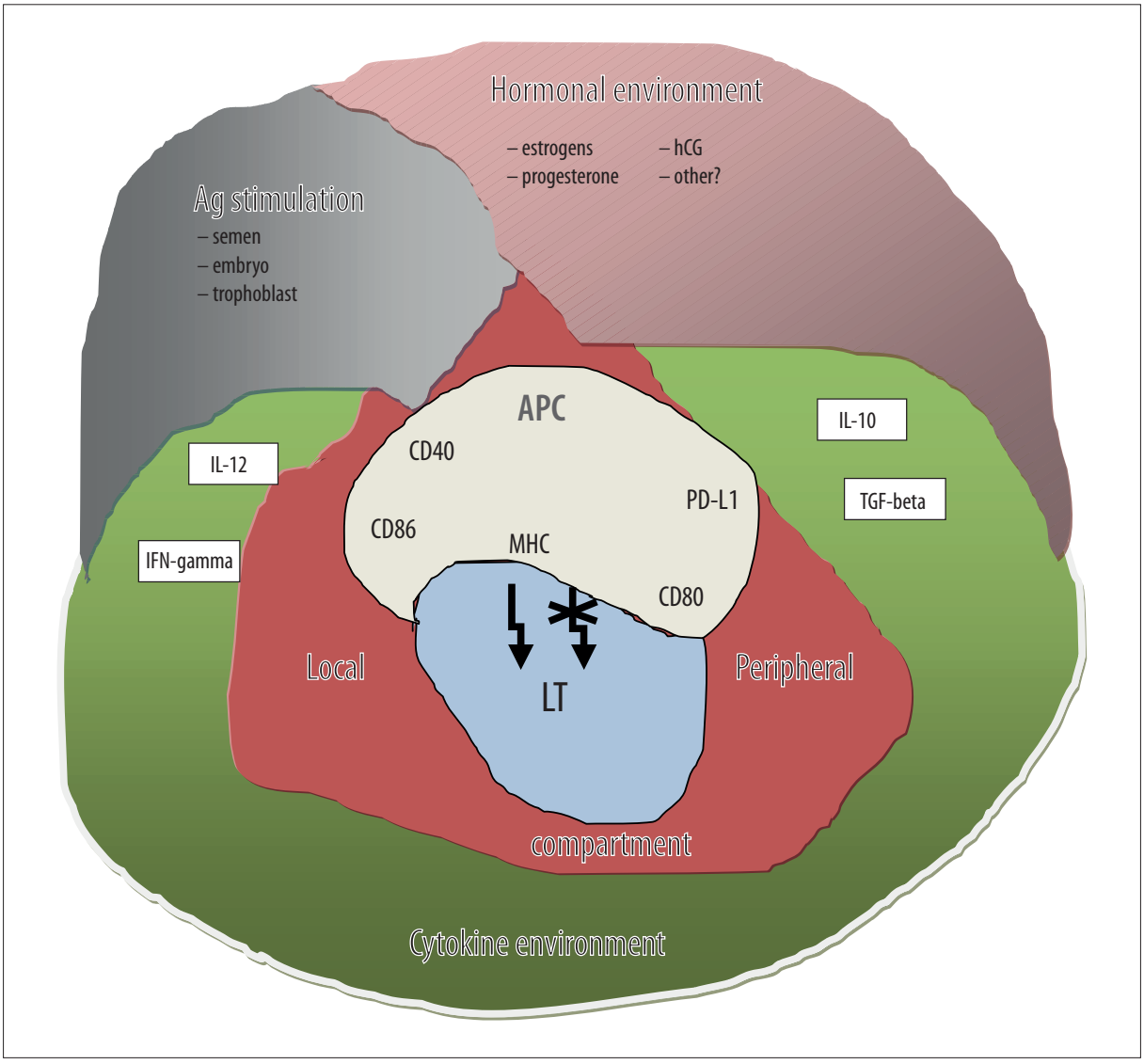

Fig. 1. Costimulatory environment of T lymphocytes during pregnancy. Antigen presenting cells are present both in local and peripheral compartment. They have putative contact with paternal antigens and are aware of trophoblast antigens. They deliver the second-costimulatory signal to naïve lymphocytes. The strength and duration on it is dependent on hormonal and cytokine environment. However, precise mechanisms of costimulation regulation remain still not well recognized

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