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The role of the endometrium in the regulation of immune cell activity

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1. ABSTRACT

The very purpose of the endometrium is human reproduction, a process made possible by the interaction between immune and endometrial cells. While endometrial cells seem to be responsible for immune cell infiltration, they also have the capacity to limit the infiltration and activity of immune cells. This cellular interaction is prominent not only during the implantation window, but also during labor. Indeed, the proper interaction between the endometrium and trophoblast and immune cells enables proper implantation and also determines placental detachment. The molecular alterations observed during implantation are well documented; however, the molecular basis of placental abruption still remains unclear. The proper placental detachment during the third stage of labor is a crucial event in the overall course of labor, whereas placental abruption leads to severe complications. The place where trophoblast and immune cell interaction begins during Fallopian tube gestation without the participation of endometrial cells is the tubal wall. This difference is most consequential during tubal rupture. The determination of the mechanisms responsible for endometrial participation in immune tolerance during pregnancy could have important clinical consequences and may prove significant in the development of immunotherapy.

2. INTRODUCTION

The uterus is an organ that undergoes constant remodeling. This process is controlled by various factors, such as hormonal changes and autocrine and paracrine endometrial cell activity (1). Immune cells constitute 7% of all endometrial cell population during the proliferative menstrual cycle phase; during the secretory cycle phase their percentage increases to 30% of all endometrial cells and, once menstruation begins, to 40% (1). Werth and Grusdew in the nineteenth century and Noe in the twentieth century proposed dividing the uterus into two parts, the archimetra and the neometra (2, 3). The archimetra is an endometrial-subendometrial unit, composed partly of the epithelial and stromal endometrium and partly of the underlying stratum subvascular of the myometrium, with a predominantly circular arrangement of muscular fibers (2, 3). The archimetra plays an important role in all reproductive processes beginning with intercourse through implantation and delivery (2, 4-10). The archimetra is controlled not only by endometrial cells, but also by immune cells. The immune system associated with the endometrium is a component of membrane associated lymphoid tissue (MALT). There are, however, some features of this system that distinguish it from MALT. White *et al.* (11), have proposed a definition of lower

reproductive tract lymphocytes as tertiary lymphatic tissue. Because of the complexity of the processes taking place within the uterus, Beier *et al.* (12), have suggested that the endometrium may in fact be an independent organ. The main feature of the endometrium that differentiates its mucous membrane from that of other organs is the periodicity of the changes in the number and activity of immune cells (13). Their functional status seems to depend, on the one hand, on the hormonal changes taking place during the menstrual cycle, but seems, on the other hand, to be directly dependent on the activity of immune regulatory cells (14), as well as on the immunomodulating activity of endometrial cells (15-17). The second feature typifying the endometrium is the profile of immune cells infiltrating the endometrium that alters according to the particular menstrual cycle phase (13), along with the special role of NK cells (18-20). These cells may constitute almost 90% of the immune cell population during the secretory cycle phase (13). Further immune cell infiltration of the endometrium is observed during menstruation; the dominant cells within the endometrium at that time are neutrophils and macrophages, while NK cells along with eosinophils constitute an important but not prominent percentage of cells (21). The similarity of the endometrium to lymphoid tissue has been noted, and it has been suggested that this similarity may be helpful in elucidating the unique immunomodulating action of endometrial tissue (22-26).

3. BEGINNING OF IMMUNE TOLERANCE PROCESS DURING PREGNANCY

The strong immunomodulating activity of endometrial cells has to be taken into consideration when analyzing the phenomena of fertilization and ovum implantation which take place within the endometrium and for which the level of immune cell activity is pivotal. The regulation of immune cell activity can be realized by factors secreted into the extra-cellular matrix such as: PRL, IL-1, IL-11, IL-13, IL-15, IL-18, LIF, RANTES (15, 27-42), as well as other proteins that behave in a similar manner (Fas, Fas-L, TNF-alpha, HOXA10) (43-49). During the changes brought about by the various menstrual cycle phases, cyclic alterations of the above mentioned immunomodulating factor expression have also been observed (41, 50). To evaluate the dynamic changes taking place during the menstrual cycle phases, the menstrual cycle has been divided into six subphases: early-, mid-, and late- proliferative, and early-, mid-, and late- secretory (51-52). This division of the menstrual cycle is precise and indicative of the dynamic changes taking place over the 28 days of the physiological menstrual cycle. The highest concentration level of immunomodulating factor expression has been observed during the mid-secretory (41, 50) and menstruation phases (16, 53-56). These two phases are the most important for endometrial activity. Tabibzadeh (23) has stated that the balance between the grade of TGF-beta activity and LEFT protein expression are essential for endometrial immunomodulating activity. A dispersion of extracellular matrix (ECM) during the mid-secretory phase of the cycle has been observed to be crucial for ovum implantation (57). In cases where fertilization and ovum implantation do not occur, the ECM dispersion intensifies, leading to its degradation by the alteration of TGF-beta/LEFT balance observed during menstruation (24, 25, 58, 59). The mid-secretory cycle phase is also typified by mononuclear cytotoxic cell accumulation within the endometrium (19, 60). It has been shown that the concentration of dNK cells (the NK cell subtype, $CD56^{bright}CD16^{neg}$, phenotype which dominates in the decidua in the late proliferative cycle phase in contrast to peripheral blood NK cells, $CD56^{dim}CD16^{+}$ phenotype) begins during the late proliferative cycle phase just before ovulation and is maintained until the mid-secretory cycle phase when their number reaches the highest level. When implantation does not occur, the number of NK cells drops slightly (13, 19, 20, 61); moreover, the simultaneous infiltration into the decidua by other immune cells has been observed at this time, with the conclusion that a change in the immune dominating profile develops during menstruation (21, 55, 56, 62). The beginning of proper decidualization within the endometrium, which takes place after the termination of the ovum implantation process, is concerned with the following increase in cytotoxic immune cell infiltration (63). The initiation of ovum implantation seems to stimulate simultaneous molecular processes leading to the development of immune tolerance during pregnancy phenomenon (64). This process, which still remains unclear, is responsible for the maintenance of the antigenically foreign fetus developing during the 40 weeks of pregnancy in the maternal uterus (65).

The cellular and molecular processes taking place during the physiological menstrual cycle in the endometrium precede implantation and prepare the endometrium for the development of the immune tolerance phenomenon. The nature of immune tolerance has so far been explained at the maternal-fetal interface, exploring the interactions between placental cells and maternal immune system cells. According to the previous reports, the molecular alterations occurring in this process are not only controlled by placental cells, but also by other fetal cells (66). The fact of fetal cell transmission through the placental barrier, including erythroblasts, lymphoblasts, as well as fetal cell fragments (apoptotic bodies originating from fetal cells) has been known for more than 50 years (67, 68, 69). Apoptotic bodies arising from these cells are also present within maternal peripheral circulation. The expression of the Fas-L antigen on the fetal cell membrane fragments circulating in maternal blood has been shown (67). Fetal cells as well as their fragments (apoptotic bodies), and even free DNA fragments originating from fetal cells undergoing apoptosis, are present in maternal circulation and might participate in the creation of the immune tolerance during pregnancy phenomenon (70-72). Additionally, soluble forms of fetal proteins are present in the maternal blood, i.e., sHLA-DR and sHLA-G, which possess strong immunomodulating activity (73-75). Recently, cytokines originating from fetal monocytes, such as IL-6, have been demonstrated to activate the maternal immune system (66). Therefore, the basis of immune tolerance during pregnancy is not the existence of the impermeable placental barrier masking the fetal presence, but the proper regulation of maternal immune system

activity. The comparison of pregnancy to an allogenic graft as a maternal immune tolerance to fetal antigens, proposed by Medawar remains still up-to-date, but is incomplete (76). The immune tolerance during pregnancy is also closely typified by Clark's proposed comparison of pregnancy to cancer (77-78). This comparison would seem ethically controversial on account of the extremely different effects of the two processes. From the molecular point of view, however, the processes taking place at the maternal-fetal interface and those at the border of cancerous and healthy tissue are similar (132). The basic difference between both mentioned concepts comes from the fact that a grafted organ participates in the regulation of the organ recipient's immune system activity level only extremely rarely. In contrast to what happens with a graft, the cancer cell is an active participant in the process of immune tolerance development, which process enables cancer growth. Regulatory mechanisms are pivotal for neoplasmatic growth and for tumor escape from immune surveillance inasmuch as they restrict immune activity against the cancer (64, 79).

Maternal immune tolerance phenomenon to fetal antigens is connected with both trophoblast and endometrial cell action. The ability of trophoblast cells to remove tryptophane from placental microenvironment –the IDO mechanism--has been observed (80). HLA-G antigens have been identified in the cell membranes of trophoblast cells, and these antigens are responsible for the inhibition of NK cell activity by their interaction with KIR receptors (81). Fas-L expression by trophoblast cells enables the induction of activated lymphocyte apoptosis when these cells have the Fas-receptor on their cell membranes (43). Moreover, the presence of $CD25^{+}CD4^{+}$ regulatory lymphocytes with CTLA-4 antigen (82), which enables the interaction with dendritic cells (with the ligand CD80-CD86), has been demonstrated within the decidua, and the growth of 2,3 IDO expression leading to the restriction of immune cell activity has also been indicated (83). They can also inhibit lymphocytes by IL-10 and TGF-beta (84). An interaction between CD200 antigen and CD200R on other immunocompetent dendritic cells or suppressory lymphocytes Tγσ, leads to the growth of Th2 cytokine secretion and the stimulation of IDO activation in the decidua (78). Maternal immune tolerance to fetal antigens is typified by dynamic, continuous, molecular changes as in Th1/Th2 balance. Pregnancy does not appear to be a simple process of the domination of one type of Th response, because during its normal course, an increase in cytokine levels produced by both types of lymphocytes, Th1 (IL-2, INF-gamma), and Th2 (IL-10, IL-4, TGF-beta) has been observed (79, 85-87).

3.1. Maternal immune tolerance phenomenon during spontaneous abortion

The development of reproductive medicine, especially *in vitro* fertilization, has indicated that the recognition of phenomena occurs in the early stages of immune tolerance. The results of a series of studies have indicated that the main types of maternal immune cells participating in the process of ovum implantation are NK cells and macrophages (19, 60, 89). The immune tolerance during pregnancy phenomenon has also been observed as not a simple process of immune cell activity inhibition (64, 90), but rather a special activation of immune cytotoxic cells (60, 91, 92). Recurrent miscarriages develop when maternal immune cytotoxic activity increases (41, 93-98), but can also be observed when a lack of proper immune cytotoxic activity within the endometrium occurs during the preconceptive period (27, 89). Spontaneous abortion is most commonly caused by embryonic aberration (94), but normal embryo development in itself does not guarantee a successful pregnancy. Spontaneous abortion is accompanied by an increase in the number and activity of immune cytotoxic cells, including NK cells (19, 99, 100), with a decrease of suppressory lymphocyte $CD4^{+}CD25^{high}$ infiltration within the decidua and in the maternal peripheral blood (101, 102). Therefore, spontaneous abortion would seem to result from the disruption of immune system regulation (93, 95, 96). The proper level of cytotoxic immune cell activity within the decidua conditions the peculiar vascularization of the maternal-fetal interface and the normal course of implantation and further pregnancy development (63, 88). In an experimental study of mouse clones deprived of dNK cells, no ovum implantation was observed in most of the cases, while in the cases where ovum implantation did occur, severe placental developmental anomalies were noted. (103). dNK cells are typified by the presence of numerous granules containing mainly granzyme-B and perforines (104). The presence of granules containing perforines has been shown to be significant in dNK recruitment to the decidua (104). Granzyme-B is a direct caspase-3 activator, while perforine participates in NK-mediated cytolysis (105) and is responsible for proper intracellular granzyme-B action. dNK granules contain proteins which are substantial mediators of apoptosis and condition cytotoxic lymphocyte activity (105). Clinically, two phases of abortion can be differentiated, according to the presence or absence of fetal structures within the uterus during abortion: inevitable abortion and complete abortion. A significant increase in the number of CD56+ and CD69 antigen expression during abortion has been shown in comparison to all six phases of menstrual cycle, but only in cases of inevitable abortion. In complete abortion, the number and activity of NK cells were comparable to those in the mid-secretory cycle phase (107, 108). These observations confirm a high preconceptive activity level of NK cells during the physiological menstrual cycle (mid-secretory cycle phase) and the possibility of change in immune cell activity during the development of abortion.

3.2. Selective suppression phenomenon

The activation of cytotoxic lymphocytes during every menstrual cycle phase is enabled by the development of mechanisms protecting adjacent cells against cytotoxic action. Such a phenomenon has been observed by Chao *et al.* (109), in the endometrium during the secretory cycle phase by analyzing CD69, CD25, and HLA-DR antigen expression. CD25 antigen expression is a marker of lymphocyte T activity; CD69 antigen expression indicates the activity of T and NK cells, while HLA-DR may demonstrate T, NK, and macrophage activity (19, 110-112). The increase in the number of $CD69^{+}CD3^{+}$ and HLA-

DR^+CD3^+ lymphocytes during the secretory cycle phase in the endometrium in comparison to the peripheral blood without simultaneous differences in the number of $CD25^+CD3^+$ lymphocytes is defined as a selective suppression phenomenon (109). Analogically, this phenomenon has been observed in TIL in breast, uterine, cervical, and endometrial cancers (113-116). CD25 is a receptor for IL-2 (IL-2Ralpha), a cytokine essential for NK and CTLs activation (117). This phenomenon has also been noted during early pregnancy development by the decrease of CD25 receptor expression on $CD4^+$ and $CD8^+$ lymphocytes within the decidua (19, 109). It seems to result from the partial restriction of cytotoxic immune cell activity by the decrease of CD25 antigen expression with a simultaneous increase of other markers of cytotoxic immune cell activity (CD69 i HLA-DR) (118). Chao *et al.* (118), have observed a decrease in CD25 antigen expression on T $CD4^+CD25^{low}$ cytotoxic lymphocytes throughout pregnancy, while the number of suppressory $CD4^+CD25^{high}$ lymphocytes increased within the decidua (118). The cells that participate in the development of selective lymphocyte suppressory phenomenon include trophoblast (118) and endometrial cells, thanks to their immunomodulating activity. As a result of these phenomena, a higher number of NK cells with restricted activity able to undergo lysis has been observed during the secretory than the proliferative cycle phase (119). During the secretory cycle phase, an alteration in immune cell activity takes place which conditions the success of implantation. In the case of no ovum implantation, the dNK cell activity increases until menstruation and the number of NK cells decreases slightly (13, 119). The restriction of immune cell activity is realized by their selective suppression and seems to result from a complex decidual immunomodulating activity. Qiu *et al.* (45), have indicated that Fas-L expression in the decidua during pregnancy is related to an inhibition of leukocyte infiltration into the decidua. Joswig *et al.* (44), have suggested that the presence of Fas-L expression in the endometrium in the surrounding of the implanting ovum is responsible for the inhibition of activated immune cells. When fertilization and implantation do not occur, the selective suppression phenomenon protects the integrity of the endometrium. At the same time, the number of activated cytotoxic immune cells increases (19, 60, 104), while the suppressive activity of trophoblast cells is replaced by decidual activity. This phenomenon conditions the direction of cytotoxic immune cell action.

3.3. The participation of RCAS1 in the development of selective suppression phenomenon

Many immunomodulating factors may participate in the development of selective suppression phenomenon, including RCAS1. RCAS1 is a membrane protein that inhibits the growth of receptor-expressing immune cells and induces their apoptosis (lymphocytes T and B and NK cells) (120). It has been shown that RCAS1 interaction with the receptor on the effector cell may lead to FADD activation and through the caspases cascade induce effector cell apoptosis (121). RCAS1 can also be expressed in a soluble form, as has been demonstrated in the blood serum derived from women with ovarian, endometrial, and head and neck cancers (122, 123). RCAS1 has been shown to be responsible for tumor cell escape from host immunological surveillance in such cancers as breast, esophageal, gastric, liver, lung, head and neck, uterine, cervical, endometrial, and ovarian (124-131). Nevertheless, since this protein has also been demonstrated in physiological conditions in the placenta, palatine tonsils, bone marrow, and the normal mucosa of the female reproductive tract, it is a poor prognostic factor in cancer (121, 130, 133-140). This protein expression has also been noted in non-neoplasmatic diseases such as immune-mediated diseases of the liver and in the case of nasal polyps (133, 141). RCAS1 seems to be responsible for the creation of immune tolerance during pregnancy (137, 142). The biological role of this protein is probably concerned with the regulation of immune cytotoxic cell activity. The increased apoptosis of lymphocytes--mainly CD3 positive cells--surrounding tumor RCAS1 positive cells and RCAS1 positive metastatic tumor cells in lymph nodes has been observed in uterine and cervical cancers (126). Such a relation between immune cell apoptosis and Fas-L and TNF-alpha expression has not been confirmed by this study. Similarly, in other reports, RCAS1 expression in tumors has been accompanied by an increased apoptosis of TIL in lung cancer (130), and also apoptotic lymphocytes have been identified adjacent to RCAS1-positive RS cells in Hodgkin's disease (135). Sonoda *et al.* (122), have demonstrated an inverse correlation between the presence of soluble RCAS1 in the blood serum and the number of peripheral blood cytotoxic lymphocytes. Similary, an inverse correlation has been observed between RCAS1 expression and the number of TIL (mainly CD3 positive cells) in breast (143) and esophageal cancer (125).

Recently, the participation of RCAS1 in the apoptosis of CD4 positive lymphocytes derived from HIV positive patients has been shown (144). The presence of RCAS1 in normal endometrium and tubal mucosa has been also demonstrated (140). The expression of RCAS1 has been observed to alter in accordance with menstrual cycle changes, growing with the increasing number of CD56 positive cytotoxic lymphocytes during the secretory cycle phase (106). By contrast, in endometrial cancer, RCAS1 overexpression has been accompanied by a drop in CD56 positive lymphocytes in the endometrium (106). The number of these cells has been significantly lower in endometrial cancer than in the endometrium during the secretory cycle phase. Nakashima *et al.* (120), have shown that RCAS1 may lead not only to cytotoxic lymphocyte apoptosis, but also inhibits the growth and restricts the activity of these cells. In physiological conditions, other than cancer, however, RCAS1 action seems mainly to be involved in the restriction of cytotoxic immune cell growth rather than in inducing apoptosis. In recent studies, it has been shown that the increase in the number of immune cells (mainly CD56 positive cells) is related to a concomitant increase in RCAS1 expression that starts in the endometrium during the periovulatory cycle phase (late proliferative and early secretory) (139). RCAS1 immunoreactivity has been analyzed with the simultaneous expression of CD69 and CD25 antigens, and it has been suggested that it participates in the selective cytotoxic

immune cell suppression phenomenon. This phenomenon indicates the proper compensation by the endometrium with regard to cytotoxic activity increase during fertilization and ovum implantation. The existence of this mechanism enables the accumulation of activated immune cytotoxic cells in selected regions.

Besides the selective suppression of immune cells, the compensation of growing cytotoxic activity in the endometrium is realized by the protection of endometrial cells from immune-mediated apoptosis through the disturbance of apoptotic signal transduction. This endometrial ability has been named resistance to immune-mediated apoptosis (145-146).

3.4. Resistance to apoptosis

Apoptosis, a phenomenon presented by Kerry in 1972, is one of the basic mechanisms that regulates the number of cells and enables changes in their activity (the interaction between immune cells and somatic cells) (147). The alterations of apoptotic levels in the endometrium corresponding to menstrual cycle changes and the layers of the endometrium have been observed. The presence of apoptosis, mainly in the superficial layer of the endometrium, has been noted during the proliferative and secretory cycle phases, while apoptosis occurring in the basal layer has been observed during menstruation. Apoptosis is more prominent during the secretory cycle phase than the proliferative; its level increases insignificantly during menstruation (55, 148). The disturbance of apoptosis leads, on the one hand, to an inability of apoptotic signal transduction, as bcl-2 level changes, and on the other hand, to an inability to receive such a signal (changes of membrane Fas expression) (149). The distribution of cells demonstrating the apoptotic changes within the endometrium does not correlate with the decrease of Bcl-2 level (148); additionally, the Fas membrane expression in the endometrium has not been seen to increase with the increase of the apoptosis level (148). Watanabe *et al.* (149), have therefore suggested that endometrial cell apoptosis may not depend on the expression of these two apoptosis markers. Tabibzadeh has demonstrated that TNF-alpha is the main apoptosis mediator in the endometrium during menstruation (149). The initiation of apoptosis seems to result from the activity of various factors. In the final stage of this process, DNA fragmentation related to the level of DNA-nuclease (DFF40) activity can be observed (150). The activation of this enzyme is processed by the fragmentation of DFF45/DFF40 complex by caspase-3. Caspase-3 has to be activated by caspase-8, which active form originates from the stimulation of DISC or cytochrome C originating from mitochondria (152). The cellular amount of DFF-45 correlates with the DFF-40 level (153) and the alterations in DFF-45 nuclear expression have been observed as participating in the process of resistance to apoptosis (133). DFF-45 expression in the endometrium during the secretory cycle phase has been observed to be higher than during the proliferative cycle phase (154). The proper intracellular Zn^{++} ions concentration is necessary for the caspase cascade enzyme activity, which seems to be especially important for caspase-3 function. The decrease of intracellular Zn^{++} ion concentration leads to the growth of caspase-3 activity (152, 156). Parry *et al.* (157), have shown that Zn^{++} ions inhibit caspase-3 activity. Intracellular Zn^{++} distribution is particularly controlled by metallothionein (MT) (158).

3.5. MT anti-apoptotic activity

Metallothionein is a cystein-rich protein that participates in the regulation of processes important for both cell proliferation and death (159-162). The connection between the increase of cytoplasmic MT expression and the decrease of caspase-3 activation has been observed. The MT cytoplasmic increase is also accompanied by a decrease in mitochondrial originating cytochrome C level (163). Two metallothionein isophormes, MT-1 and MT-2, are ubiquitous in humans (164, 165). MT expression is regulated by hormones, cytokines, and stress-induced factors (such as heavy metals) (166, 167). Following cytokine influence, is the MT expression: IL-1 (163), IL-6 (168), TNF-alpha (169) i INF-gamma (170). MT is an important potential factor responsible for the sensitivity of cells to induced apoptosis; it is an inhibitor of apoptosis (161, 171). An increase in the spontaneous apoptosis level has been observed in mouse fetal cells deprived of MT-1 and MT-2 isophorme genes (172). Kondo *et al.* (169), have suggested that MT anti-apoptotic activity may complete Bcl-2 function. In MCF-7 breast cancer cells a decrease in MT resulted in the spontaneous apoptosis of these cells (173). It has also been suggested that MT protects cells against p-53-dependent apoptosis (174). Cui *et al.* (160), have shown a bilateral regulation between MT-1 and ECRG2. The ECRG2 gene expression product is responsible for the inhibition of the proliferation and induction of apoptosis, while MT intensifies proliferation and restricts apoptosis (160). MT seems to participate in the modulation of the intracellular signal that develops after the activation of TNFR-1 and activation of cytoplasmatic death domains (175, 176). MT participates in the interaction between immune cells and tumor cells (177). Young *et al.* (177), have shown that MT decreases immune cell cytolytic activity and seems therefore to participate in the suppression of the cytotoxic immune response. The intracellular MT expression seems to be responsible for protection against cytotoxicity, while nuclear expression seems to protect against genotoxicity (174, 178). The ability of endometrial cells to be resistant to apoptosis is realized by the intracellular MT level alterations. MT expression has been observed to alter in accordance with the menstrual cycle phases, its highest level being noted during the mid-secretory cycle phase (179). MT endometrial expression growth has been accompanied by an increase in CD56 positive cell infiltration and in the activity of such cells (106). The presence of MT in the endometrium and its increasing level during the beginning of decidualization indicates the participation of this protein in the process of compensation of the growing cytotoxic immune infiltration.

In sum, the ability of the endometrium to compensate for the growing immune cytotoxic response during reproductive processes in early pregnancy is realized by the development of resistance to apoptosis and

the phenomenon of selective immune suppression. The participation of these processes in the development of Fallopian tube pregnancy seems to be significant.

4. ALTERATIONS IN IMMUNE TOLERANCE PROCESS DURING TUBAL RUPTURE

An evaluation of the course of immune tolerance during ectopic pregnancy along with an explanation of the role of the endometrium in this process is interesting in light of ovum implantation and fetal development. Tubal rupture is an example of the sudden termination of the immune tolerance process during pregnancy. Exploring the mechanisms responsible for the interaction between immune cells, tubal mucosal cells, and ectopic localized trophoblast cells might be useful in finding a marker for tubal rupture. The occurrence of ectopic pregnancy rates is 18 cases per 1,000 pregnancies with the most frequent cases--80%--involving tubal localization. Tubal surgery, *in vitro* fertilization, and inflammation of the reproductive tract increase the risk of ectopic pregnancy twofold (181-184). The reason for extra-uterine ovum implantation still remains unclear. It has been suggested that the ectopic localization of pregnancy is the result of a disturbance in the embryo's chemotactic process or, alternatively, an abnormal uterine peristaltic wave. The diagnosis of an ectopic pregnancy is problematic, and early diagnosis is the most important factor in the patient's future fertility and for the success of treatment. Unfortunately, ectopic pregnancy still remains a chief cause of maternal death during pregnancy (183), and for this reason, markers of extra-uterine pregnancy progression, for example, CA-125 markers and cytokines, such as IL-8, are sought; however, these markers have no established clinical application (185, 186). Additionally, the risk of tubal rupture has not been correlated with chorionic gonadotropin (beta-HCG) serum levels in women with ectopic pregnancies (187-189).

4.1. The characterization of the immune system associated with Fallopian tube mucosa

The tubal mucosa constitutes a component of the immune system associated with the reproductive tract mucosa, which is in turn a component of MALT and has been defined as a tertiary immune system (11). The indirect proof of the functional aspect of the reproductive tract mucosa associated lymphatic tissue is the quantitative and qualitative changes observed within the immune cell population in the endometrium concomitant with pathologic processes taking place in tubal mucosa, as in the case of tubal hydrops and recovery following surgery for tubal hydrops (190). Mononuclear immune cells predominate within the tubal mucosa, with numerous T CD3 positive cells (191-194), macrophages, and neutrophilic granulocytes (195); however, NK cells are not as common as they are in the endometrium, and lymphatic follicules are rarely found (194).

4.2. Immunological basis for tubal rupture

The observation of fetal heart-rate in ectopic pregnancy indicates that a normal embryo can be implanted in the case of an ectopic pregnancy (196). In Proll's study, HLA-G expression on external cytotrophoblast cells has been on a level comparable to that found in the uterus and in the uterine tube during implantation (197). Recently, the presence of apoptotic bodies and free fetal DNA in patients with extra-uterine pregnancy serum has been discovered (198), and this phenomenon is one that has been described in normal uterine pregnancy (70-72). During trophoblast invasion within the uterine tube wall, a decrease of trophoblast cell apoptosis has been noted in comparison to trophoblast invasion within the uterine cavity (199). Increased trophoblast invasiveness has been identified as a factor determining the process of perforation (199). If a normal embryo is able to be implanted in an extra-uterine location, the difference in trophoblast invasiveness may result from the altered properties of the adjacent environment. The number and quality of immune cells within the tubal mucosa during embryo implantation differs from those within the endometrium (199, 200). On the one hand, the research of Von Rango and Vassiliadou has indicated that the environment of the implanting embryo in the tubal mucosa is infiltrated predominantly by $CD3^+$ positive cells and macrophages, with a complete lack of dNK ($CD56^+CD16^-$) cells and sporadic presence of NK ($CD56^+CD16^+$) cells, in contrast to the endometrium with predominant dNK cell infiltration (60, 196). On the other hand, Stewart-Akers has shown that during the ovum implantation in the uterine tube, both $CD3^+$ and $CD56^+$ positive cells have been observed at a level comparable to that found in the uterine cavity decidua (201). The discrepancy in these two studies may have resulted from the different stages of advancement of pregnancy in the ectopic pregnancies analyzed. The increase in interleukin-8 (IL-8) blood serum in women with ectopic pregnancies indicates the possibility of the participation of this cytokine in the chemotaxy of lymphocytes infiltrating the tubal wall during the development of pregnancy (186). $CD56^+CD16^+$ cells are sensitive to chemotactic Il-8 action (202). Il-8 concentration was observed to increase significantly in the blood serum when fluid accumulated in the pouch of Douglas during ectopic pregnancy, although IL-8 concentration remained independent of tubal diameter (hematosalpinx) (186). It has been shown that tubal rupture is associated with an increase in cytotoxic immune cell infiltration ($CD56^+$) (108, 155). The number of cytotoxic immune cells within the tubal wall has been found to be significantly higher in cases where the tubal wall perforation was confirmed during surgery in comparison to cases where the surgery preceded tubal perforation. Similarly, tubal rupture has been accompanied by an increase in the activity of immune cells. Because the immunomodulating activity of decidual cells determines the activity of immune cells infiltrating the decidua, the evaluation of the immunoregulative activity of the tubal mucosa has to be performed (especially the evaluation of compensation of the increasing cytotoxic immune activity).

The increase in immune cell infiltration in unruptured EP with hemorrhage in comparison with that of unruptured EP without bleeding has been associated with an increase in RCAS1 immunoreactivity level. The next stage of tubal rupture accompanied by further infiltration of immune cells has apparently not been compensated for by a further increase in RCAS1 immunoreactivity level. At the

same time, the RCAS1 level in the endometrium during unruptured EPs has statistically been significantly higher than in the tubal wall. In ruptured EPs, no such differences have been observed. In sum, the drop in RCAS1 level, which could be a result of an insufficiency in the compensatory immune response mechanisms (selective suppression phenomenon) in the tubal mucosa (although these mechanisms are simultaneously preserved in the endometrium), leads to tubal perforation (Figure 1.). In our recent study, higher numbers of CD56 and CD69 positive lymphocytes in the tubal wall during tubal rupture have not been associated with a sufficient increase in MT expression (just as in spontaneous abortion) (180). However, an increase in MT expression and in the number of CD3 positive cells in the initial stages of tubal rupture has been observed; also observed was further infiltration of immune cells in the later stages of tubal rupture accompanied by a decrease in MT immunoreactivity level. At the same time, the immune cell infiltration in the endometrium increased with a concomitant increase in MT immunoreactivity level. If the infiltration decreased, so did the MT immunoreactivity level. Thus, while compensatory mechanisms are active in the endometrium, they seem to be disturbed in the tubal mucosa (155).

Tubal perforation seems to be linked to a concentration of immune cells in the tubal mucosa and an increase in their activity without a corresponding increase in the level of proteins compensating for immune cell response.

Tubal perforation suddenly ends the development of Fallopian tube pregnancy; similarly, placental abruption is related to the sudden termination of intra-uterine gestation. A comparison of these mechanisms is intriguing.

5. PLACENTAL ABRUPTION

5.1. Changes in immune tolerance level during labor

Labor is a complex molecular and clinical process; to enable its proper course the sequence of events must be preserved. The occurrence of regular uterine contractions accompanies cervical ripening while expulsive contractions should occur at the termination of cervical ripening. Placental abruption appears subsequent to fetal expulsion and is accompanied by uterine tonic contractions, as observed in clinic. Each clinically observed phenomenon has its own molecular basis, and the sequence of phenomena is also precisely determined. The stages of labor that can be observed in clinic are accompanied by immunological alterations. Physiological changes in the immune tolerance process are observed during each stage of labor. An increase in lymphocyte activity during labor was demonstrated in the 1980s by Szekeres-Bartho *et al.* (203). Abadia-Molina *et al.* (204) have observed the presence of lymphocytes with a prominent expression of antigens, such as$CD25^+$, $CD69^+$, and HLA-DR, showing their activity, in the decidua basalis during labor at term. The expression of CD25, CD69, and HLA-DR, as well as the presence of dNK($CD56^+CD16^-$) and classical NK cells ($CD56^+CD16^+$), has been shown in the decidua basalis and in decidua parietalis during labor at term in elective cesarean section (without the spontaneous initiation of labor) by Sindram-Trujillo *et al.* (206, 207). The number of dNK cells has been observed to be higher in the decidua parietalis than in the decidua basalis, while the number of NK cells has been found to be higher in the decidua basalis than in the decidua parietalis (207, 208). Also, an increase in the number of T-lymphocytes and $CD16^+$ cells (209), CTLs (210), T-lymphocytes (CD3), and NK/K (Leu7) (211) has been noted in the reproductive tract during labor at term. The number of dNK cells in the decidua following the spontaneous initiation of labor has statistically been shown to be significantly higher than following cesarean section (206). The changes in the lymphocytes infiltrating profile have been discovered mainly in peripheral NK cells (206-208). One of the most important mechanisms responsible for immune tolerance during pregnancy phenomenon is $HLA\text{-}G_1$ expression by trophoblasts, cytotrophoblasts, and syncytotrophoblasts, which is restricted during labor (74,212), resulting in an increase in maternal cytotoxicity level (100, 213, 214). It has been demonstrated that the number of $CD4^+CD25^{high}$ suppressory lymphocytes in the decidua during vaginal labor decreases (207, 208).

An increase in the IL-6 level in the amniotic fluid during labor at term (cytokine mediating in the immune system activity during labor; responsible for the inhibition of $CD4^+CD25^{high}$ regulatory suppressory lymphocytes and IDO positive dendritic cells) has also been demonstrated (84, 215). Spontaneous labor has been accompanied by an increase in leukocyte blood serum level and a corresponding decrease in lymphocyte level (216). This may indicate that the initiation and course of labor is controlled by peripheral lymphocytes, passaging and infiltrating the decidua. The presence of adhesive molecules, the expression of which has been identified within the entire uterus, has been related to leukocyte transition into the uterine cervix and myometrium (ICAM-1, VCAM, PECAM) (217). The expression of adhesive molecules has been shown to increase throughout the entire course of pregnancy until the beginning of labor (217, 218). Thomson *et al.* (218), have noted the infiltration of leukocytes ($CD3^+$lymphocytes, macrophages, and neutrophilic cells) into the upper and lower uterine regions during the spontaneous initiation of vaginal labor. Winkler *et al.* (219), have confirmed this observation, analyzing the number of leukocytes in the lower region of the uterus. Osman *et al.* (220), have not discovered any changes in the number of macrophages and neutrophilic cells in the decidua after the initiation of spontaneous labor. The immune cells infiltrating the decidua are a source of various cytokines, such as IL-1β, IL-6, IL-8, and TNF-alpha (221), but these cytokines may also originate from the decidua itself (220). The activation of fetal APC, including mainly macrophages and the concentration of IL-6 within umbilical blood, also accompany labor at term. IL-6 concentration may originate from activated fetal monocytes (66).

Fetal cytotoxic response deficit, which results from an immature fetal immune system, in the case of exposure to maternal antigens that are able to transit

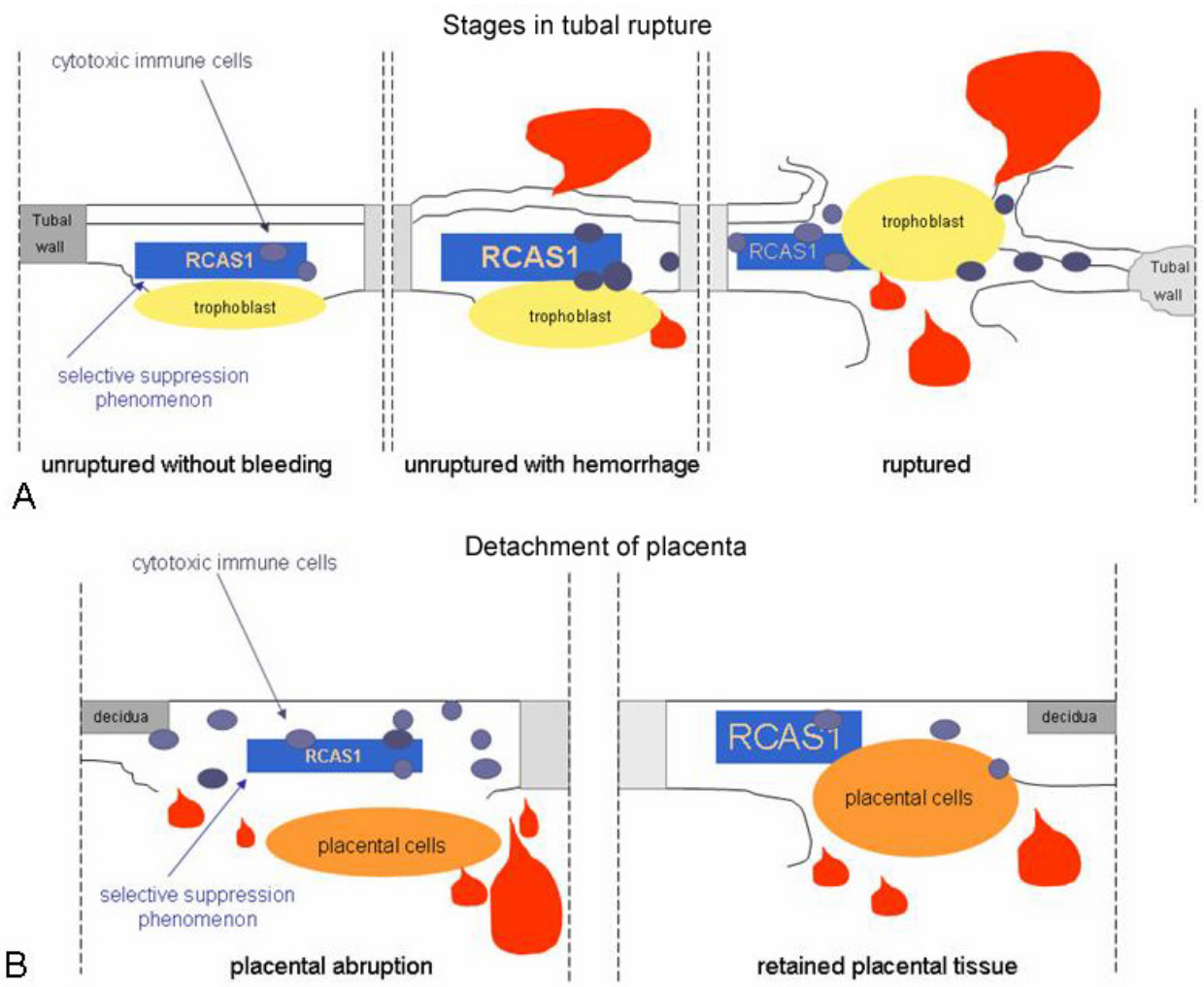

Figure 1. The participation of RCAS1 in the development of selective suppression phenomenon during tubla rupture (A) and placental abruption (B).

through the placental barrier, leads to an increase in fetal macrophage activity (66). Common maternal-fetal activation of the maternal immune system initiating the labor may also take its course in the above mentioned way. The process of cervical ripening is also an event of maternal reproductive system adaptation to labor. The disintegration of collagen results from an increase in the activity of MMPs that are secreted by neutrophilic cells and macrophages infiltrating the lower region of reproductive tract (219, 222). Winkler *et al.* (219), have analyzed the number of macrophages and neutrophilic cells in the uterine cervix and has noted that a sudden increase in their number accompanies cervical ripening to 2cm and lasts until 4cm; similar changes in IL-6 and MMPs concentration have been observed. Contrary to these findings, the concentration of factors inhibiting metalloproteinases (TIMP-1) begins to increase when the uterine cervical ripening reaches 4cm and 6 hours after the beginning of the labor (223).

IL-8 is the basic chemotactic factor for macrophages and neutrophils (219). Osmer *et al.* (224), have analyzed the bioptates--derived from the inferior part of the uterus and decidua--obtained during cesarean sections performed with unripe cervix and has found that IL-8 concentration appears in the decidua earlier than in the uterine cervix. IL-8 is responsible for NK chemotaxy and the most sensitive cells for this cytokine are NK cells (202). Sportiz *et al.* (225), have shown that the dNK decidual decrease observed during the third trimester of pregnancy might result from the degranulation of these cells, and Sidram-Truillo *et al.* (206), have observed that cells infiltrating the decidua during labor were mainly peripheral NK cells. The alterations taking place at the maternal-fetal interface seem to precede the occurence of phenomena in the uterine cervix. Elective cesarean section is a surgical procedure performed without the symptoms of the spontaneous initiation of labor when the mechanisms responsible for the beginning of labor and its further course have not yet begun. The performance of cesarean section

after the spontaneous beginning of labor means that the molecular processes have been initiated and are being broken. The observed prominent placental RCAS1 decrease during cesarean section when performed with a ripe cervix and with dilation above 2cm seems to confirm this finding (226). Steinborn *et al.* (66), have revealed that during induced labor and elective cesarean section, the activation of the fetal immune system, which is an important element of the mechanism initiating spontaneous labor, has not been observed. Balakundi *et al.* (13,109), have observed spontaneous vaginal labor to be preceded by a reduction in Fas-L expression of placental cells (227), while Pongcharoen *et al.* (43), have shown a lower level of Fas-L expression in the placenta at term in comparison to early pregnancy. Moreover, Hackmon *et al.* (212), have noted a HLA-G placental expression decrease during spontaneous vaginal labor. Finally, a decrease in RCAS1 placental expression has been observed in spontaneous labor in comparison to induced labor (228). The above presented mechanisms responsible for the activity of the immune system and gradual alterations of maternal immune tolerance during labor seem to affect the course of placental abruption.

5.2. Molecular processes during placental abruption

Placental abruption complicates 1% of pregnancies (229, 230). The etiology of this complication is still unknown (229, 231); however, the risk factors have been identified and include: repeated fetal loss, previous stillbirths, preeclampsia, intra-uterine growth restriction, maternal age, multiple pregnancy, prior placental abruption (232, 233), pre-term premature rupture of membranes (234), and previous cesarean section (235). All the presented epidemiological risk factors for pre-term placental abruption seem to be related to the regulation of maternal immune system activity. Ananth has suggested that pre-term placental abruption is a chronic process (229). Increased risk of placental abruption has been observed to be accompanied by an increased infiltration of macrophages and neutrophilic cells in the uterus (229). The disruption of proper immune control of activated NK and T cells may result in pre-term placental abruption. A significant decrease of sHLA-DR in maternal serum has been observed (74). A soluble form of HLA-G1 is responsible for the induction of lymphocyte apoptosis through the activation of the Fas/Fas-L pathway (236). Placental abruption has also been accompanied by a decrease in sHLA-DR concentration in the maternal blood serum (73). Moreover, an increase in the maternal humoral response in blood serum (the increase in the level of antibodies against paternal HLA which is present in fetal cells) during placental abruption has been observed (75). RCAS1 placental expression has statistically been shown to be significantly higher in cases with retained placental tissue than in patients with placental abruption (138). In patients with retained placental tissue in the third stage of the labor, RCAS1 placental expression has been observed to be at a level comparable to that observed in induced labor, while during placental ablation, it has been determined to be at a level comparable to that observed during spontaneous labor (138). These findings seem to confirm the hypothesis that placental ablation occurs when molecular changes at the maternal fetal interface are terminated without an accompanying termination of uterine cervical ripening. Analogically, if the molecular changes at the maternal fetal interface responsible for placental ablation are not terminated while accompanying processes of uterine cervical ripening are fully underway, retained placental tissue during the third stage of labor occurs (138).

The presented results would seem to indicate that the deregulation of local mechanisms controlling the immune tolerance might induce placental ablation. The course of this process is regulated by the concentration of mediators originating from the maternal immune system, the placenta, the fetal immune system, and the decidua. Recently, placental abruption has been shown to result from a high maternal cytotoxic response level associated with the restriction of suppressory decidual activity. RCAS1 immunoreactivity has been statistically significantly higher in decidual tissue samples derived from patients with retained placental tissue than in those derived from patients who suffered from placental abruption. An increase of RCAS1 decidual immunoreactivity has been shown to be associated with a lower number of CD56+ and CD3+ cells (237) (Figure 1). The selective immune suppression process accompanies pregnancy and in placental abruption seems to be suppressed precociously. In the case of retained placental tissue during the third stage of labor, an opposite phenomenon has been observed in the decidua, namely, restriction of the infiltration of activated immune cells and increasing suppressory activity of decidual cells. The selective immune suppression process is continued independently of newborn expulsion. The proper course of labor seems to proceed through successive diminishment of the level of immune tolerance. The phasic course of labor, from its initiation to newborn expulsion, is typified by clinical manifestations based on molecular alterations. The decrease of immune tolerance level results from, amongst other factors, a diminishment of suppressory placental action, the unblocking of active lymphocytes prepared by the mother throughout the pregnancy, and the alteration of decidual compensatory mechanism activity.

6. SUMMARY AND PERSPECTIVES

The activation of immune cells during spontaneous labor indicates the existence of mechanisms responsible for the regulation of immune tolerance level during pregnancy. This activation probably results from molecular changes not only in the placenta, but also in the endometrium. Because the tubal epithelium does not demonstrate the same unique immunomodulating properties as the endometrium, ovum implantation within the tubal wall leads to tubal rupture. While on the one hand, tubal rupture demonstrates the activity of mononuclear cell extension, on the other hand it highlights the unique properties of the endometrium. Analogical activity of immune cells in the endometrium during spontaneous labor and spontaneous abortion does not lead to the same consequences as in the Fallopian tube. However, a similar level of immune cell activity in the endometrium in cases with concomitant deregulation of immunomodulatory mechanisms leads to placental abruption. The determination of mechanisms responsible for the changes

in immune tolerance might help with the development of the immunotherapy in high-risk pregnancies. Immunotherapy could resolve the problems related to pre-term labor and complications of vaginal delivery and cesarean section. Since trophoblast cells use the same molecular mechanisms as cancer cells, the evaluation of the immunological background of normal labor could help to improve the efficacy of cancer immunotherapy.

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Abbreviations: Receptor- binding cancer antigen expressed on SiSo cells (RCAS1), metallothionein (MT), human leukocyte antigen (HLA), transforming growth factor (TGF), interleukin (IL), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), matrix metalloproteases (MMP), leukemia inhibitory factor (LIF), interferon (INF), tumor necrosis factor (TNF), death-inducing signal complex (DISC), Reed-Sternberg (RS), tissue inhibitor of metalloproteinase-1 (TIMP-1), anitgen presenting cells (APC), extracellular matrix (ECM), mRNA transcripts encoding regulated upon activation, normal T-cell-expressed and –secreted (RANTES), Indoleamine 2,3 dioxygenase (IDO), MALT (membrane associated lymphoid tissue).

Key Words: Endometrium, Immune Tolerance, Placental Abruption, Tubal Rupture, Spontaneous Labor, Review

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