molecules expressed on the membrane of trophoblast cells were able to increase IL-10 production by uterine T cells during pregnancy. Both IL-4 and IL-10 could inhibit the development and function of Th1 cells and macrophages, thus preventing the fetoallograft rejection. Th17 cells, which produce IL-17, represents a new additional effector CD4+ T cells besides the Th1 and Th2 cells, described as Th1 to mediate immunological rejection. This cell subset is present in the decidua of suffering from unexplained recurrent abortion and women with successful pregnancy. The production of IL-17 seems to be under the control of a factor present in the uterine microenvironment.

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Galectin-1: a lectin with immunomodulatory functions during pregnancy

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Miscarriages are the most common form of pregnancy failure in humans. In general, genetic, endocrinologic, immunologic, anatomic or microbiologic causes have been listed to account for the onset of a miscarriage. Blastocyst implantation and the perpetuation of pregnancy depend on a coordinated adaptation of the immune and endocrine systems. Galectin-1 (Gal-1), a member of a conserved family of β-galactoside-binding animal lectins, can modulate the immune responses. In particular, Gal-1 has powerful immunoregulatory effects in vivo due to an apoptotic activity on activated $CD8^+$ T cells, Th1 and Th17 $CD4^+$ cells. In an established murine model, abortions can be triggered by exposing the mice to stress during early gestation. Recent data from this model indicated that uterine Gal-1 expression is down-regulated in challenged murine pregnancies. Consistently, Gal-1−/− mice exhibited increased fetal rejection rates compared to wild-type mice, even in undisturbed pregnancies. Treatment with recombinant Gal-1 prevented fetal rejections and restored multiple tolerance mechanisms; including expansion of regulatory T cells in vivo, up-regulation of Th2 cytokines and activation of negative inflammatory pathways (i.e., TGF-β1 and Stat-3). This study also led to the identification of a subset of $CD11c^+$ uterine DC with a Gal-1^{bright}, CD80/86^{low}, IL-10^{high} phenotype potentially involved in immunoregulatory processes during gestation. Finally, we provide evidence for a functional cross-talk between Gal-1 and the LH/progesterone axis in the maintenance of pregnancy. Interestingly, data from a prospective study on human pregnancy revealed that women with a clinically normally progressing pregnancy but low levels of Gal-1 during the first trimester eventually suffered from a miscarriage. These data indicate a novel role for Gal-1 as a pivotal and upstream messenger in the maintenance of fetomaternal tolerance and identifies a novel therapeutic target aimed at restoring immune tolerance in threatened pregnancies. Gal-1 may constitute a useful marker to identify a putative thread to pregnancy progression in humans.

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Neuroendocrine mechanisms underlying stress-induced imbalance in pregnancy cytokines and pregnancy failure

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For some time it has been recognised that stress increases the risk of pregnancy failure, but the neuroendocrine mechanisms linking stress perception by the brain and the peripheral mediators which precipitate embryo loss are unknown. Stress has acute and prolonged effects on many hormones; two key systems affected are the hypothalamo-pituitary-adrenal axis (resulting in glucocorticoid secretion), and the gonadotrophins. Peripheral factors that have been identified include reduced progesterone secretion and Th1:Th2 cytokine imbalance, which are co-dependent, and furthermore are influenced by both glucocorticoids and gonadotrophins. We have investigated the effects of stress on secretion of such hormones in early pregnancy in mice, including in the DBAxCBA pregnancy failure mouse model. Stress strongly increases glucocorticoid secretion similarly in virgin and pregnant mice and, since glucocorticoids are anti-inflammatory, may play a protective role, particularly peri-implantation. However, the gonadotrophins are differentially responsive. We have focussed on prolactin, which is a cytokine-like neuroendocrine signal in early pregnancy. Prolactin drives progesterone secretion in rodents but, importantly, it also independently modulates implantation and is a medi-

ator of the immunoneuroendocrine network in both rodents and women. Also, low serum prolactin correlates with miscarriage in women. Various stressors acutely and robustly inhibit prolactin secretion in the peri-implantation period and we have shown that this is due to augmentation of the main prolactin inhibitor, dopamine; responses are even more exaggerated in the DBAxCBA model. This is expected to acutely reduce progesterone secretion but may also have a more prolonged effect. Since stress also increases Th1 pro-inflammatory cytokines, especially in pregnancy, we predict that they bind to dopamine neurones to adversely interact with prolactin-feedback and therefore prolong the enhanced dopamine responses and increase the risk of pregnancy failure. This may explain why women or animals with elevated pro-inflammatory cytokine load may be more susceptible to stress-induced pregnancy failure.

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The cord as a source of stem cell therapies

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The 20th anniversary of the first use of umbilical cord blood (UCB) as a source of donor cells for haematopoietic stem cell transplantation was celebrated in 2008. Transplantation with UCB is effective in the treatment of children with hematological malignancies, marrow failure, immunodeficiencies, hemoglobinopathies and inherited metabolic diseases. Yet, today, cord blood is donated and banked for unrelated-donor transplantation on a routine basis. There are more than 400,000 units banked in inventory in more than 100 unrelated-donor banks, facilitating more than 14,000 unrelated-donor cord blood transplants worldwide (Kurtberg, 2009). On the other site, umbilical cord is a rich cell source for mesenchymal stem cells (derived from Wharton Jelly) and vascular/endothelial cells (derived from cord vein). The study of MSC trafficking is clinically relevant for minimally invasive cell therapy to promote regeneration of damaged tissue, to treat inflammation, and to promote angiogenesis. A promising approach in the tissue engineering field might be the cellularisation of tissue scaffolds using in vitro repopulation with cord derived MSCs coupled with physically appropriate conditioning prior to implantation. Therefore, in future the basic principle will be seeding of cells onto a matrix scaffold and use of physically interactive bioreactors for the functional differentiation of MSCs with 3-dimensional scaffolds in vitro (Karp et al., 2009). Given the systemic nature of many diseases and the desire to have minimally invasive therapies, systemic infusion of MSCs that can promote tissue regeneration and immunosuppressive effects represents an attractive therapeutic approach. The number of potential therapeutic applications and their efficiency and efficacy will continue to grow as the fundamental biology that is responsible for the MSC regenerative properties and homing responses continues to be elucidated.

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L39

Fetal somatic progenitor cells: future of clinical application

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There are several types of stem cells (SCs): intranatal SCs, i.e. embryonic (from blastocyst) and fetal; postnatal SC, i.e. somatic (obtained from cord blood, placenta), and adult mesenchymal (from bone marrow, adipose tissues). A lot of regenerative effects of stem and progenitor cells were shown in animal models and experiments. Regenerative cell therapy implies variously derived SCs: autologous and allogenic. The correct choice of the cells source is the guarantee of our success in clinical applications. Application of autologous SCs allows to avoid immune conflict but the effect of these cells is limited due to the phenomenon of self SC aging, limited plasticity of cells, hidden genetic and functional defects. Allogenic fetus-derived SCs seem to be of most interest for basic research, current biotechnologies and clinical application based on the maximum plasticity, high