ABSTRACTS

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Establishment and maintenance of pregnancy are the result of a balanced interaction of hormones, immune cells, paracrine and autocrine factors, and both the maternal and the fetal part contribute to the success. In the bitch, progesterone (P₄) is essential for the establishment and maintenance of pregnancy (1). Progesterone has been found to promote the endometrial synthesis of the cytokine leukemia inhibitory factor (LIF; 2), which together with the presence of its receptor on the surface of trophoblast cells is considered to be important for trophoblast growth and differentiation, and for a shift towards the intrauterine predominance of T helper (Th) 2 cells (3). Recently we investigated the relative expression of P₄ receptor (PR) and LIF in uterine tissues from early pregnant bitches by means of quantitative RT-PCR. Hypothesis was that a relation exists between the biological effect of P₄ after its binding to the receptor and the uterine change in LIF expression, as has been described in primates. We assessed a significant decrease in the relative uterine expression of PR mRNA from day 10 (preimplantation) to day 30 (placentation, p<0.01). However, at the same time, the relative expression of LIF mRNA increased until placentation (p<0.05; own unpublished results). In addition, from the phase of embryo invasion until placentation, PR was no longer detectable in the fallopian tube. We therefore suppose, that LIF participates essentially in the establishment of canine pregnancy and that a direct or indirect effect of receptor bound P₄ on the uterine expression of LIF exists. In addition, the effect of P₄ on the intrauterine activity of enzymes as well as the paracrine secretion of cytokines and other factors has to be elucidated. In a former study we found, that before and during implantation, the average activity of matrixmetalloproteinase (MMP) -2 was significantly higher in serum of pregnant bitches than in serum of non-pregnant animals (4). In the same study, a positive correlation between MMP-2 and -9 activity and serum P₄ concentrations was observed, suggesting a regulating effect of P₄ on enzyme activity. However, later on we detected a down regulation of PR towards placentation and in non-pregnant bitches, a negative correlation between serum P₄ concentrations and endometrial PR was detectable (5). Since serum P₄ concentrations do not differ significantly between pregnant and non-pregnant animals, it must be questioned, whether the down-regulation of PR during implantation and placentation is a regulatory signal for MMP activity. It seems more probable, that factors secreted by the preimplantation embryos participate in the regulation of protease activity. In humans, trophoblast secreted interleukin (IL) -6 is known to activate MMP-2 and -9. Recently, beside other factors, we found mRNA of IL-6 and MMP-2,-9 in preimplantation canine embryos (6). We additionally assessed significantly higher MMP-2 activity in the endometrium and myometrium of pregnant bitches than in non-pregnant animals which is important for trophoblast invasion (7). However, collagenase activity is probably regulated by additional inhibitory substances. During human in vitro studies, decidual natural killer cell derived IFN-γ was found to regulate trophoblast invasion by decreasing MMP-2 activity (8). We recently detected IFN-γ in the preimplantation uterus and at placentation sites (6; own unpublished results). Despite a probable protease regulatory function, IFN-γ could support embryo survival by its known anti-proliferative effect as well as by regulating gestational endometrial angiogenesis (9). IFN-γ is also known to increase the expression of surface molecules such as major histocompatibility complex (MHC) -I and –II (10). In dogs, MHC I is supposed to serve as a receptor for cytotoxic T lymphocytes (11). In a recent study we assessed that the relative expression of MHC-I mRNA did not change significantly from the preimplantation to the placentation stage, however, the relative expression of MHC-II mRNA increased significantly (p<0.05; own unpublished results), which might be a reaction to endometrial contact with...
fetal antigen. In contrary, no MHC molecules were detected in preimplantation embryos, which resembles the conditions in human embryos and is supposed to be essential for embryonic survival (6). We additionally found, that CD-8, IL-4 and IFN-γ were the factors exclusively expressed in the early pregnant uterus. However, during implantation, the growth factors IGF-2 and GM-CSF additionally appeared and are therefore supposed to have growth supporting and probably also immune modulating effects during the invasion phase of the canine embryo (own unpublished results). In conclusion, to date, only a few studies could be performed, investigating the physiological intrauterine immunological milieu during early canine pregnancy as well as foeto-maternal interactions. However, we need more knowledge about the physiology to be able to study the effect of pathogens, rheumatic and autoimmune diseases on the pregnant canine uterus. Future studies should elucidate the immune modulatory effects of progesterone and the preimplantation embryo on the cellular and humoral level, and in addition the presence and distribution of lymphocyte subsets, especially decidual NK cells, in the uterus of pregnant bitches.