Pro-Inflammatory Interleukin 1β Affects the Function of Decidualized Uterine Stromal Cells – Clues from the Canine Model

Miguel Tavares Pereira[1]; Mariusz P. Kowalewski[1]
1. Institute of Veterinary Anatomy, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

Well-timed uterine immune dynamics are crucial for the establishment and outcome of pregnancy. For instance, both implantation and parturition are events marked by increased immune activity, whereas the maintenance of pregnancy is associated with decreased intrauterine immune activity in several species, including the dog. A disproportionate immune response is frequently associated with loss of pregnancy. Indeed, in dogs, inflammatory and infectious uterine diseases rank among the main causes of abortion, but underlying mechanisms still remain unexplored. The transcriptional availability of interleukin 1β (*IL1β*), key mediator of inflammatory responses, is increased in the canine uterus during placentation, but not in the matured placenta. Conversely, this cytokine is recurrently described as being upregulated in the canine uterus during inflammatory and infectious events.
The outcome of pregnancy in dogs is tightly linked to a proper function of maternally-derived decidual cells, mainly due to their unique expression of the progesterone receptor (PGR) in the canine placenta. Indeed, interference with the activity of decidual cells, e.g., by blocking PGR function, results in preterm pregnancy termination. Previous works using an *in vitro* model of canine decidualization, the immortalized dog uterine stromal (DUS) cells, identified possible immunoactive mechanisms in decidual cells, including an increased transcriptional availability of the IL1β receptor 1(*IL1R1*). However, functional studies are still missing. Following this, the present work aimed to investigate the modulatory effects of IL1β in the canine placenta, mainly focusing in decidual cells function.
To further support the proposed responsiveness of decidual cells to IL1β, the expression and localization of IL1R1 were investigated in samples of pregnant dogs throughout gestation (n = 3-5 animals/pregnancy stage), spanning from pre-implantation to prepartum luteolysis. The intrauterine transcriptional availability of *IL1R1* was increased in the mature placenta, namely during mid-gestation (days 35-40 of pregnancy) and prepartum luteolysis, when compared with the time of implantation (day 17) or early placentation (days 18-25) ($P < 0.05$). Furthermore, IL1R1 could be localized with immunohistochemical staining in decidual cells, in addition to endothelial cells and trophoblast, in placentae collected during mid-gestation. The functional effects of IL1β were explored by exposing DUS cells decidualized *in vitro* with cAMP to different concentrations of IL1β (0.1, 1 or 10 ng/ml) for 24h. All tested concentrations of IL1β significantly decreased the transcriptional availability of factors linked to decidual function, such as the decidualization markers *IGF1*, *PTGES* and *PTGS2/COX2* ($P < 0.001$), but also the extra-cellular matrix components *ECM1* and *TIMP2* ($P < 0.01$). Finally, transcriptional availability of the gap junction component CX43, but also its protein amounts detected with immunofluorescence, were decreased by IL1β in decidualized DUS cells ($P < 0.001$).
These findings suggest that IL1β can disturb placental tissue homeostasis, at least in part, by disrupting the function of decidual cells. This may comprise one of the underlying mechanisms leading to pregnancy loss (abortion) in bitches, but also in other species with decidual placenta, during inflammatory/infectious events.