CHAPTER 3

IL-10 and Pregnancy

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Introduction

Soon after the principles of nonself immunological recognition were discovered, it was realized that the state of pregnancy seemingly presents a paradox. In an outbred population, half of the fetal genes are paternal, thus the fetus may be considered a semi-allograft. Yet, unlike the outcome of a surgical tissue graft, the mother tolerates and nurtures the fetus.

Research into this problem has yielded deeper insights into the immunology of pregnancy. The pregnant uterus and the site of a surgical tissue graft may be thought of as analogous, but they exhibit important dissimilarities. Both sites express pro-inflammatory cytokines such as IFN-γ and IL-1β. These cytokines mediate anti-graft responses and have been shown to adversely affect pregnancy. However, unlike the site of a tissue graft, the maternal-fetal interface also expresses many anti-inflammatory cytokines and other factors that limit immunological aggression towards the fetus. It is thought that the balance of locally produced pro-inflammatory and anti-inflammatory cytokines is critical to the success of pregnancy. Among these locally-produced factors, IL-10 seems to be the most potent immunosuppressive and anti-inflammatory molecule. First discovered as a molecule that could inhibit cytokine production and proliferation of T cells, IL-10 has been shown to exhibit a wide array of immunosuppressive activities on various immune cells. Among these include the inhibition of antigen presenting cell function, inhibition of expression of inflammatory cytokines, inhibition of cytotoxic T cell (CTL) responses and induction and function of regulatory T cells, and regulation of the survival and proliferation of B cells. Additionally, IL-10 has been shown to both inhibit and promote the growth of tumors. IL-10 is known to downregulate MHC class I expression on tumor cells, thus inhibiting CTL killing of these cells. However, downregulation of MHC class I molecules might render tumor cells susceptible to NK cell killing. In addition, subpopulations of regulatory T cells have been shown to produce IL-10 to regulate inflammatory responses. Interestingly, a recent report suggests that CD4⁺CD25⁺ T cells expand during pregnancy and promote successful pregnancy outcome. It remains to be seen whether pregnancy-associated regulatory T cells exert their function via IL-10.

IL-10 Gene, Protein, and Expression

The protein and gene structure of both human (hIL-10) and mouse (mIL-10) share a high degree of homology. The cDNA clones of hIL-10 and mIL-10 display greater than 80% nucleotide sequence homology, the inclusion of a human Alu repetitive sequence in the 3'-untranslated region of the hIL-10 cDNA being the only major disparity.

The protein products of hIL-10 and mIL-10 are quite similar, exhibiting 73% amino acid homology. Human IL-10 is an 18kDa polypeptide lacking N-glycosylation sites. T cell-derived mIL-10 exists as three heterogeneously glycosylated proteins of 17, 19, and 21 kDa. Glycosylation has no apparent effect on the biological activity of mIL-10 as mutant proteins.
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Figure 1. The location of the IL-10 gene on human and mouse chromosome 1 (A). Signal transduction of IL-10 begins with ligand binding to the IL-10 receptor (B). This leads to activation of the Jak1 and Tyk2 kinases and their phosphorylation of IL-10R1, which then recruits Stat3 (C). Jak1/Tyk2 phosphorylates the bound Stat3 leading to Stat3 homodimerization (D). The Stat3 dimers translocate to the nucleus, and drive the expression of IL-10-induced genes (E).

lacking N-linked glycosylation sites retain biological activity. mIL-10 has not been shown to be biologically active on human cells, although hIL-10 is active on cells of both species.

Both human and mouse IL-10 genes are on chromosome 1 of each species (Fig. 1A). Transcriptional activation of the IL-10 gene results in -2 kb (hIL-10) and -1.4 kb (mIL-10) mRNAs. IL-10 is expressed in a wide variety of cell types. Among immune cell populations, IL-10 expression has been observed in T cells, B cells, macrophages, dendritic cells, and NK cells. Many nonimmune cell populations also express IL-10; most prominently both mouse and human placental trophoblast cells and decidual stromal cells.

Regulation of IL-10 gene expression has been associated with diverse pathological conditions. Although IL-10 transcriptional regulation is not currently well defined, Sp1 and Sp3 transcription factors are constitutively involved in many cell types. Importantly, the promoter region of the human IL-10 gene is known to harbor multiple polymorphic sites. Several reports have described the presence of three linked single nucleotide polymorphisms (SNPs) found at -1082(G/A), -819(C/T), and -592(C/A) base pairs upstream from the transcriptional start site. These SNPs are in linkage disequilibrium and are thus inherited as haplotypes. The following major haplotypes of the -1082, -819, and -592 SNPs are found in the human population: GCC, ACC, and ATA. These polymorphisms have been shown to have effect on IL-10 production in vitro. Most studies suggest the GCC haplotype is associated with high in vitro IL-10 production and the ACC and ATA haplotypes are associated with low IL-10 production. These haplotypes combine to form genotypes associated with high