Cytokine-like and cell cycle regulatory effects of the Progesterone induced blocking factor (PIBF)

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PIBF is a progesterone target gene, localized on chromosome 13 in the humans and chromosome 14 in the mouse. The full length molecule is a 90 kDa, however, several smaller molecular weight isoforms are produced by alternative splicing. Upon activation, the smaller molecular weight PIBF isoforms enter the secretory pathway and are transported into the surrounding microenvironment. The full length PIBF shows a peri-nuclear localization is associated with the centrosome and has been identified as a component of the pericenteolar satellite. PIBF plays a role in the maintenance of murine pregnancy. Increased resorption rates in mice, - due to high NK activity or to progesterone receptor block - are corrected by PIBF treatment, whereas PIBF depletion in pregnant mice results in altered cytokine pattern and fetal loss.

Both trophoblast and tumor cells express high levels of the PIBF and the expression of this molecule is inversely related to trophoblast invasiveness. Invasiveness is a common feature of trophoblast and tumors; however, while tumor invasion is uncontrolled, trophoblast invasion is strictly regulated both in space and time. PIBF differentially regulates invasion tumor and trophoblast. Silencing of PIBF increased invasiveness as well as MMP-2,-9 secretion of trophoblast-, and decreased those of tumor cells. In trophoblast cells PIBF induced fast, but transient Akt and ERK phosphorylation, whereas in tumor cells, PIBF triggered sustained Akt, ERK, and late STAT 3 activation. The late signaling events might be due to indirect action of PIBF. PIBF induced the expression of EGF and HB-EGF in HT-1080 cells. The STAT 3-activating effect of PIBF was reduced in HB-EGF-deficient HT-1080 cells, suggesting that PIBF-induced HB-EGF contributes to late STAT 3 activation. PIBF binds to the promoters of IL-6, EGF, and HB-EGF; however, the protein profile of the protein/DNA complex is different in the two cell lines. We conclude that in tumor cells, PIBF induces proteins, which activate invasion signaling, while—based on our previous data—PIBF might control trophoblast invasion by suppressing pro-invasive genes.