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The function of the progesterone induced blocking factor (PIBF) protein in allowing escape of cancer cells from immune surveillance and the role of progesterone receptor modulators in treating various cancers

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There is evidence that rapidly growing cancer cells, similar to rapidly growing trophoblast cells utilize a unique protein, not present in normal tissue, to help evade immune surveillance. This protein known as the progesterone induced blocking factor (PIBF) has been found to stabilize perforin granules in natural killer (NK) cells, thus abrogating their mechanism for cytolysis and help cause a shift of TH1 to TH2 cytokines. PIBF has been found to be overexpressed in biopsies of uterus, breast, stomach, and brain cancer and in several cancer cell lines including leukemia, glioblastoma multiforme, and adenocarcinoma of the ovary, cervix, and breast. The parent form of PIBF measures 90 kDa and is associated with centrosome on chromosome 13 in the vicinity of BRCA-1 and P53. Isoforms of PIBF are produced by alternative splicing and includes ones measuring 34 kDa, 57 kDa, 67 kDa. Progesterone has been found to up-regulate the 34 kDa splice variant of PIBF on human leukemia cell lines and the 57 kDa isoform in human glioblastoma cells lines. PIBF, though present intracellularly in both the rapidly growing trophoblast cells and cancer cells, one distinction between pregnancy vs. cancer is that serum PIBF rises abruptly after progesterone exposure (even when not pregnant) in the serum but not increased in the serum even in tumors that are positive for progesterone receptors or even BRCA-1 breast cancer, which by making a mutated ubiquitin is associated with diminished capacity to degradate the progesterone receptor. Adding the progesterone receptor modulator mifepristone to culture media causes down-regulation of the 34 isoforms in leukemia and glioblastoma multiforme cell lines. However, mifepristone fails to lower serum PIBF. There is evidence that suppressing the conversion of the 90 kDa nuclear parent form to the intracellular isoforms can provide significant palliative benefit to a large variety of metastatic human cancers including colon, renal cell carcinoma, small and non-small cell lung cancer, glioblastoma multiforme, breast cancer, transitional cell carcinoma of the renal/pelvis and thymic epithelial cell cancer. It is suggested, but not proven for sure, that the mechanism for causing improved longevity and quality of life by retarding tumor growth is by inhibiting the production of intracellular PIBF which allows natural killer cells (and possibly T-cells also) to attack the cancer cells. Measuring serum PIBF does not appear to be a worthwhile test to determine who would benefit from mifepristone treatment nor the knowledge of progesterone receptor status.

Biography:

Jerome H. Check, M.D., Ph.D. has been a Professor of Obstetrics and Gynecology and Division Head of Reproductive Endocrinology and Infertility at Cooper Medical School of Rowan University (formerly known as University of Medicine and Dentistry of Robert Wood since 1989. He is also board certified in internal medicine and medical endocrinology and metabolism. He received his Ph.D. in reproductive biology in 1997 and his thesis was "The role of progesterone in promoting implantation and inhibiting spontaneous abortions may be through the stimulation of immunomodulatory proteins". He has published over 750 publications in peer review journals involving obstetrics/gynecology, reproductive and medical endocrinology and infertility, internal medicine, and cancer research. Much of his present cancer research relates to his concept published in the journal Medical Hypothesis in 2011 entitled "A model for potential tumor immunotherapy based on the knowledge of immune mechanism responsible for spontaneous abortion.