Toll-like receptor 3 regulates angiogenesis and apoptosis in prostate cancer cell lines through hypoxia-inducible factor 1 alpha.

Abstract:
Toll-like receptors (TLRs) recognize microbial/viral-derived components that trigger innate immune response and conflicting data implicate TLR agonists in cancer, either as protumor or antitumor agents. We previously demonstrated that TLR3 activation mediated by its agonist poly(I:C) induces antitumor signaling, leading to apoptosis of prostate cancer cells LNCaP and PC3 with much more efficiency in the former than in the second more aggressive line. The transcription factor hypoxia-inducible factor 1 (HIF-1) regulates several cellular processes, including apoptosis, in response to hypoxia and to other stimuli also in normoxic conditions. Here we describe a novel protumor machinery triggered by TLR3 activation in PC3 cells consisting of increased expression of the specific I.3 isoform of HIF-1 alpha and nuclear accumulation of HIF-1 complex in normoxia, resulting in reduced apoptosis and in secretion of functional vascular endothelial growth factor (VEGF). Moreover, we report that, in the less aggressive LNCaP cells, TLR3 activation fails to induce nuclear accumulation of HIF-1 alpha. However, the transfection of I.3 isoform of hif-1 alpha in LNCaP cells allows poly(I:C)-induced HIF-1 activation, resulting in apoptosis protection and VEGF secretion. Altogether, our findings demonstrate...
that differences in the basal level of HIF-1 alpha expression in different prostate cancer cell lines underlie their differential response to TLR3 activation, suggesting a correlation between different stages of malignancy, hypoxic gene expression, and beneficial responsiveness to TLR agonists.