IL-6 induced proliferation is suppressed post TGF-β2 exposure in HCC

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ABSTRACT

Pro-inflammatory cytokines infiltrate uninterruptedly in hepatocellular carcinoma (HCC) tumor milieu facilitating tumor progression, proliferation and epithelial-mesenchymal transition (EMT). However, the intricate cytokine interactions and their roles in HCC progression remains unexplored. While exploring the underlying mechanism, we recently reported that IL-6 induces p65 coupled STAT-3 dependent proliferation in HCC. TGF-β, another pre-dominant pro-inflammatory cytokine in HCC tumor milieu was found to induce SMAD dependent EMT along with cell growth arrest. Nevertheless, our study revealed the dominance of TGF-β over IL-6 signaling when crosstalk between IL-6 and TGF-β signaling in HCC was examined. From our study, IL-6 induced pro-proliferative effects were diminished through decrease in IL-6 receptor (IL-6R) transcript levels, reduced expression of IL-6-induced STAT-3 and its nuclear localization upon addition of TGF-β along with IL-6. Paradoxically, a decrease in IL-6 induced p65 levels were diminished with TGF-β and IL-6 combinatorial exposure. Interestingly, TGF- β induced SMAD levels remained unperturbed and cells showed TGF-β like phenotype. Importantly, we observed elevated TGF-β induced histone repressive mark H3k27me3, while, IL-6 induced elevated p65 mediated open chromatin mark H3K4me3. Our study provides valuable cues on therapeutic regime and crosstalk between two pro-inflammatory cytokines.

Keywords: IL-6, TGF- β, proliferation, STAT-3, p65