Critical role of IL-23 signaling in prostatic cancer

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Interleukin 23 (IL-23) belongs to interleukin 6 super-family [1]. IL-12/23 p40 is the common subunit for them, which is covalently linked to either a p19 subunit to form IL-23 or a p35 subunit to form IL-12 [2]. Both cytokines are mainly expressed by activating dendrite cells or macrophages under the stimulation of pathogens. IL-23 was also reported to be secreted by tumor associated macrophages in tumor microenvironment [3].

Interestingly, IL-23 spur different immune pathways [4]. IL-12 induces IFN-γ-producing Th1 cell development and enhances cytotoxic, anti-microbial and anti-tumor responses; whereas IL-23 expands Th17 cells, which is mainly involved in the pathology of autoimmunity and chronic inflammatory disease [5].

Although the role of Th17 in tumor progression remains controversial, the role of IL-23 in tumor incidence and metastasis was established in the mouse model. For example, mice lacking IL-23p19 were resistant to DMBA/TPA-induced skin papilloma [6-7]. Recently, IL-23 was also reported to promote carcinogenesis and metastasis in the 3′-methylcholanthrene induced fibrosarcoma through suppressing the innate immune response [8]. However, the role of IL-23 in metastatic prostate cancer is unclear. In this study, we found that IL-23 was highly expressed in metastatic prostate cancer cells. We further proved that IL-23 could directly promote prostate cancer metastasis via a STAT3/ROR gamma signal, so we further explored the relationship between IL-23 and STAT3/ROR gamma in prostate metastasis. We found that IL-23 and STAT3/ROR gamma were highly correlated in metastatic prostate cancer cell lines directed.

STAT3 belongs to the signal transducer and activator of transcription (STAT) family of signal responsive transcription factors, which consists of seven members encoded by distinct genes. In non-stimulated cells, STAT3, like other STATs proteins, are kept in an inactive

cytoplasmic form. Then, once activated, STAT3 translocate into the nucleus where it behaves as a transcription activator for a broad array of targeted genes. Typically, STAT3 activation is induced by phosphorylation on a critical tyrosine residue (Tyr 705) that triggers STAT3 dimerization thanks to reciprocal phosphotyrosine-SH2 domain interactions. Even if multiple tyrosine kinases have been described as intracellular activators of STAT3 activity (such as EGFR, Src, ERK), the phosphorylation of STAT3 on tyrosine 705 is mainly regulated by members of Janus-activated kinases with JAK1 as key modulator [9]. In addition to tyrosine 705 phosphorylation, STAT3 is also activated through serine (Ser 727) phosphorylation. This phosphorylation is commonly regulated by protein kinase C, mitogen-activated protein kinases, and CDK5.

It is now well established that STAT3 signaling is a major intrinsic pathway driving apoptosis, inflammation, cellular transformation, survival, proliferation, invasion, angiogenesis and metastasis of cancer [10-11]. However, compelling evidence has now shown that STAT3 is constitutively activated in many human cancers [12]. Indeed, many receptor-signaling pathways are. Many regulated genes induced by STAT3 in turn activate the same STAT3 pathways and keep a stable feed forward loop going between tumor cells and tumor-interacting immune cells. In addition, the own tumorigenic properties of STAT3 highlight its oncoprotein status by driving malignant properties related to chronic inflammation [13].

Thereby, this explains that STAT3 has been characterized as a central actor for inflammation-induced cancer. STAT3 activation occurs in both cancer and stromal cells thereby allowing a crosstalk between these two cellular types. This activation is rapid and transient under normal biological conditions and mediated by a large number of extracellular stimuli including cytokines (IL-6, IL-10, IFNs, TNF-α) and growth factors.

This review investigated, for the first time, the role of IL-23 in prostatic cancer patients showing a significant increase respect the control group. However, further validations are needed in larger studies to better investigate the implications of IL-23 increase in these patients.

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