Why Interleukin-17A is the most Potential Next Generation Drug Target in Angiogenesis-mediated diseases

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Significance | Despite the use of IL17A in the rheumatoid arthritis, it is not used as therapeutic target in cancer. Targeting IL17A can control the hundreds of the bio-markers in cancer.

Graphical Abstract

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Md Shamsuddin Sultan Khan

Cancer treatment is investigated worldwide using various resources. The molecular pathogenesis of cancer gives us advantages to find potential anticancer drugs. Scientists are now more prone to develop drugs that bind in a specific site to decrease the potential side effects and prolong the cure. The treatment of cancer can be divided into different categories. Surgery is the first line treatment for solid tumors and the early stages of cancer. Even benign growths can be removed by this technique (Abeloff, 2008; Edmund et al., 2007). The goal of radiation treatment is the direct killing of cancerous cells. Chemotherapy is the most widely used drug for cancer treatment and prevention but it is not widely accepted for its chronic side effect. Hormonal drugs are designed to prevent the signaling process for continued growth and division of cells that are hormone dependent. Antibodies work as specific inhibitors either depriving the signal for cancer cells or inducing cell death. Complementary and alternative medicines are used to slow down the cancer progress. Vaccines, biological response modifiers and targeted therapies are very recent inclusions in the fight against cancer. From these vast treatment sciences, only molecular targeted drug could be the next generation anticancer therapy. Molecular scientists are searching for the crucial biological factors that cause tumor development and subsequent metastatic phase. Recently, it was found that Interleukin-17 has an association to human malignancy (Tartour et al., 1999; Numasaki et al., 2003; Kato et al., 2001). IL-17 is the core factor to promote tumor development, tumor growth and angiogenesis. Thus, this molecular targeted drug can be investigated to cure cancer. Ligand mediated drugs can be designed to target this IL-17 protein with very few side effect.

**Potential next generation drug target in cancer**

A pro-inflammatory cytokine is produced by activated CD4+ memory T cells in carcinogenesis to generate interleukin-17 A (IL-17A). IL-17A induces neoplastic transformation of JB6 Cl41 cells through activation of the tumor progression locus 2 (TPL2). IL-17A dose- and time-dependently increases TPL2 phosphorylation in JB6 Cl41 cells through the IL-17A receptor. IL-17A activates mitogen-activated protein kinase/extracellular signal-regulated kinase kinases, c-jun N-terminal kinases and STAT3 signaling pathways, which are inhibited by a TPL2 kinase inhibitor (TKI). Furthermore, IL-17A activates c-fos and c-jun promoter activity, resulting in increased activator protein-1 (AP-1) activity. When small interfering RNA against IL-17A receptor (IL-17R), IL-17A and TPL2 were introduced into JB6 Cl41 cells, IL-17A-induced AP-1 activity was significantly decreased compared with control cells. Similarly, TPL2 inhibition suppressed AP-1 activity induced by IL-17A. The knockdown of IL-17R and TKI in JB6 Cl41 cells resulted in decreased IL-17A-induced cell transformation. IL-17A-induced TPL2 signaling pathway supports the notion of cancer-associated inflammation in the tumor micro-environment. Therapeutic approaches that target this pathway may effectively inhibit carcinogenesis (Garam et al., 2012). IL-17-induced MMPs have a role in PIN-to-cancer transition. IL-17 promotes prostate cancer formation and growth via induction of MMP expression (Zhang et al., 2014).

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Pro-inflammatory cytokine IL-17 is produced by activated CD4 T-cells and CD8 T-cells (in human) (Yao et al., 1995; Shin et al., 1999). IL-17 and IL-6 promote the tumorigenicity of human cervical cancer, ovarian cancers and promotes tumour angiogenesis due to the enhancement of vascular endothelial growth factor (VEGF) (Tartour et al., 1999; Pages et al., 1999; Kato et al., 2001; Numasaki et al., 2003; Takahashi et al., 2005; Wong et al., 1999). There is a correlation between vascularity and invasive behaviour in CRC (Choi et al., 1998). IL-1 and IL-6 have been associated with colorectal cancer (Komoda et al., 1998). IL-17 induces IL-1 from macrophages to stimulate epithelial and fibroblastic cells to secrete IL-6 (Jovanovic et al., 1998; Fossiez et al., 1996). IL-17 is demonstrated to increase the production of active metalloproteinase MMP-9 (Prause et al., 2004). The role of metalloproteinases in the progression of human malignancies is well documented in numerous reports (Matrisian et al., 1994; Roeb et al., 2001). [To be continued...]

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Competing financial interests

The editor(s) declare no competing financial interests.

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