The role of integrin linked kinase in senescence and immunosuppressive tumor microenvironment in colon cancer

Background:

The integrin linked kinase (ILK) is an adaptor and mediator protein linking the extracellular matrix with downstream signaling pathways (1). It is broadly expressed in many human tissues and cells. It has been established for about two decades that ILK overexpression and dysregulation is associated with the development and progression of different cancers. In accord with this, ILK interacts with different signaling pathways that are implicated in cancer and inflammation.

This project focuses on the role of ILK in the senescence process. This cellular process in cancer has a dual role. When the senescence associated secretory phenotypes (SASPs) are produced by senescent cells, they attract and recruit immune cells for elimination, which in turn suppresses tumorigenesis. However, when the immune cells fail to eliminate the senescent cells, then they can have a negative effect in a tissue microenvironment. A senescence-inflammatory response (SIR) can switch the role toward tumour promotion. The most prominent pro-inflammatory cytokines of SASP are IL-6, IL-1alpha, IL-1beta and others. Also, NF-kB p65 is activated in senescent cells and it is considered as a master control of SASP. Targeting the SIR by anti-inflammatory agents affects tumour growth. Our laboratory has found that ILK deficiency in colitis inhibits these proinflammatory cytokines as well as reduces inflmmatory cells infiltration (2,3). In contrast, a different study showed that the senescence is induced by ILK deficiency in normal and tumor skin and benign colon adenoma (4). Therefore, it is hypothesised that ILK Knockdown (KD) may have an important role in tumor supression by inducing senescence and regulating inflammation.

CAR T cell immunotherapy has shown much promise in liquid tumours. On the other hand, there are different barriers to use of CAR T cell immunotherapy in solid tumours, including infiltration of immunosuppressive inflammatory cells, cytokines, chemokines and activation of signalling pathways. Different studies have indicated that some of these barriers have interactions with ILK or its downstream signalling pathways including AKT, mTOR, NF-kB and PTEN (a negative regulator of ILK). Deleting tumor suppressor (PTEN) in HCT116 colon cancer cells leads to constant expression of AKT which in turn make cells resistant to cytotoxic T-lymphocyte in vitro, as well as to adoptively transferred murine splenocytes in vivo. A combination treatment with the CAR T cell immunotherapy may have a potential effect in solid tumors and it is hypothesised that ILK KD may increase the efficacy of CAR T cell immunotherapy.

References:

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