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Mutational landscape of cytokine genes across major tumour types identifies new targets

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Abstract

Introduction: Components of immune system communicate extensively in tumour micro environment. Normally, immune system engages with tumours to inhibit its further progression. Simultaneously, cancer cells learn cues derived from immune system to its own growth advantage. Cytokines are cell signaling messengers that affect disease pathogenesis, non-specific response to infection, specific response to antigen, etc. A battery of cytokines are produced in the tumour microenvironment, when released in response to infections and inflammations, can function to inhibit tumour development and progression. Cancer cells also release cytokines that promote growth, extenuate apoptosis and perform invasion and metastasis.

Hypothesis: Alterations in cytokine signaling genes might help tumour to misguide immune system. The aim of the study is to identify such genomic alterations in cytokine genes that may drive major human cancers.

Methods: We did extensive literature survey to prepare a list of known cytokine genes (n=776) which were validated in multiple databases. To know the baseline DNA variation in cytokine genes, we analyzed DNA variations in healthy human population from the 1000 Genome project dataset. Somatic mutational landscape for cytokine genes were analyzed in 32 different human cancer types (TCGA data). Significantly mutated genes were detected using MutSig2CV and Oncodrive FM analysis. Genes found significant in both analysis were tabulated. Standard statistical and bioinformatics analysis were done further to identify putative driver events.

Result: We detected 9 significantly mutated cytokine genes across major tumor types. *EDN1* was found to be most significantly mutated, in multiple tumour types; apart from genes like *CDH1, B2M, HLA-B, IL4, TRIM22, TGFB1, GDF1* and *CRABP2*.

Discussion: Our systematic survey of somatic mutations in cytokine genes, in major tumour types, identified novel genes targets such as *EDN1* gene. *EDN1* is a chemokine, also a potent vasoconstrictor. *EDN1* signaling modifies tumour microenvironment by regulating contribution of cells around tumor stroma through both autocrine and paracrine mechanisms, by promoting tumour cell proliferation, neovascularization, etc. Other significantly mutated genes are associated with antigen presentation, cell proliferation and chemoattraction. Rational combination therapy with current inhibitors to disrupt these signaling networks in tumor microenvironment, may improve clinical outcomes in patients.