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Pro-inflammatory cytokine and chemokines genes drive prostate cancer progression and metastasis

Pro-inflammatory cytokine and chemokines genes drive prostate cancer progression and metastasis: molecular mechanism update and the science that underlies racial disparity

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Abstract

In 2010 we reported prostate cancer grows more rapidly in African American men (AAM) than in European American men (EAM) and/or can have earlier transformation from latent to aggressive prostate cancer. In that report, an autopsy study was conducted among AAM and EAM who died from causes other than PCa. PCa started at the same time among men but reached distant disease at a three-fold greater rate and at a younger age among AAM than EAM accounting for the mortality rate disparity. Castrate resistant PCa is responsible for death from this disease and there is growing genetic evidence to support racial disparity of castrate resistant PCa and mortality rate [1].

Introduction

In 2013 we reported that with the use of bioinformatics and ingenuity pathway network analysis we were able to identify functional driver genes that were differentially expressed among a large population of African American men (AAM) and European American men (EAM). Pro-inflammatory cytokine genes were found to be more interactive and more expressed among AAM and have been found to be functional drivers of aggressive prostate cancer (CaP) and aggressiveness in other solid tumors (figure 1). We examined these genes and biological pathways initiated by these cytokines in primary CaP tissue [2].

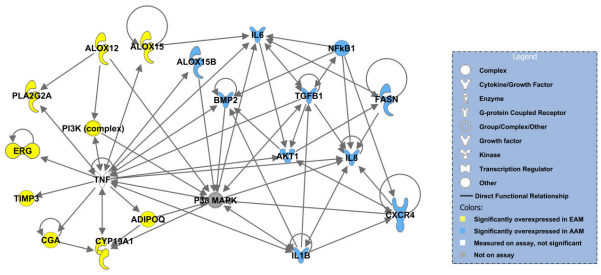

Figure 1. Functional Interaction Network from analysis of genes upregulated in prostate tumors from AAM or EAM.

Method

The network derived from Ingenuity Pathways analysis demonstrates a high degree of inherent, functional interrelatedness for a subset of factors from the analyzed gene expression data sets (AAM blue, EAM yellow). AAM and EAM prostate tumors are distinguished at gene level with NFKB and pro-inflammatory cytokine factors primarily upregulated in PCa from AAM; EAM upregulated genes are centered on TNF. Edges (lines) linking members of both sets to P38MAPK, TNF and PI3K/AKT genes suggest that the associated pathways are operating to some extent in both EAM and AAM contexts.

We unravel the gene network and identified biologic pathways that impacted activation of the androgen receptor, mesenchymal epithelial transition (invasion) and chemokines associated with metastasis in the CaP tissue from 639 radical prostatectomy specimens [3].

Results

Biologic pathways identified by unraveling pro-inflammatory genes from our network, more expressed among AAM compared to EAM, were tumor necrosis factor (TNF), IL1b, IL6, and IL8. IL6 and IL8 are downstream of TNF activity and are known activators of androgen receptor and through mediators promote CaP cell proliferation. TNF and IL1b mediate tumor cell invasiveness through the activation of MMP (matrix metalloproteinase) which down regulates E-Cadherin to initiate epithelial mesenchymal transition (EMT) which allows cells to become invasive in the microenvironment. Ultimately our network analysis indicates that TNF and IL1b activate CXCR4 receptor on CaP cells, which facilitates metastatic progression reportedly by binding to CXCL12 on lipid rafts and tumor implantation in the bone marrow [3].

Discussion

Our data complements and integrates what has been published in separate studies elsewhere. We demonstrate multiple biologic pathways initiated by pro-inflammatory cytokines and chemokines that activate intermediaries that activate the androgen receptor and subsequently cell cycling genes and cell proliferation. We also illustrate pathways initiated by pro-inflammatory cytokines contributing to EMT, dedifferentiation and heterogeneity which may be responsible for drug resistance. And finally, we identify a pathway initiated by pro-inflammatory cytokines and chemokines that leads to metastasis. These are cascading genetic events responsible for these biologic pathways. Two other important pathways are oxidative stress that causes DNA damage and Angiogenesis both initiated by pro-

inflammatory cytokines and chemokines. These pro-inflammatory cytokines and chemokines are more expressed among AAM than EAM and are upstream of the androgen receptor. They are not impacted by testosterone or mechanisms such as antiandrogens, which block the synthesis of testosterone or compete for receptors of testosterone. Therefore, these mechanistic functions should be considered active in and responsible for driving castrate resistant CaP pathways [3].

Conclusion

Our retrospective biologic mechanistic model reveals a set of pro-inflammatory cytokines and chemokines that drive CaP aggressiveness, tumor heterogeneity, progression and metastasis. A prospective multi-institutional study needs to be conducted for clinical validation as well as consideration of targeted therapy.

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