ERG induces persistent inflammatory and senescence-associated responses in prostate cancer

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Gene fusions between the ETS family transcription factor ERG and the regulatory region of an androgen receptor (AR)-regulated gene (mainly TMPRSS2) are the most frequent genomic rearrangements in prostate cancer (PCa), present in about 40-50% of both primary and advanced tumors. ERG fusions are considered an early event in PCa tumorigenesis and *in vivo* work confirmed a causal role of ERG in initiating PCa when combined with other mutations (e.g., PTEN loss or AKT activation) or expressed at high levels. The dependency of advanced PCa models on ERG activity further highlights its relevance. Although the oncogenic potential of ERG is clear, how ERG promotes PCa tumorigenesis and progression remains elusive. In line with the observation that loss of cell plasticity often characterizes primary PCa, studies have reported a role of ERG in favoring the AR signaling and the PCa cell luminal lineage. On the other hand, functional studies showed that ERG disrupts lineage-specific differentiation in PCa by inducing epithelial-mesenchymal transition (EMT), repressing the AR signaling, and activating the H3K27 methyltransferase EZH2.
Given these two conflicting models for ERG oncogenic activity, we used a lentiviral vector encoding for the *TMPRSS2-ERG* fusion transcript under the control of a doxycycline-inducible promoter to further elucidate ERG-induced oncogenic features. In all the analyzed cell lines, ERG overexpression reduces their fitness *in vitro* by inducing cell cycle arrest and senescence, but not apoptosis. TP53 is stabilized and activated by ERG, however, its inactivation does not rescue the ERG-mediated cell cycle arrest and senescence. Gene expression analyses confirm senescence activation and identify several inflammatory pathways and EMT as upregulated upon ERG overexpression, altogether suggesting that, although ERG-overexpressing cells poorly proliferate, they acquire oncogenic features, such as increased cell plasticity, and create a pro-tumorigenic microenvironment.
Accordingly, we observed that ERG induces key EMT transcription factors (ZEB1 and SOX9), upregulates both prostate luminal and basal signatures, and increases the percentage of prostate cells with concomitant expression of luminal and basal markers. These double-positive cells are also detected in ERG-positive human tumor samples and are characterized by increased expression of stem cell-related genes. Furthermore, by querying previously published data, we detected ERG binding to senescence-associated and inflammatory genes and higher expression of senescence and inflammatory signatures in ERG-positive primary tumors.
This study shows that ERG oncogenic activity drives the induction of EMT and cell plasticity, which favor a hybrid luminal-basal cell population with stem cell-like features. Further, the identified activation of inflammation and senescence-associated responses as key elements in the ERG oncogenic toolbox uncovers novel mechanisms induced by ERG to promote tumorigenesis, potentially associated with treatment response.

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