ERG promotes transcriptional reprogramming of prostatic epithelial cells toward a cancer stem cell phenotype

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Abstract

Genomic rearrangements that result in aberrant expression of the proto-oncogene member of the erythroblast transformation-specific family of transcription factors, ERG, occur in almost half of prostate cancers. The most frequent rearrangements are the result of an interstitial deletion that results in fusion of androgen-responsive elements of serine 2-erythroblast transformation-specific-related gene with variable amino terminal ERG open reading frame exons. These TMPRSS2-ERG fusions are the most common cancer-associated mutation. They occur early in prostate cancer initiation, are associated with high Gleason score, and aggressive disease. When amplified and/or expressed at high level, TMPRSS2-ERG is associated with poor prognosis. Mirroring its functions in normal chondrocyte and endothelial cell differentiation, ERG expression in prostatic epithelial cells drives aberrant activation of transcriptional programs promoting migration, invasion, and epithelial-mesenchymal transition. Additionally, TMPRSS2-ERG status appears to enhance resistance to abiraterone and taxane therapies. We hypothesized that ERG expression can promote transformation of prostatic epithelial cells by directing transcriptional reprogramming towards a cancer stem cell phenotype. Transcriptional analysis of ERG-expressing RWPE1 prostatic epithelial cells (ERG-RWPE1) demonstrated up-regulation transcription of a panel of stem cell-related genes. When cultured under non-adherent conditions, ERG-RWPE1 cells selectively demonstrated the ability of form serially passable spheroids and dramatically increased expression of stem cell markers, PROM1, c-KIT and CD33. When re-plated in adherent conditions, cells re-established the expression pattern of parental adherent cultures. Transcript analysis of ERG-RWPE-1 spheroid cultures also revealed activation of transcriptional reprogramming events related to acquisition of stem cell-like capacity, including up-regulated expression of a panel of "Yamanaka-related" stem cell genes (OCT3/4, SOX2, MYC and KLF4), epigenetic control (PRC1, PRC2 and Homeobox C family genes), and genes belonging to DNA methyltransferase, long noncoding RNA and hypoxia pathways. Gene ontology assessment of the transcriptional profile of ERG-RWPE1 prostaspheres ranked Pluripotency, Maintenance, and Differentiation as the top functional groups. The gene signatures of this family of functional groups form an interconnected network of interactions that identify key features of early transforming events in TMPRSS2-ERG positive prostate cancers. Androgen receptor pathway inhibitors are an incomplete means of inhibiting ERG expression. Transcription factors, such as estrogen receptor, can upregulate TMPRS2-ERG transcription, and ERG can upregulate itself and thus promote expression off of wild-type ERG alleles. Additionally, the androgen receptor remains active in more than two thirds of androgen receptor pathway inhibitor-resistant cancers, so ERG expression and function remain active in end-stage disease. This system, therefore, provides a valuable model to interrogate the molecular mechanisms of transformation and control of stem cell characteristics in TMPRSS2-ERG prostate cancers to aid the design of new therapies.

Conflict of Interest I am a co-discoverer, and will discuss investigational use, of compounds covered by: Cherkasov A, Rennie PS, Cox ME, Hsing MMK, Butler MS, Roshan-Moniri M. HUMAN ETS-RELATED GENE (ERG) COMPOUNDS AS THERAPEUTICS AND METHODS FOR THEIR USE. US Provisional Patent, (Serial Number: 62/458,085); File Date: 2/13/2017.

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