O02 Mechanisms of ETS family transcription factors that promote prostate cancer

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Introduction & Objectives: The most common genomic lesion in prostate cancer is a chromosomal rearrangement that fuses the promoter and 5' UTR of a gene expressed in prostate cells to the open reading frame of a gene encoding an ETS family transcription factor. The resulting expression of a normally silent ETS factor in prostate epithelial cells is oncogenic. There are 28 ETS genes in humans, but only three are commonly involved in prostate cancer rearrangements. At least 14 other ETS genes are expressed in the normal prostate, and rather than being oncogenic, some of these are tumor suppressive. It is therefore important that any treatments targeting ETS factors in prostate cancer specifically target the oncogenic family members.

Results: We have found that four ETS family members, including all three commonly rearranged in prostate tumors (ERG, ETV1, and ETV4), and one rearranged in rare prostate tumors (ETV5), are the only ETS family members that can promote cellular migration in prostate epithelial cells, indicating a common function. We have recently discovered that these same four ETS factors are the only ETS family members that can interact with the RNA-binding protein EWS. We find that this interaction with EWS is absolutely critical for oncogenic ETS functions. Furthermore, fusion of EWS to non-oncogenic ETS family members imparts oncogenic functions. We show that EWS acts as a trancriptional co-activator for oncogenic ETS factors.

Conclusions: EWS is a member of the FET family of RNA binding proteins that can interact with the RNA polymerase II C-terminal domain, and have roles in transcriptional elongation and alternative splicing. Interestingly, EWS-ETS fusions are the major oncogenes that cause Ewing's sarcoma, therefore our results link the molecular mechanisms of Ewing's sarcoma and prostate cancer formation. Therefore our work indicates that targeting mechanisms of EWS-ETS function may have therapeutic benefit for both prostate cancer and Ewing's sarcoma.