

## **Changing faces of FUS: FUS/TLS represses androgen receptor activity through disruption of the transcriptional complex**

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**Background:** Prostate Cancer is the most common cancer diagnosed in Western men and its growth is dependent upon the androgen receptor, a ligand-dependent transcription factor which exerts its effects on transcription in concert with cofactor proteins (coactivators and corepressors). We have previously shown that FUS/TLS, a multi-functional protein, is down-regulated in response to androgen receptor signalling and that it has tumour suppressor properties in prostate cancer cells.

**Methods and Results:** To better understand what FUS regulates to block tumour growth, the transcription responses of the androgen-dependent prostate cancer cell line LNCaP was investigated in response to FUS over-expression. This analysis identified a high degree of overlap between FUS-regulated genes and those regulated by the androgen receptor. Further, FUS was found to predominantly repress androgen receptor activity and this was confirmed using reporter assays. Mammalian 2-hybrid and trans-repression assays demonstrated that FUS interacts with the androgen receptor via its RNA recognition motif (RRM) domain and contains both transrepression and activation domains. Interestingly, the transrepression domains are HDAC independent and do not contribute to the repressive action of FUS upon the androgen receptor. Instead, it appears that FUS represses androgen receptor activity as a result of competition for coactivators. A modified mammalian 2-hybrid assay demonstrated that the N-terminal activation function of FUS interacts with coactivators such as SRC1, and chromatin immunoprecipitation studies demonstrated that FUS inhibits the formation of the active androgen receptor transcriptional complex. In agreement with our previous findings, FUS levels were reduced in prostate cancer, but interestingly were elevated in the aggressive, castrate resistant stage of the disease. It therefore appears that FUS is down regulated in prostate cancer, reducing the levels of an androgen receptor repressor. In contrast, FUS levels are increased in advanced therapy resistant prostate cancer suggesting that it may play a different role in this stage of the disease.

**Conclusions:** The androgen-downregulated RNA-binding protein FUS can act as both a corepressor and coactivator of androgen receptor activity. We found the corepressor properties to predominate in prostate cancer, although it may switch in advanced disease. We mapped both repression and activation functional domains in the FUS protein and delineated functional interactions between them. Variation in these interactions may explain the seemingly contradictory roles of this multifunctional protein.

**Conflicts of interest:** None

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