

Regulating nuclear signalling in cancer

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Research findings published recently in *Nature Communications* describe a completely new way in which TGF β receptors regulate nuclear signalling. The findings are significant given that this new signalling pathway seems to be restricted to tumour cells.

Transforming growth factor β (TGF β) is a cytokine that plays an important role during normal embryogenesis due to its multifunctional effects on cellular responses such as proliferation, differentiation, apoptosis and migration.

In recent years, TGF β has become recognised as a potent regulator of cellular plasticity; a central event during embryogenesis and tumour progression. TGF β signals through its binding to the type II and type I serine/threonine kinase receptors (T β RII and T β RI, respectively) to cause their heterooligomerisation, which subsequently activates different intracellular signalling pathways.

Traditionally, the activated T β RI phosphorylates the latent transcription factors Smad2 and Smad3 in early endosomes, to induce complex formation with Smad4 and nuclear translocation of the activated transcription factors to regulate target genes.

This research shows that TGF β promotes the cleavage of T β RI and the formation of an intracellular fragment, or T β RI-intracellular domain (ICD), that is translocated to the nucleus, where it promotes the expression of genes involved in tumour invasion.



These findings stem from an ongoing collaborative research project led by scientists in Uppsala University, Sweden and involving Conway Fellow, Professor Johan Ericsson and Dr Maria Bengoechea-Alonso.

The contribution of the Ericsson group has primarily focused on the experiments demonstrating that T β RI-ICD associates with a global transcriptional coactivator, p300, both in vitro and in vivo. This interaction could potentially explain the transcriptional activity of the cleaved T β RI.

Additionally, they demonstrated that the T β RI-ICD is a direct substrate for the acetyltransferase activity of p300, suggesting that p300 could regulate the function of the cleaved T β RI in the nucleus.

Professor Ericsson said, "We now hope to determine how and why this signalling pathway is activated in tumour cells, especially as this could identify potential therapeutic targets. The next step will be to determine how the T β RI-ICD regulates the expression of specific target genes in response to TGF β signalling. It will be especially important to identify nuclear proteins phosphorylated by the T β RI-ICD."

More information: *Nature Communications* 2:330 <u>doi:10.1038/ncomms1332</u>

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