IN BRIEF

APOPTOSIS

The tumor suppressor Par-4 activates an extrinsic pathway for apoptosis

Burikhanov, R. *et al. Cell* **138**, 377–388 (2009)

The overexpression of prostate apoptosis response 4 (PAR4; also known as PAWR) is known to lead to the induction of apoptosis in cancer cells through an intracellular pathway. However, a recent study has shown that PAR4 can also mediate apoptosis through an extracellular pathway, which could have implications for the potential of PAR4 in anticancer therapies.

Vivek Rangnekar and colleagues found that cultured human prostate cancer cells (PC-3) and normal cells both secreted PAR4. PAR4 was also present in the serum from *Par4*-transgenic mice that are resistant to spontaneous tumour growth. Extracellular PAR4 was functionally active and induced apoptosis in cancer cells.

The authors found that secreted PAR4 binds to the heat-shock protein GRP78 (also known as HSPAS) on the surface of PC-3 cells and that this interaction is necessary for PAR4-mediated apoptosis, as treatment of PC-3 cells with neutralizing GRP78-specific antibodies blocked apoptosis. Moreover, knockdown of endogenous PAR4 in PC-3 cells using RNA interference led to a decrease in exogenous PAR4-dependent apoptosis. The depletion of intracellular PAR4 resulted in the reduced expression of cell surface GRP78, suggesting that intracellular PAR4 is essential for trafficking GRP78 to the cell membrane, where it interacts with extracellular PAR4.

PROSTATE CANCER

Androgen receptor regulates a distinct transcription program in androgen-independent prostate cancer

Wang, Q. *et al. Cell* **138**, 245–256 (2009)

The lethal progression of prostate cancer is associated with a transition from an androgen-dependent to an androgen-independent state. The androgen receptor (AR) is important in both androgen-dependent prostate cancer (ADPC) and androgen-independent prostate cancer (AIPC), but until now its role in AIPC has been poorly characterized.

Myles Brown and colleagues generated gene expression profiles from AIPC (LNCaP-abl) and ADPC (LNCaP) cell lines, and found that the expression of M phase cell cycle genes was greater in AIPC cells than in ADPC cells. Moreover, M phase genes were also upregulated in AIPC clinical samples. Using ChIP–chip experiments, they identified AR-binding sites that were preferentially occupied by AR in AIPC cells, and found greater levels of AR binding near the M phase regulatory genes *CDC20*, *UBE2C*, *CDK1* and *ANAPC10*.

The authors examined the epigenetic marks near AR-bound enhancers and found increased levels of histone H3K4 methylation and binding of the FOXA1 transcription factor in AIPC cells. This led to enhancer activation and overexpression of M phase genes. These results indicate that the AR directs different transcriptional programmes in AIPC and ADPC cells.