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p53-dependent regulation of mitochondrial energy production by the NF-κB RelA subunit

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The NF-κB transcription factors are key players in cell stress and inflammatory responses. Abnormal regulation of NF-κB has been linked to human cancers, and the RelA (p65) subunit has been shown to regulate cell proliferation and tumour progression in co-ordination with the p53 tumour suppressor. We discovered that RelA may also play a role in tumour cell metabolism, by regulating ATP production by oxidative phosphorylation in a p53-dependent manner. p53 was found to regulate this mitochondrial function of RelA by inhibiting its interaction with the molecular chaperone Mortalin (hsp70), which is necessary to transport RelA into mitochondria. As U2-OS osteosarcoma cells were grown in culture, an increase in passage number was accompanied by a decrease in p53 levels, and an increase in RelA-Mortalin binding and RelA presence in mitochondria. In the mitochondria, RelA was shown to bind mitochondrial

DNA and down-regulate gene expression, resulting in reduced oxygen consumption and cellular ATP levels. These effects could be reversed by knocking down RelA. The ability of RelA to affect mitochondrial gene expression was dependent on its conserved C-terminal transactivation domain, and not its DNA binding domain, suggesting the need of a direct interaction with mitochondrial transcription factors. Taken together, we identified a new role for RelA in regulating cellular energy production, providing new insights into how the activity of NF-κB and loss of p53 may alter cell metabolism in tumourigenesis.

Biography

Ini-Isabée Witzel conducted her PhD studies in Cellular and Molecular Biology at the Dundee Wellcome Trust Biocentre (Scotland) and Bristol University (UK), funded by Cancer Research UK. She subsequently spent two years working as a molecular biologist in diagnostics in New Zealand, designing and validating biochemical tests for the detection of infectious diseases. Since December 2013, she has been conducting her Post-doctoral studies at Khalifa University in Abu Dhabi. Her research interests lie in unraveling changes in gene expression and regulation that contribute to the development of complex diseases, such as cancer and inflammatory disorders, to ultimately enhance diagnosis, prognosis and treatment.

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