

**P009** Promotion of differentiation and apoptosis by militarinone A-triggered ROS production

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We recently discovered that militarinone A, a fungal metabolite from *Paecilomyces militaris*, was able to stimulate neuronal outgrowth in primed PC12 cells under defined conditions within 24 hours. Its ability to induce differentiation was due to activation of the PI3-K and the MAPK pathways, and phosphorylation of CREB. Application of militarinone A to other cells such as the murine neuroblastoma cell line N2a, however, resulted in immediate onset of apoptosis.

We show here that both events are due to the generation of reactive oxygen species (ROS) by modulation of membrane fluidity of both cellular and mitochondrial membranes, and subsequent stabilisation and phosphorylation of p53. In both cell lines, militarinone A-treatment resulted in independent activation of diverse signalling cascades and transcription factors binding to the consensus sequences of antioxidant responsive element (ARE), NF- $\kappa$ B, and AP-1. In PC12 cells, these events were long-lived and resulted in neuronal differentiation within one day, but programmed cell death within three days. In N2a cells activation of ARE, NF- $\kappa$ B and AP-1 was transient and apoptosis was induced within hours by caspases, but also caspase-independent pathways, as pre-treatment with Z-VAD-Fmk only slightly prolonged life-span, and nuclear translocation of AIF was observed.