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Smac mimetic induces an early wave of gene expression via NF-κB and AP-1 and a second wave via TNFR1 signaling

Nadine Schmidt, Tinka Haydn, Ines Schneider, Hauke Busch, Melanie Boerries, Simone Fulda

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Abstract

Smac (second mitochondria-derived activator of caspases) mimetics are considered as promising cancer therapeutics, but little is yet known about how they alter gene expression. In this study, we used an unbiased genome-wide expression array to investigate gene regulation induced by the Smac mimetic BV6 in breast cancer cell lines. Here, we discover that tumor necrosis factor (TNF)α/TNF receptor 1 (TNFR1) auto-/paracrine signaling regulates Smac mimetic-stimulated changes in gene expression in a time-dependent manner. TNFR1-independent and -dependent genes account for two subsequent waves of BV6-induced gene expression. While the first wave mostly comprises TNFR1-independent genes and involves nuclear factor-kappa B (NF-κB) and activator protein (AP)-1 transcription factors, the second wave largely depends on TNFR1 signaling. Interestingly, disrupting auto-/paracrine TNFα/TNFR1 signaling by knockdown of TNFR1 strongly attenuates the BV6-induced second wave of gene expression and upregulation of many pathways, including NF-κB, apoptosis and immune signaling, while activation of mitogen-activated protein kinase (MAPK) signaling occurs also in TNFR1 knockdown cells. Thus, BV6 alters gene expression in a time- as well as TNFR1-dependent manner.