

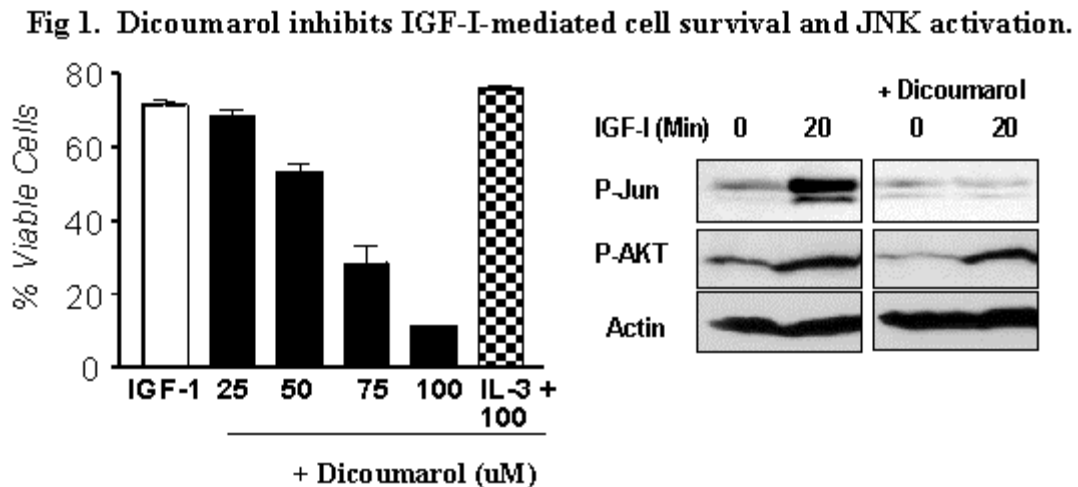
STRESS-ACTIVATED PROTEIN KINASES (SAPKS) IN IGF-I MEDIATED CELL SURVIVAL

Darren Krause, Anthony Lyons, Patrick Walsh, and Rosemary O'Connor

Cell Biology Laboratory, Biochemistry Department, Biosciences Research Institute, National University of Ireland, Cork, Ireland

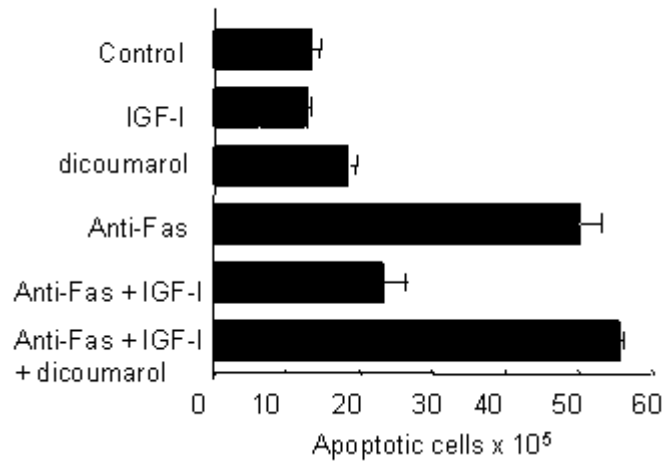
INTRODUCTION. The IGF-I receptor is a potent mediator of cell survival in response to diverse death stimuli in different tissues. Several signalling pathways can be activated by the IGF-IR including the PI-3 kinase/AKT pathways leading to cell death regulators. However, there is also evidence for IGF-I-mediated survival signalling that is not dependent on PI-3 kinase and AKT activation. Here, we investigated the stress activated protein kinases (SAPKs) including Jun N-terminal kinase (JNK) and p38 as candidate mediators of PI-3 kinase independent survival signalling.

RESULTS. Initial experiments demonstrated that IGF-I elicits transient phosphorylation of JNK and c-Jun in FL5.12/IGF-IR cells (1) even in the presence of the PI-3 kinase inhibitor LY294002. To determine if JNK contributes to IGF-I-mediated survival signalling we used the quinone reductase inhibitor dicoumarol, which inhibits JNK activation (2). Dicoumarol suppressed IGF-I-induced phosphorylation of c-Jun and caused a dose-responsive abrogation of IGF-I-mediated protection from IL-3 withdrawal, but did not affect AKT activation (Fig. 1).



DISCUSSION. We found that JNK and c-Jun are phosphorylated by IGF-I stimulation of activated T cells, and as shown in (Fig. 2) IGF-I protects activated T cells from Fas-induced apoptosis. However, this protection is completely suppressed by dicoumarol.

Fig. 2



We also assessed the status of the p38 kinase in FL5.12 cells and found that although p38 was constitutively phosphorylated in these cells the p38 inhibitor SB203580 could suppress IGF-I-mediated protection from IL-3 by approximately 50%. Altogether, these data demonstrate that transient activation of Jun kinases by IGF-I occurs in a PI-3 kinase independent manner, and suggests that activated SAPKs are required for IGF-I survival signalling.

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