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Impact of activation of MAP kinase family members on endocrine response and survival in clinical breast cancer

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There is increasing evidence implicating aberrations in peptide growth factor signal transduction in the phenomena of *de novo* and acquired antihormonal resistance in breast cancer. Of particular interest in this regard is the extracellular-signal related kinase (ERK) 1/2 mitogen-activated protein kinase (MAPK) phosphorylation cascade which, in addition to its classical mitogenic route, appears to phosphorylate the oestrogen receptor (ERα) in experimental systems. Importantly, therefore, the present *in vivo* immunocytochemical study has demonstrated an association between increased ERK 1/2 MAPK activation and a poor quality ($P=0.011$) and duration ($P=0.012$) of endocrine response, as well as with a shortened survival ($P=0.05$) in primary breast cancer patients. These data, thus, confirm the predicted importance for the MAPK signalling network in breast cancer *in vivo* and may provide prognostic and therapeutic information highly relevant in the future management of the disease. Interestingly, parallel monitoring of the Jun Kinase (JNK) and p38/Hog 1 phosphorylation revealed that their co-expression improves both the endocrine response and survival of ERK 1/2 positive patients ($P=0.026$ and $P=0.057$, respectively). These 'stress-activated' MAP kinase family members may, thus, 'counterbalance' ERK 1/2 MAPK signalling and may prove valuable targets for its manipulation. Finally, while relationships were apparent between ERK 1/2 activation and the expression of known MAPK pathway elements (e.g. EGFR ($P=0.015$); TGFα ($P=0.056$), no supportive evidence of MAPK 'cross-talk' with ERα signalling was noted. This discordance with *in vitro* transfection studies certainly emphasises the complex biology underlying ER/growth factor signalling pathway interactions in the control of tumour expansion.

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Increased vascularity in norethisterone-based hormone replacement therapy compared with the natural cycle

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1. Introduction

Postmenopausal sex steroid administration is associated with the initiation of withdrawal bleeding. In 50% of instances, such bleeding is irregular, leading to approximately 50% of women discontinuing the treatment. Women on cyclical sequential norethisterone (NET), exhibit two patterns of bleeding; early bleeders who bleed before the completion of the progestogen phase of cyclical sequential hormone replacement therapy (HRT) cycle, and late bleeders who bleed after the completion of the progestogen phase. This suggests a different response of the endometrial vas-

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