THE ROLES OF MAP KINASES IN CONTROLLING CANCER METASTASIS

Alessandro Alessandrini

Medical Services, Massachusetts General Hospital, Department of Medicine, Harvard Medical School

INTRODUCTION

MEK (Map/Erk Kinase) family members are key components in an intracellular signaling pathway called the ERK (Extracellular-signal Regulated Kinases)/MAP kinase pathway, implicated in the transition of cells from Go to G1 in the cell cycle (1-3). Members of this kinase cascade are highly conserved between species from yeast to mammals (3). In addition, proteins with sequence similarity to ERK/MAP kinases and MEK participate in other cellular signaling pathways; for instance those responding to stresses such as osmotic shock and UV-induced DNA (4). The MAP/Erk kinase cascade is activated following stimulation of a wide variety of cell types with growth factors, hormones, or mitogens. The binding of these various ligands to the appropriate cell surface receptor results in receptor activation, which in turn leads to GTP binding of Ras complexed to members of the Raf family of serine/threonine kinases. Raf family members then activate the kinases MEK1 and MEK2 by phosphorylating them on serines 218 and 222 for MEK1, or 222 and 226 in the case of MEK2. MEKs, as dual specificity kinases, subsequently activate their downstream targets, ERK-1 and ERK-2, by phosphorylating them on threonine and tyrosine. ERKs then phosphorylate both cytoplasmic substrates and nuclear transcription factors, which, thus modified, contribute to the early response of the cell after stimulation. Although there are seven known members of the MEK family of kinases at present, only two of them, MEK1 and MEK2, have been shown to play a role in the ERK/MAP kinase pathway (4-10).

“Stress response protein kinases” (reviewed in (11, 12)), are only minimally activated by growth factors but are markedly activated by genotoxic stress, osmolar stress, and inflammatory cytokines (TNF and IL-1). The stress response MAP kinases, however, are also activated by agonists with heterotrimeric G protein-coupled receptors, including Ang II, ET-1, and α-adrenergic agents, which play important roles in hypertension, hypertrophy, and diabetic nephropathy. In addition, they are activated by cell stretch and shear.

stress. One family, which has 54 and 48 kDa isoforms encoded by at least three genes, has been designated either stress activated protein kinases (SAPKs), since they are activated by cellular stress, or c-Jun N-terminal kinases (JNKs), based on the ability of the kinases to phosphorylate the amino terminus of c-Jun (11, 13, 14). The other stress kinase family includes p38a, the mammalian homolog of HOG-1, a yeast kinase involved in the response to osmolar stress, and three related kinases, p38B, p38g, and p38d. Like ERK1/2, the SAPKs and p38 are proline directed and require phosphorylation on both tyrosine and threonine residues for activation (15). Unlike the TEY motif of the ERKs, the SAPKs contain a TPY motif and p38 a TOY motif within kinase subdomain VIII which, when phosphorylated, activates the kinases. Overall, there is 40-50% identity in the catalytic domains when comparing the ERKs, SAPKs, and p38 (16).

1. THE MAP KINASE PATHWAYS

Growth factors, such as platelet derived growth factor (PDGF), epidermal derived growth factor (EGF), fibroblast growth factor (FGF), insulin, insulin-like growth factor-1 (IGF-1), colony stimulating factor-1 (CSF-1), nerve growth factor (NGF), etc., as well as cellular stresses, have been shown to activate signal transduction pathways, such as the MAP kinase pathways. These growth factors may play an important role in cell growth and differentiation. This chapter will specifically deal with the role that MAP kinases play in metastasis.

1.1 The MEK/ERK Pathway (Figure 1)

The MAP/ERK kinase cascade is activated following stimulation of a wide variety of cell types with growth factors, hormones, or mitogens. The binding of these various ligands to the appropriate cell surface receptor results in receptor activation, which in turn leads to GTP binding of Ras complexed to members of the Raf family of serine/threonine kinases. Translocation of Raf-1 to the plasma membrane by Ras is necessary for the activation of Raf-1 (17, 18). However, co-incubation of purified GTP-loaded Ras with c-Raf-1 fails to fully activate the latter, suggesting that a membrane-localized co-factor may be necessary.