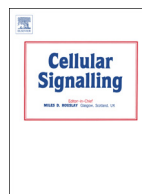




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MAPK-induced Gab1 translocation to the plasma membrane depends on a regulated intramolecular switch

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ABSTRACT

The timely orchestration of multiple signalling pathways is crucial for the integrity of an organism and therefore tightly controlled. Gab family proteins coordinate signal transduction at the plasma membrane (PM) by acting as docking platforms for signalling components involved in MAP kinase (MAPK), PI3 kinase (PI3K), phospholipase C (PLC) and Rho family GTPase signalling. The interaction with these components as well as the targeting of the docking platform to the PM underlies complex spatial and temporal regulatory mechanisms. Deregulated Gab1 activation and membrane binding have been observed in some haematopoietic malignancies and solid tumours, thereby contributing, for example, to the development of Philadelphia chromosome-negative myeloproliferative neoplasms and certain lung cancers. Previously, we could demonstrate that the presence of PIP3 in the PM, which is increased in many cancer cells, is not sufficient for constitutive Gab1 membrane recruitment. In addition, MAPK-dependent phosphorylation of Gab1 at serine 552 (Ser552) is vital for Gab1 membrane binding. Here, we confirm our hypothesis that in the absence of MAPK activity an intrinsic part of Gab1 prevents binding to PIP3 at the PM. This epitope of Gab1, which encompasses Ser552, interacts directly with the Gab1 PH domain. Two arginines located in positions +4 and +8 of Ser552 are essential for the interaction with the PH domain, as well as for the inhibition of membrane recruitment of unphosphorylated Gab1. Ser552 phosphorylation is dispensable in respective arginine to alanine mutants of Gab1. Gab1 recruitment to the PM is highly dynamic and continuous PI3K and MAPK activities are both essential for sustained Gab1 membrane localisation. Our data document the existence of a sophisticated and robust control mechanism that prevents Gab1 translocation and signalling complex assembly after the activation of either MAPK or PI3K alone.

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1. Introduction

Cytokines initiate the simultaneous and well-orchestrated activation of several signalling events. The coordination of these processes is of crucial importance for the homeostasis of an organism. Interleukin-6 (IL-6) signals through the Janus kinase (Jak)/signal transducer and activator of transcription (STAT) pathway. In addition, IL-6 also activates the mitogen activated protein kinase (MAPK) cascade and the phosphoinositide-3-kinase (PI3K) cascade. As shown in detail by the work of Ernst and colleagues [1] unbalanced JAK/STAT3 and MAPK signalling leads to severe proliferative and immunological diseases. Activation of these signalling pathways by a constitutively active mutant of JAK2, namely JAK2-V617F, is found in many Philadelphia chromosome-negative myeloproliferative neoplasms such as polycythemia vera, essential thrombocythemia, or primary myelofibrosis [2,3]. STAT3-independent signalling is coordinated by the adapter protein Grb2-associated binder 1 (Gab1) [4–6].

Abbreviations: Crk, CT10 regulator of kinase; CRKL, Crk-like protein; ERK, extracellular signal regulated kinase; FCS, foetal calf serum; Gab1, Grb2-associated binder 1; Grb2, growth factor receptor bound protein 2; IL-6, interleukin-6; JAK, Janus kinase; HEK, human embryonic kidney; PI3K, phosphatidylinositol-3-kinase; MAPK, mitogen activated protein kinase; MAPPIT, mammalian protein–protein interaction trap; MPN, myeloproliferative neoplasms; PH, pleckstrin homology (domain); PIP3, phosphatidylinositol-trisphosphate; PLC, phospholipase C; PM, plasma membrane; RasGAP, Ras-GTPase activating protein; PVDF, polyvinylidene-difluoride; SHP2, Src-homology domain containing phosphatase 2; STAT, signal transducer and activator of transcription

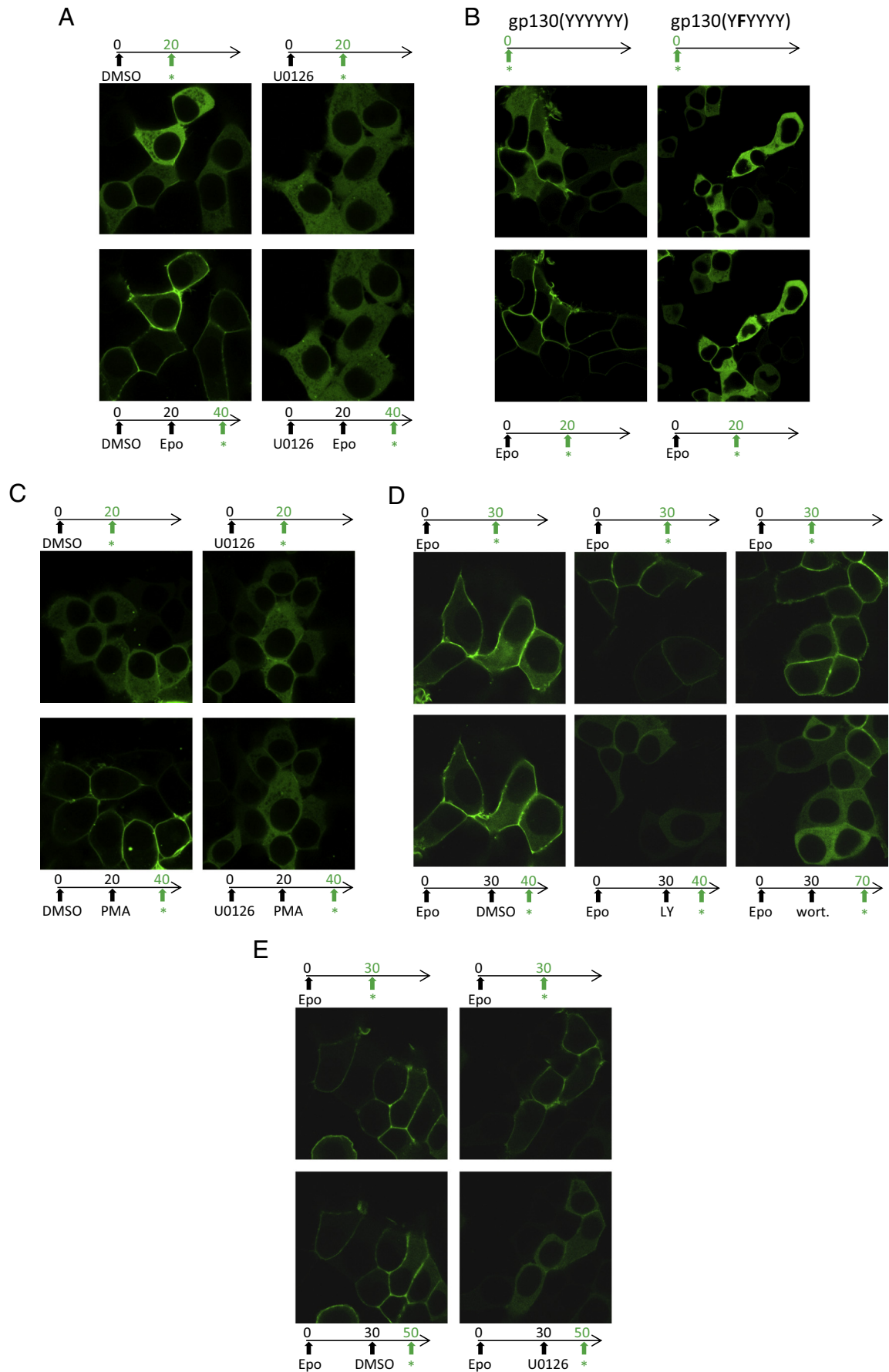
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