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Signalling networks in focus

The TAK1–TRAF6 signalling pathway

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ABSTRACT

Cellular responses to pathogens, growth factors, cytokines, extra- or intra-cellular stress, is a prerequisite for the cell to adapt to novel and potentially dangerous situations. If the changes in the extra- or intra-cellular milieu causes DNA-damage or revoke a signalling pathway utilized during morphogenesis, the epithelial cells might be forced to undergo programmed cell death (apoptosis) in the benefit for the whole organism or transform to a mesenchymal cell type (epithelial to mesenchymal transition; EMT), in respond to a specific stimuli. An overview is presented over the current knowledge for the key components in signal transduction in homeostasis, inflammation and cancer. A handful of transcription factors are crucial for the determination of the specific cellular responses, where the transforming growth factor-β (TGF-β) is an important factor as discussed in this review.

1. Introduction

Transforming growth factor-β activated kinase-1 (TAK1) is a serine/threonine kinase in the mitogen-activated protein kinase kinase kinase (MAPKKK) family. TAK1 is a key player in the cascades of cellular responses evoked by changes in the environment, as its activity is regulated by various cytokines including interleukin-1 (IL-1), transforming growth factor-β (TGF-β) and by toll-like receptors (TLR), CD40 and B cell receptors. Once activated, TAK1 will in turn, activate crucial intra-cellular kinases; the p38 MAPK, c-jun N-terminal kinase (JNK) and I-kappa B kinase complex (IKK). p38 MAPK and JNK control the transcription factors activator protein-1 (AP-1), while nuclear factor-kappa B (NF-κB) is activated by IKK. Recently, TAK1 has also been implicated in activation of the tumor suppressor protein the LKB1 kinase. Transcriptional responses initiated by these pathways are of fundamental importance for the whole organism as they determine cell fate and protect us from microbes and changes in osmolarity.

TAK1 was originally characterized by Matsumoto and coworkers, who demonstrated that the kinase activity of TAK1 was activated in response to TGF-β and bone morphogenetic protein, to regulate p38 MAPK and gene transcription (Yamaguchi et al., 1995). TAK1 regulates cell survival, differentiation and inflammatory responses via a number of specific transcription factors (Fig. 1a; for further reading see this reveiew; Adhikari et al., 2007). Recently, TAK1 has also been implicated in activation of the tumor suppressor protein, the LKB1 serine/threonine kinase (Fig. 1b; Adhikari et al., 2007; Xie et al., 2006). LKB1 can in turn directly activate a family of 14 kinases related to AMPK [adenosine monophosphate (AMP)-activated protein kinase] in order to control cell metabolism, growth and polarity (Shaw, 2009). However, the downstream kinases crucial for the tumor suppressor functions of LKB1 have not been clarified until recently, when the LKB1-dependent kinase salt-inducible kinase 1 (SIK1) was identified (Cheng et al., 2009). The fact that TAK1 is acting upstream in all of these important pathways underscores the crucial role of TAK1 to determine cellular responses to growth factors, cytokines or stress. In this review I will give an overview over our current understanding for the signalling pathways that regulate the activity of TAK1 to confer its function as a central, key regulatory sensor for extra-cellular cues.

The ability of cells to respond to their environment is determined by its membrane-bound receptors classified according to their protein composition and presence of kinase domains. The cell membrane-bound receptors become activated when the specific

Abbreviations: ALK, activine like kinase; AMPK, adenosine monophosphate (AMP)-activated protein kinase; AP-1, transcription factors activator protein-1; BCR, B-cell receptor; BMP, bone morphogenetic protein; CYLD, cylindromatosis; CUE domain, Cue1-homologous; DUB, deubiquitination enzymes; E2, ubiquitin-conjugating enzyme; EMT, epithelial–mesenchymal transition; GTPase, guanosine triphosphatases (GTPase); IKK, I-kappa B kinase complex; IL-1, interleukin-1; IL-6, interleukin-6; JNK, c-jun N-terminal kinase; MAPKKK, mitogen-activated protein kinase kinase kinase; MARKs, microtubule affinity-regulating kinases; MEFs, mouse embryonic fibroblasts; NEMO, NF-κB essential modulator; NF-κB, nuclear factor-kappa B; NIK, NF-κB inducing kinase; NZF, novel zinc-finger; PAI-1, plasminogen activator inhibitor-1; PI3K, phosphoinositide-3-kinase; RIP, receptor interacting protein-1; SADs, synapses of the amphid defective; SBE, Smad-binding elements in different promoters of genes; SIK, salt-inducible kinase 1; TAB1, TAK1-associated binding protein-1; TAK1, transforming growth factor-β activated kinase-1; TβRII/I, TGF-β receptors, type II and type I; TCR, T-cell receptor; TGF-β, transforming growth factor-β; TLR, toll-like receptors; TRAF6, tumor necrosis factor-6; TRIKA1/TRIKA2, TRAF6-regulated IKK activators 1 and 2.

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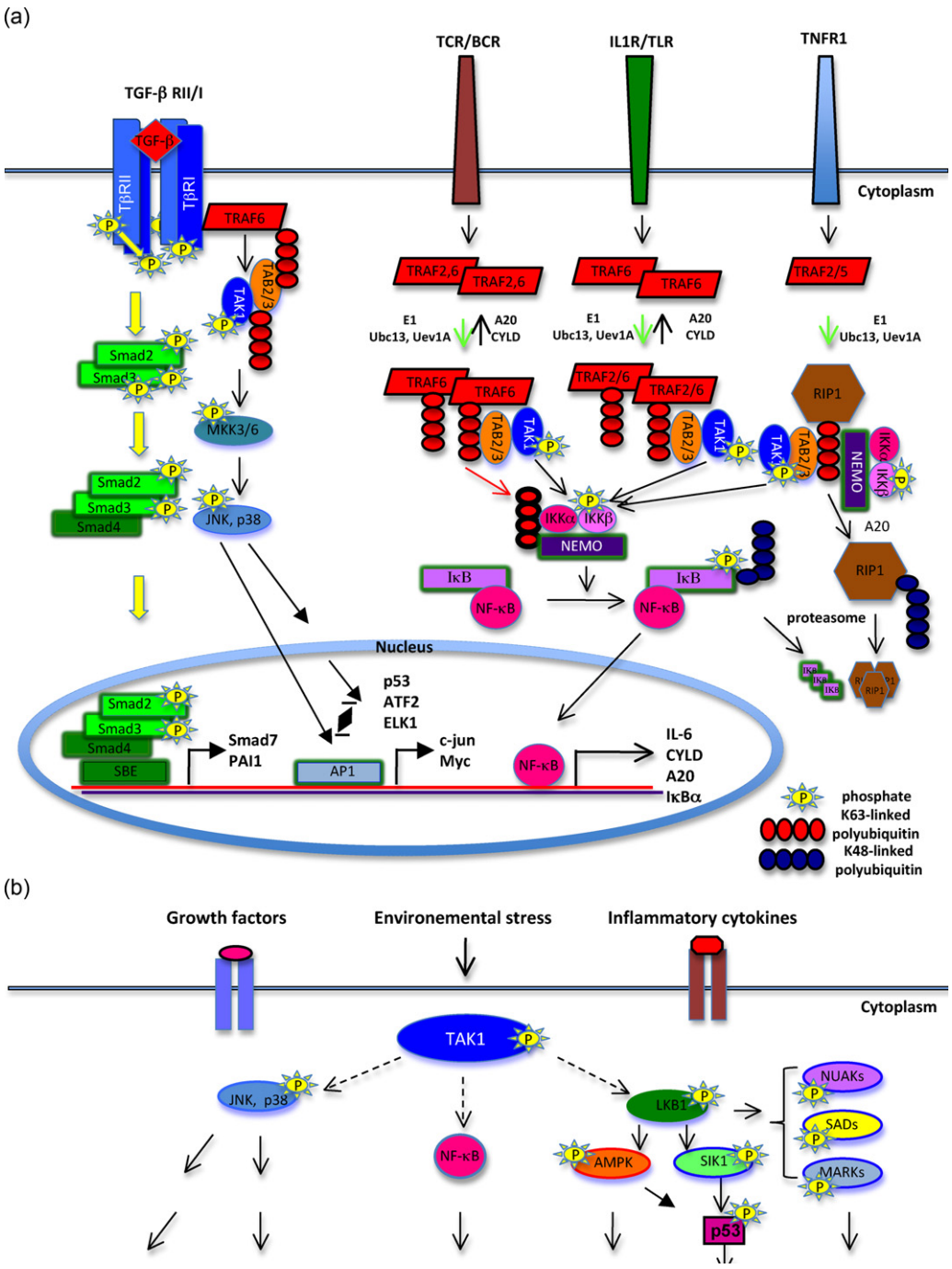

Fig. 1. (a) Ubiquitin-mediated activation of TAK1, p38/JNK and IKK by TGF-β as well as in innate and adaptive immunity pathways. Exposure of cells to growth factors, proinflammatory cytokines and pathogens, causes activation of a single or pairs of specific ubiquitin ligase (E3-ligase); TRAF2, TRAF5 or TRAF6. The E3-ligase causes then Lys-63-linked polyubiquitination of their specific targets; receptor interacting protein-1 (RIP1), downstream of TNF-α receptors, TRAF2 and/or TRAF6; downstream of TGF-β receptors (TβRII/I), interleukin-1 receptor (IL1R), toll-like receptors (TLR), T-cell receptor (TCR), B-cell receptor (BCR). Lys-63-linked polyubiquitination attracts the TAB2/TAB3 proteins which also promote activation of TAK1, which in turn can directly phosphorylate MKK3/6 and IKKβ in the p38/JNK and NF-κB pathway, respectively. The deubiquitinating enzymes (DUB) A20 and CYLD can counteract the activity of IKK and JNK. Lys-48-linked polyubiquitination confer proteasomal degradation of RIP1 and IκB, to release NF-κB and promote its nuclear accumulation (for further details see Adhikari et al., 2007). The canonical Smad-signalling pathway is not dependent of TRAF6 (Sorrentino et al., 2008; Yamashita et al., 2008). TGF-β-activation results in activation of Smad proteins, binding to Smad-binding elements (SBE) in different promoters of genes (Derynck and Zhang, 2003; Heldin et al., 2009; Massagué, 2008a,b; Wakefield and Roberts, 2002). Activation of p38/JNK and NF-κB occurs downstream of the TRAF6–TAK1 pathway. The p38 MAPK- and JNK-regulated gene transcription can counteract each other (Wagner and Nebreda, 2009). Activation of NF-κB results in transcription of the pro-inflammatory cytokine interleukin-6 (IL-6), DUBs which thereby can inhibit further signalling and IκBα. (b) Changes in the extra-cellular milieu causes activation of TAK1, which in turn causes activation of p38/JNK, NF-κB and the serine/threonine kinase LKB1. LKB1 can directly activate a family of different kinases related to AMPK (adenosine monophosphate (AMP)-activated protein kinase) to regulate cell metabolism and cellular growth. LKB1 also regulate the microtubule affinity-regulating kinase (MARKs), synapses of the amphid defective (SADs) and NUAKs, to control cell polarity. The salt-inducible kinase1 (SIK1) has recently been found to be a tumor suppressor as it regulate a specific form of apoptosis and activity of the tumor suppressor p53 (Cheng et al., 2009; Shaw, 2009).