TAK1: Kinase at the Crossroads

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Since its identification as a mediator of TGFb signals in 1995 [1], TGFb-Activated Kinase, or TAK1, has been implicated in an increasingly diverse array of cellular activities, including embryonic development, apoptosis, innate immunity, and inflammation. TAK1 has also been shown to act as a tumor suppressor in liver [2] and prostate [3] tissues. More recently, it has emerged as a potential therapeutic target for treatment of ischemia [4] and cancer [5]. A key component of multiple signaling pathways, TAK1 generates highly specific responses in different cell types and processes. Thus, a thorough delineation of the biochemical mechanisms underlying this specificity is critical to our understanding of TAK1 function and to advances in the development of therapies targeting TAK1.

TAK1 is activated in response to several different ligand-receptor interactions, including TGFb, the TGFb-related Bone Morphogenetic Proteins (BMPs), and several members of the wnt family in the non-canonical "wnt/calcium" pathway (Figure 1). It also mediates signaling in response to Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) [5]. Activation can occur via heterodimerization with the TAK1-Binding Protein TAB1 and subsequent autophosphorylation. In inflammation and innate immunity pathways, polyubiquitination of TAK1 and subsequent binding to TAB2/3 are required for rapid activation of NF-kB. Activation via different pathways may lead to differences in localization: following activation by the noncanonical wnt signaling, TAK1 translocates to the nucleus, while TAK1 activated in response to BMPs apparently acts predominantly in the cytoplasm. The TAB proteins are thought to contribute to substrate selectivity; behavior and localization of the TAB proteins may be regulated by post-translational modifications, including phosphorylation, ubiquitination, or addition of N-acetylglucosamine.

TAK1, a MAP Kinase Kinase Kinase family member (MAP3K7), phosphorylates and activates MAP Kinase Kinase (MAP2K) family members, including MKK4, MEK6, and MEK7, which phosphorylate and activate the MAP kinases p38 or Jun N-terminal kinase (JNKs).

Figure 1: TAK1 is an effector in multiple signaling pathways. Specific pathways including ligands, receptors, and targets of TAK1 regulation, are identified by color. The upstream component triggering TAK1 phosphorylation of AMPK is unknown.

However, TAK1 also activates the MAP kinase-related Nemo-like Kinase (NLK), which regulates multiple transcription factors, and it contributes to the activation of NF-kB via phosphorylation of IkB-Kinase-a (IKKa). In addition, TAK1 has been shown to phosphorylate AMP-Activated Kinase (AMPK), a key regulator of cellular metabolic activity. Most if not all of these interactions are highly conserved across the animal kingdom.

TAK1 in Inflammatory and Immune Responses

The biochemical mechanisms underlying TAK1 regulation and function have been most clearly delineated in the context of the interleukin-1 (IL1) or Tumor Necrosis Factor-a (TNFa) pathway activating NFkB during inflammation or the innate immune response. Binding of either cytokine to its receptor leads to recruitment of Il1 Receptor Associated Kinases (IRAKs), which interact in turn with TNF-Receptor-Associated Factor 6 (TRAF6). TRAF6 recruits the E2 ubiquitin-conjugating enzymes UBC13 and UEV1A; these enzymes are responsible for the K63-linked polyubiquitination that activates TAK1 [6]. The establishment of a multi-protein complex including TAK1, TAB2/3, MKK3, and TRAF6 is necessary for the phosphorylation of IKKa by TAK1, which mediates the rapid activation of NFkB.

TAK1 in Embryonic Development

TAK1 contributes to early developmental processes in both vertebrate and invertebrate embryos. During *C. elegans* development, noncanonical wnt signaling activates the TAK1 orthologue MOM-4; MOM-4 phosphorylates the NLK orthologue lit-1, which in turn phosphorylates the TCF family member POP-1. Once phosphorylated, POP-1 translocates from the nucleus to the cytoplasm, which terminates transcriptional activation by canonical wnt/b-catenin signals [7]. This pathway is critical to the establishment of anterior-posterior polarity in *C. elegans* embryos.

In vertebrate development, TAK1 mediates multiple independent processes in the establishment of dorsal vs. ventral cell types. A TAK1/Stat3 pathway is required for the specification of dorsal mesoderm in response to the TGFb family members' activin or nodal [8]. TAK1 also functions in BMP-dependent specification of ventral mesoderm, however: TAK1 mediates feed-forward activation of the BMP4 effector Smad1 via antagonistic crosstalk with erk MAPK, which is a negative regulator of Smad1 [9]. Interestingly, TAK1 has also been shown to bind to Smads, retaining them in the cytoplasm [10]; this sequestration of Smads may establish an "upper limit" on Smad activity.
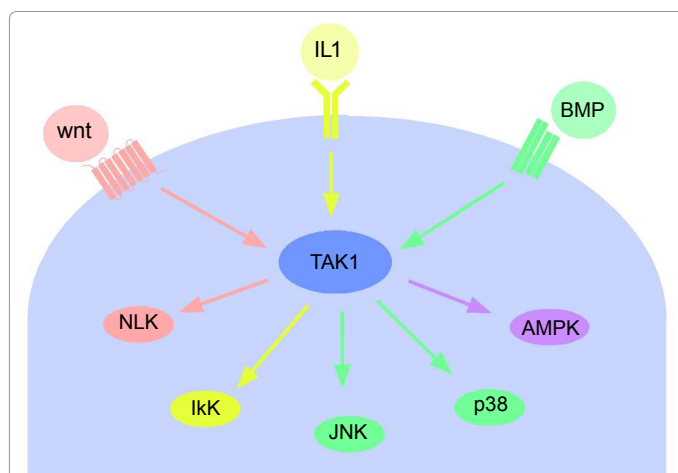
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Role of Ubquitination

While ubiquitination is essential for proper localization and function of TAK1 in the inflammatory response, there is little evidence regarding a role for ubiquitin-mediated TAK1 function in other pathways. It appears that ubiquitination is not required for activation of TAK1 by the TGFb receptor complex. In the latter instance, TAK1 is complexed with TAB1; while in the IL1 pathway, TAK1 interacts with TAB2/3, which are known to bind ubiquitin moieties. It is unclear whether post-translational modification or specific binding proteins are needed for nuclear functions of TAK1, such as phosphorylation of AMPK, HIPK2, or NLK. Alternatively, TAK1 may be recruited by distinct scaffolding proteins that would also be responsible for incorporating appropriate protein targets for phosphorylation.

TAK1 and AMPK

Perhaps the most intriguing question concerns the role of TAK1 in the regulation of AMPK. AMPK is the component responsible for sensing the ratio of intracellular AMP to ATP, an indicator of the energy balance of the cell. With a wide range of targets encompassing key metabolic enzymes, translational components, transcription factors, and chromatin proteins, it plays a pivotal role in the regulation of metabolic activity at both transcriptional and post-transcriptional levels [11]. Three kinases, including Calcium/Calmodulin Kinase II (CaMKII), Liver Kinase B1 (LKB1), and TAK1 have been shown to phosphorylate mammalian AMPK at a single site on the catalytic a-subunit. It is unclear whether TAK1 regulates AMPK activity in response to extracellular signals. If so, TAK1 might represent the means by which paracrine signals provide input into the regulation of cellular metabolic states. Since alterations in cellular metabolism are a hallmark of cancer cells, the regulation of AMPK by TAK1 may offer a new point of regulation or therapeutic intervention in the treatment of malignancies.

Our current view of TAK1 suggests that it plays significant roles in a diverse array of intracellular processes. Moreover, TAK1 has considerable potential as a therapeutic target in inflammation, ischemia, cancer, and possibly some metabolic disorders. Elucidation of the biochemical mechanisms underlying the target specificity of TAK1 will enlarge our understanding of its multifunctionality.

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