The films could be used in the spot cooling of electronics if they can be produced quickly and cheaply. More importantly, the studies prove that thermoelectric materials with $ZT >> 0.9$ are possible at room temperature.

An all-solid thermoelectric refrigerator that could cool below the transition temperature of a cuprate superconductor would be extremely attractive for a variety of proposed electronic applications. Kanatzidis (Michigan State University) reported the only new bulk material, $CsBi_4Te_6$, with a high value for ZT below room temperature (0.8 at 225 K) (*7*). A prototype thermoelectric refrigerator with $CsBi_4Te_6$ is being evaluated for possible use near liquid nitrogen temperatures (≈100 K). Singh (Naval Research Lab) predicted that some fully filled skutterudites (complex materials whose chemical formula is $ReTm_4Pn_{12}$, where Re is a rare earth material, Tm is a transition metal, and Pn is P, As, or Sb) should have excellent thermoelectric properties around 100 K. This prediction needs to be tested experimentally.

The most promising new materials for power generation applications are filled skutterudites such as $CeFe_4Sb_{12}$ and $Yb_{0.2}Co_4Sb_{12}$ (*8*, *9*), Zn_4Sb_3 (*10*), Tl_2SnTe_5 (*11*), Tl_9BiTe_6 (*12*), and clathrates (see the right panel in the second figure) such as $Sr_8Ga_{16}Ge_{30}$ (*13*). Caillat (Jet Propulsion Laboratory) is evaluating advanced multistage power generation modules that incorporate both filled skutterudites and Zn_4Sb_3. The thallium compounds have good ZT values, but the toxicity of thallium may be a barrier for many applications.

Most terrestrial power generation applications are focused on the conversion of waste heat into useful electricity. Automobiles, steel, and chemical industries could in theory benefit from thermoelectric generators. Peter Hagelstein (MIT) and Yan Kucherov (Eneco) presented the development of an improved device for waste heat power generation (*14*). This device could be important if other scientists can verify the results.

Today you can go to your local supermarket and purchase a thermoelectric picnic cooler powered by the cigarette lighter in your car. Will thermoelectric devices ever extend beyond such niche markets? Maybe. The hard work by many researchers over the past 5 to 10 years suggests nanostructures as a possible path to materials with higher values of ZT. If we can self-assemble in large quantities the types of structures that are now produced with molecular beam epitaxy (a very slow and expensive method), thermoelectrics may become a multibillion dollar industry.

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PERSPECTIVES: SIGNAL TRANSDUCTION

Scaffolding Proteins—More Than Meets the Eye

Gary Johnson

Enzymes called mitogen-activated protein kinases (MAPKs) are crucial components of many signaling pathways that regulate cellular activities as diverse as motility, gene expression, cell division, and programmed cell death (*1*). MAPKs are activated by addition of a phosphate group (phosphorylation) to a tyrosine/threonine (TXY) motif in the activation loop of their catalytic domain (*2*). The MAPK activation pathway consists of a three-kinase "phosphorelay" arrangement. Upstream signals, such as cytokine receptor activation, the inflammatory response to infection, or cell-shape changes, activate a MAPK kinase kinase (MKKK), which in turn phosphorylates and activates a MAPK kinase (MKK). MKKs are selective in recognizing specific MAPKs and phosphorylate both the tyrosine and threonine residues in the TXY motif of the MAPK activation loop (*3*). At last, as reported by Ge *et al.* (*4*) on page 1291 of this issue, a different pathway for MAPK activation has been discovered. The authors show that the TAB1 scaffolding protein binds to a MAPK called p38α, inducing this MAPK to phosphorylate itself (autophosphorylation) and become activated. TAB1, a scaffolding protein that organizes other proteins into complexes, is not a kinase and apparently has no catalytic activity (*5*). The Ge *et al.* discovery of TAB1-mediated autophosphorylation and activation of p38α dispels the notion that MAPKs are regulated only by a three-kinase phosphorelay module. Furthermore, their work implies that MAPKs can be activated by protein interactions that are independent of phosphorylation mediated by MKKs.

Using recombinant purified TAB1 and p38α, the authors show that TAB1 binds to p38α and stimulates autophosphorylation of its TGY motif, resulting in the initiation of kinase activity. Wild-type p38α is unable to phosphorylate a second kinase-inactive p38α in the presence of TAB1, indicating that autophosphorylation is likely to be an intramolecular and not an intermolecular (transphosphorylation) event. TAB1 does not appear to bind to other isoforms of p38 or to the related c-Jun NH_2-terminal kinases (JNKs).

What do we know about TAB1? Human TAB1 is 504 amino acids in length and has an evolutionarily conserved motif in its carboxyl terminus, which binds and activates TGF-β–activated protein kinase 1 (TAK1). Indeed, the TAB1 carboxyl terminus induces autophosphorylation and activation of both TAK1 and p38α (*5*, *6*). TAB1 has been characterized as an adaptor protein that forms complexes with other components of the interleukin-1 (IL-1) receptor signaling pathway (*6*). More recently, TAK1-TAB1 complexes have been found to include a second scaffolding protein, TAB2 (*7*). TAK1-TAB1-TAB2 complexes are involved in regulation of the transcription factor NF-κB by TRAF6, and in MAPK signaling. When cells are treated with IL-1β, a chain of ubiquitin molecules is added to TRAF6 (polyubiquitination), altering its interactions with other proteins and resulting in TAK1 acti-

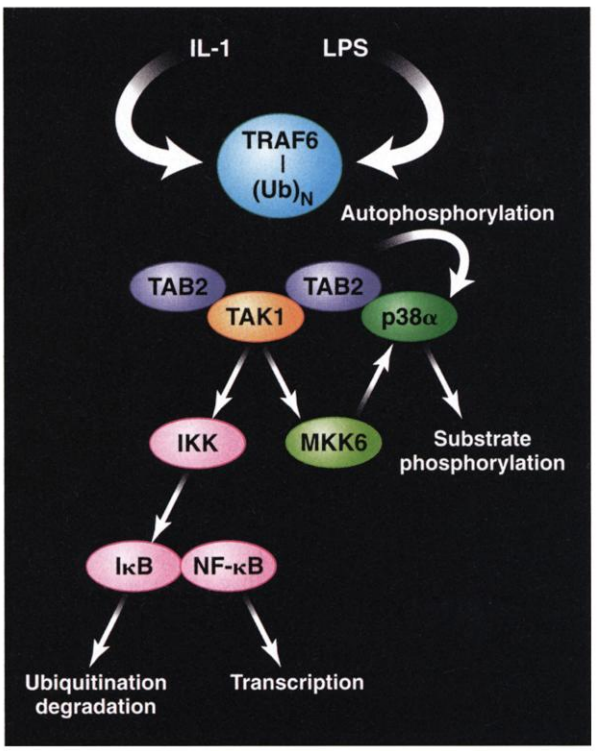
The author is in the Department of Pharmacology, University of Colorado Health Sciences Center, Denver, CO 80262, USA. E-mail: gary.johnson@uchsc.edu

vation (*8*). TAK1 then activates IκB kinase (IKK) leading to NF-κB activation, and MKK6 resulting in p38α activation.

The Ge *et al.* work indicates that p38α can be activated by either of two pathways: the usual MKK6 pathway or a second pathway involving TAB1-dependent autophosphorylation. The investigators made this discovery using an inhibitor of the p38 active site, SB203580. This inhibitor blocks auto- but not transphosphorylation of p38α, enabling discrimination between the two phosphorylation events. Treatment of cells with SB203580 inhibited p38α phosphorylation induced by tumor necrosis factor–α and peroxynitrite but not by sorbitol (which induces hyperosmolarity in cells). In a B cell line, SB203580 blocked phosphorylation of p38α induced by CpG oligonucleotides and bacterial lipopolysaccharide but not by bacterial lipoproteins. Unfortunately, the authors did not test the effect of SB203580 on cells treated with IL-1β, which would have indicated whether this inhibitor blocks TRAF6-dependent p38α activation.

Not surprisingly, TRAF6 is found associated with TAB1 and p38α when all three are coexpressed in cultured cells. Cells expressing the TLR4 receptor for lipopolysaccharide show increased coimmunoprecipitation of transfected TRAF6-TAB1-p38α, suggesting that the complex is regulated by stimulation of the lipopolysaccharide receptor (see the figure). Because recombinant purified TAB1 can induce the autophosphorylation of p38α in vitro, TRAF6 does not appear to be required for p38α activation per se, but may be necessary for regulation of oligomeric signaling complexes formed in response to lipopolysaccharide or other specific stimuli.

It is not clear how the binding of TAB1 to p38α, inducing its autophosphorylation, bypasses the TAK1-MKK6 pathway. For that matter, it is not clear how TAB1 can induce the autophosphorylation of TAK1. TAB1 purified from insect cells or bacteria does not seem to be covalently modified, for example, through phosphorylation or ubiquitination, in any way that could explain its ability to regulate p38α autophosphorylation. We also have no clue about the factors that might regulate the interaction of TAB1 with p38α. Because TAB1-TAK1 complexes also include TAB2 and can recruit TRAF6, it is likely that TAB1 is regulated by its association with these other proteins. The interactions of TAB1 with other components of the complex may regulate its differential activation of p38α and TAK1. When TAK1 is activated, both the MKK6-p38 and IKK–NF-κB pathways are stimulated. This is in contrast to direct TAB1 activation of p38α, which is independent of the NF-κB pathway. Thus, TAB1 appears capable of differentially regulating the activity of both a MKKK (TAK1) and a MAPK (p38α).



TAB1 and p38α activation. TAB1 is a scaffolding protein found in a complex with TAK1 and TAB2. Appropriate receptor stimulation by IL-1 or lipopolysaccharide (LPS) recruits TRAF6 into the complex. During IL-1 receptor activation by its ligand, TRAF6 becomes polyubiquitinated, which may be an important step for the formation of a functional TAK1-TAB1-TAB2 signaling complex. IL-1 stimulation of cells leads to activation of TAK1, the MAPK kinase kinase in the complex. TAK1 then phosphorylates and activates IKK and MKK6, leading to NF-κB and p38 activation, respectively. Other stimuli such as LPS appear to activate p38α by an alternative mechanism involving TAB1-dependent autophosphorylation of p38α. Intriguingly, other isoforms of p38 cannot be activated by TAB1. TAB1-induced p38α autophosphorylation is the first demonstration of MAPK activation by a scaffolding protein that is independent of an MKK.

To date, there are no other studies defining a nontransphosphorylation mechanism for MAPK activation. Scaffolding proteins such as Ste5 in the pheromone-responsive Fus3 pathway in yeast, JIP (c-Jun NH_2-terminal kinase inhibitory protein) in the JNK pathway, and MP-1 in the ERK1/2 (extracellular signal-regulated kinase 1/2) pathway have been shown to orchestrate the MKKK-MKK-MAPK phosphorelay module, rather than activating MAPKs through inducing autophosphorylation (*8*). Similarly, the cyclin-dependent kinases are regulated through transphosphorylation by CDK-activating kinases. In contrast, calcium-calmodulin–dependent kinase II (CaMKII) is activated by autophosphorylation when it binds to calmodulin through the active-site release of its pseudo-substrate sequence from the kinase active site. This mechanism differs from that for p38α activation where no pseudo-substrate sequence is encoded within the p38α protein. The structure of the TAB1-p38α complex will need to be resolved to define exactly how TAB1 interacts with p38α, inducing its autophosphorylation.

So what is the significance of the Ge *et al.* finding that the interaction of TAB1 with p38α induces autophosphorylation and activation of this MAPK? Every week there are reports in the literature describing the assembly and disassembly of oligomeric protein complexes regulated by either guanosine triphosphatases or covalent protein modifications including phosphorylation, sumoylation, ubiquitination, and proteolysis. Many of these protein-protein interactions regulate the catalytic activity of one or more of their binding partners. The discovery of TAB1-dependent autophosphorylation and activation of p38α reveals a previously unknown way in which MAPKs can be activated. No doubt many such surprises lie in wait as we proceed with our analysis of all of the proteins encoded by the human genome. Surveillance of eukaryotic genomes predicts many proteins that have no known catalytic domain and often no apparent protein interaction motif. Many of these proteins are likely to be scaffolding proteins involved in the organization of protein complexes, and some, like TAB1, may activate MAPKs as well as other cellular signaling proteins. The TAB1 story emphasizes the importance of defining all protein interactions in cells to ensure that unsuspected regulatory responses do not continue to go undetected.

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