Editorial Comment

Big Mitogen-Activated Protein Kinase: A New Player in Vascular Remodeling

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Big mitogen-activated protein kinase (BMK1), also termed extracellular signal regulated kinase 5 (ERK5), is the most recently identified mitogen-activated protein (MAP) kinase family member, and has twice the molecular mass of other MAP kinases. Similar to ERK1/ERK2, the N-terminal half of BMK1 contains both a kinase catalytic domain and a TEY activation motif, while its C-terminal tail is unique and is involved in BMK1-specific molecular functions, including the regulation of the transcription activity of target molecules (*1*, *2*).

As in the cases of the other MAP kinases, BMK1 is activated in response to a variety of stimuli, namely oxidative stress, hyperosmolarity, serum and growth factors (*1*). In response to these stimuli, the BMK1 cascade is activated by sequentially activated kinases, which consist of the kinases MEKK2/MEKK3, MEK5, and then BMK1 (*1*, *2*). BMK1 signaling plays roles not only in physiological cellular responses, including cell proliferation, differentiation, and survival, but also under pathological conditions such as carcinogenesis and cardiovascular diseases (*1*).

In a genetic model of hypertension and congestive heart failure, BMK1 activity was shown to be increased during left ventricular hypertrophy and then reverted to normal during the period of congestive heart failure (*3*). Overexpression of the constitutively active form of MEK5, a highly specific upstream kinase for ERK5, induced cardiomyocyte elongation by interfering with parallel assembly of sarcomeres *in vitro* (*4*). Furthermore, cardiac-specific overexpression of activated MEK5 in mice resulted in rapidly decompensating eccentric cardiac hypertrophy and sudden death, indicating that MEK5-BMK1 plays a role in the induction of eccentric cardiac hypertrophy *in vivo* (*4*). In contrast, BMK1 has also been reported to play a protective role in ischemia/perfusion-induced cardiac injury (*5*).

BMK1 is activated in endothelial cells (EC) by shear stress (*6*), and activation of BMK1 protects EC from apoptosis (*7*), indicating that the action of BMK1 in EC is atheroprotective. Indeed, in recent genetic studies, endothelial-specific knockout mice demonstrated embryonic lethality due to the effect of BMK1 knockout on endothelial function and resultant impaired blood vessel integrity, suggesting that the BMK1 pathway is essential for endothelial survival and the maintenance of blood vessel integrity *in vivo* (*8*).

Platelet-derived growth factor (PDGF) is recognized as a major mitogen in serum and one of the most important growth factors promoting the proliferation of vascular smooth muscle cells (VSMC) and atherogenesis (*9*). The MAP kinases including ERK, c-Jun N-terminal kinase (JNK) and p38 had been reported to participate in both PDGF-induced VSMC proliferation and migration (*10*). Although BMK1 was initially reported to be poorly activated in rat VSMC following stimulation with PDGF (*11*), several recent reports have indicated that stimulation with aldosterone (*12*) and growth factors including PDGF and fibroblast growth factor-2 (FGF-2) (*13*, *14*) do activate BMK1, which then plays a role in VSMC proliferation.

Migration of VSMC is one of the essential processes in the progression of atherosclerosis. In an article appearing in this issue of *Hypertension Research*, Izawa *et al*. demonstrate a new role of BMK1 in VSMC migration (*15*). Namely, their

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research shows that VSMC migration was mediated by PDGF-induced BMK1 activation through the interaction of Grb2-associated binder 1 (Gab1) and SH2 domain–containing protein tyrosine phosphatase (SHP-2). In addition, activated BMK1 was increased in the femoral artery, especially in the tunica media, injured by cuff placement. These findings strongly support the hypothesis that activation of BMK1 in VSMC could promote inflammatory vascular remodeling and the resultant progression of atherosclerosis.

The currently available data concerning the *in vitro* and *in vivo* functions of the BMK1 pathway indicate two contrary effects against cardiovascular diseases. As suggested in this paper by Izawa *et al*. (*15*), BMK1 activation might play a role in the progression of vascular remodeling. Further studies are required to elucidate the *in vivo* functions of BMK1 in vascular remodeling and to provide a novel perspective on a therapeutic strategy for atherosclerosis using the modification of BMK1 signaling.

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