MAPK15 is an attractive therapeutic target for gastric cancer

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We recently reported a study on the functional and clinicopathological significance of mitogen-activated protein kinase (MAPK)15 overexpression in patients with gastric cancer. Our data suggest that patients who overexpress MAPK15 in normal or premalignant stomach tissues may progress to invasive cancer [1]. In this research highlight, we summarize three features of MAPK15 as a potential target for treating gastric cancer. MAPK15 is specifically overexpressed in gastric cancers but not normal tissues. MAPK15 is involved in cell proliferation and tumorigenesis by regulating at least three signal pathways, such as c-Jun activity, telomerase activity, and autophagy. In addition, MAPK15 also has structural potential for development of a specific inhibitor. Based on these observations, MAPK15 may be a novel therapeutic target for gastric cancer.

Keywords: MAPK15; Gastric Cancer; c-Jun; Targeted Therapy

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Mitogen-activated protein kinases (MAPKs) are a family of proline-directed serine/threonine kinases that regulate cell proliferation, differentiation, and survival through a coordination of complex signaling from a variety of extracellular and intracellular stimuli [2]. Currently, 14 MAPKs have been characterized in mammalian cells. The conventional MAPKs are comprised of extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun amino (N)-terminal kinases 1/2/3 (JNK1/2/3), p38 isofoms [a, β, γ, and δ], and ERK5. Atypical MAPKs include ERK3/4, ERK8, and Nemo-like kinase (NLK). MAPK15 is known as ERK 8 for human or ERK7 for mice and rats, and is a recently identified member of the mammalian MAPK family [3]. Human MAPK15 gene is located at chromosome band 8q24.3 and encodes a protein of 544-amino acid with a MAPK catalytic domain and a long C-terminal domain containing two putative SH3-binding sties. However, MAPK15 is considered an atypical MAP kinase due to the lack of specific MAPK kinases upstream, making it different from conventional MAPKs, such as ERK1/2, JNK, p38s, and ERK5 [3-5]. The MAPK15 protein interacts with SRC, TGFB1I1, ESRR, PCNA, and GABARAP through domains in its C-terminal region and plays roles in cell pathophysiological processes [3, 8-9].

Typical MAPK pathways consist of a set of sequentially acting kinases cascade: a MAPK kinase kinase (MAPKK/MEKK), a MAPK kinase (MAPKK/MEK), and a MAPK. The MAPKKK is Ser/Thr kinase, whereas MAPKK stimulates MAPK activity through dual phosphorylation of a highly conserved Thr-Glu-Tyr (TEY) motif within the MAPK15 kinase domain. Although phosphorylation of both Thr-175 and Tyr-177 residues is essential for the enzymatic activity of MAPK15 [2], there has been no evidence that MAPK15 is placed in a typical MEK-MEK-MAP signaling cascade. Conversely, phosphorylation of TEY motif seem to be catalyzed by MAPK15 itself and dephosphorylated by dual specificity phosphatases [10]. Therefore, MAPK15 activity is determined by the balance between the rates of autophosphorylation and
dephosphorylation \cite{10}, and its expression level is known to be regulated by ubiquitination, considering the tight regulation of MAPK15 expression by the ubiquitin-proteosome pathway \cite{11}.

Expression levels of MAPK15 in human cancers show striking tissue-specificity. Low to moderate expression levels of MAPK15 are detected in normal tissues, such as breast, lung, liver, stomach, colon, and kidney \cite{12, 13}. In addition, Chia et al reported that MAPK15 downregulation in breast and lung carcinomas can drive the cancers aggressively by activating cell motility \cite{14}. In contrast, MAPK15 is highly expressed in anaplastic thyroid carcinoma cell lines (ARO, Cal62, and Kat4) and a colon cancer cell line (HCT15) but is expressed at a very low level in the JB6 Cl41 normal mouse epidermal cell line \cite{15, 16}. Our recent study on a set of 45 gastric cancer tissues also revealed that MAPK15 was overexpressed at a high frequency in carcinomas (37%) compared to that in concurrent normal tissues (2%) and adenomas (21%) \cite{1}. In addition, seven (44%) of the 16 patients with MAPK15 overexpression had the overexpression in concurrent adenoma and carcinoma lesions. This finding suggests that MAPK15 overexpression may contribute to the malignant transformation of gastric mucosa and patients with MAPK15 overexpression in benign tumor may be susceptible to the progression of the disease.

Despite the frequent overexpression of MAPK15 in human cancers, the mechanisms underlying overexpression of MAPK15 are unclear in gastric cancer. Although the protein levels of MAPK15 are predominantly controlled by the ubiquitin-proteosome pathway \cite{11}, some oncogenic pathways, such as c-Src non-receptor tyrosine kinase, RET/PTC3, and Abl oncogenes are known to stimulate MAPK15 activation in cancer cells \cite{3, 15, 17}. There is no report on the mutation of MAPK15 in gastric cancer to date, but we found copy number gains in 15 (17%) of 88 gastric cancer tissues and in 7 (44%) of 16 gastric cancer cell lines. Several other studies have also revealed high-level copy number gains of MAPK15 at 8q24 in gastric cancers \cite{18-21}. In our study, the copy number gains of MAPK15 were correlated with increased expression of MAPK15 in vivo. However, no significant correlation between MAPK15 mRNA and protein levels in 16 gastric cancer cell lines was observed. Based on these observations, MAPK15 expression in vitro may be regulated by post-transcriptional and/or post-translational mechanisms.

MAPK15 plays an important role in regulating cell proliferation, but the exact molecular mechanisms involved
in MAPK15-mediated cell proliferation are poorly understood. Our recent study showed that artificial transfection of Myc-DDK tagged MAPK15 enhanced cell proliferation in AGS cells with low copy number [1]. In contrast, MAPK15 knockdown using siRNA in gastric cancer cells significantly suppressed cell proliferation, resulting in cell cycle arrest at the G1-to-S phase. The suppression of cell proliferation by inhibiting MAPK15 is also observed in other cancer cell lines, such as anaplastic thyroid carcinoma cells (ARO, Cal62, and Kat4), colorectal cancer cells (HCT15), and human breast epithelial cells (MCF-10A) [10, 15, 16]. Blocking MAPK15 expression in HCT15 cells significantly reduces their tumorigenic properties in vivo, and the rate and size of tumors in HCT15-MAPK15-knockdown–injected mice are significantly lower and smaller, respectively, than in mice inoculated with HCT15-MAPK15-normal cells [16].

Three possible mechanisms underlying the proliferative and tumorigenic properties of MAPK15 have been proposed in human cancer. First, MAPK15 may regulate cell proliferation through c-Jun phosphorylation. C-Jun is an early response transcriptional factor that is involved in cell growth and cell transformation by forming the AP-1 complex with c-Fos [22]. Fibroblasts derived from c-Jun+/− mouse fetuses exhibit a severe defect in proliferation, resulting in inefficient G1-to-S phase progression [23]. MAPK15 knockdown suppresses c-Jun (Ser63/73) phosphorylation and AP-1 promoter activity in HCT15 colorectal cancer cells [16]. We also observed reduced phosphorylation and half-life of c-Jun in MAPK15-knockdowned gastric cancer cells. In addition, MAPK15-induced c-Jun activation was independent of JNK, MEK1/2, and p38 in gastric cancer cells [1]. Taken together, these results suggest that MAPK15 plays an important role in cell proliferation by inducing c-Jun activity (Figure 1).

Second, MAPK15 may control cell proliferation and survival through telomerase activity. The high activities of c-Src tyrosine kinase and telomerase in gastric cancer have been reported by a number of groups [24-26]. c-Src is a non-receptor tyrosine kinase that promotes proliferation, survival, angiogenesis, and invasion pathways upon activation. Telomerase is a reverse transcriptase that adds de novo telomeric repeats “TTAGGG” to the 3’ end of telomeres to cap and protect chromosome ends. Cerone et al. [24] reported that inhibiting MAPK15 reduces telomerase activity and elicits characteristics of telomere dysfunction in HeLa, MCF7, and CAL51 cells. Silencing MAPK15 significantly reduces human telomerase reverse transcriptase (hTERT) mRNA levels, whereas c-Src knockdown, which is upstream of MAPK15, results in significant induction of hTERT mRNA. Third, autophagy is one of the major responses to stress in cancer cells and can suppress tumor progression. Tumor cells with defects in apoptosis and autophagy allow prolonged survival, and inhibiting autophagy restores chemosensitivity and enhances tumor cell death [27-30]. MAPK15 induce autophagy by interacting with ATG8-like proteins (MAP1LC3B, GABARAP, and GABARAPL1) in the cytoplasm [9].

Targeting the Ras-Raf-MEK-ERK cascade has been the subject of intense research and pharmaceutical scrutiny to identify target-based approaches to treat cancer [31,32]. Extensive arrays of specific ERK1/2, JNK, and p38 inhibitors have been evaluated in preclinical and clinical trials, but the value of a MAPK15 inhibitor to treat cancer has not been tested. Some studies have used Ro-318220 to inhibit MAPK15 kinase activity but this molecule is a typical selective protein kinase C inhibitor [14, 24, 33]. A three-dimensional analysis of the MAPK15 domain revealed a high percentage of scaffolds to develop specific kinase inhibitors [34].

In summary, three features of MAPK15 allow us to conclude that MAPK15 can be developed as a novel therapeutic target for gastric cancers. First, MAPK15 is specifically overexpressed in gastric cancer tissues but not in normal tissues. Second, inhibiting MAPK15 suppresses cancer cell proliferation and tumorigenesis by regulating c-Jun activity, telomerase activity, and autophagy. Finally, MAPK15 has the structural potential to be developed as a specific MAPK15 kinase inhibitor.

Conflicting interests

The authors have no conflicts of interest.

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References


