



Correspondence

TPL2, a therapeutic potential target for cancer



Dear Editor,

We read with great interest the paper by Pyo et al [1], who elucidated the clinicopathological significance and prognostic role of TPL2 expression in colorectal cancer (CRC) and found that high TPL2 expression was significantly correlated with distant metastasis, low immunoscore and poor overall survival. Chorzalska et al [2] also evidenced that TPL2 was overexpressed in a cellular model of chronic myeloid leukemia (CML) of resistance to imatinib mesylate (IM). Their data indicated that the overexpression of TPL2 was accompanied by increased activity of SFKs, MEK–ERK, and NF- κ B in IM-resistant cells. Consequently, they suggested combined inhibition of SFK, MEK, and NF- κ B pathways may present a new therapeutic option to target CML stem cells unresponsive to IM therapy. Furthermore, Lee et al [3] verified that TPL2 was overexpressed in human cutaneous metastatic squamous cell carcinoma (SCC) and keratoacanthoma (KA) clinical specimens compared with normal skin, validating TPL2 as a possible drug target for the treatment of SCC/KA. In addition, Li et al [4] researched the potential role of TPL2 in nonalcoholic fatty liver disease (NAFLD) associated hepatocellular carcinoma (HCC) development. And they revealed that *Tpl2* knockout mice had significantly down-regulated levels of mRNA expression of pro-inflammatory cytokines (IL-1 β , IL-18, M α p-1 and Nalp3) and significantly lower incidences of liver tumor compared with wild-type mice.

Tumor progression locus 2 (TPL2) is a mitogen-activated protein kinase (MAPK) kinase kinase (MAP3K) that conveys various intra- and extracellular stimuli to effector proteins of cells provoking adequate adoptive responses. Gkirtzimanaki et al [5] detected the role of TPL2 in lung cancer patients and found that low TPL2 levels correlated with reduced lung cancer patient survival and accelerated onset and multiplicity of urethane-induced lung tumors in mice. Similarly, Boldrini et al [6] found TPL2 expression was significantly higher in patients with non-small cell lung cancer with good prognosis (disease-free interval $P = .009$; overall survival $P = .024$), when compared with those having poor prognosis. Furthermore, Lee et al [7] demonstrated that TPL2 was the fundamental molecule provoking progression and metastasis of castration-resistant prostate cancer. Conversely, they found TPL2 overexpression and downregulation showed

significant stimulatory and inhibitory effects on tumorigenic and metastatic potential of androgen depletion-independent prostate cancer cells, respectively.

In conclusion, TPL2 participates in many decisive molecular processes of tumor development and progression. Moreover, TPL2 is closely associated with cytokine release of inflammatory cells, which has crucial effects on not only tumor cells but also tumor microenvironments. However, TPL2 contradictorily works as a tumor suppressor in some cancers [5,6]. Thus, clinical application of TPL2 as a novel therapeutic target for cancers needs to be further validated for its double-sided effects on different kinds of cancers.

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References

- [1] Pyo JS, Park MJ. TPL2 expression is correlated with distant metastasis and poor prognosis in colorectal cancer. *HUM PATHOL* 2018;79:50-6.
- [2] Chorzalska A, Ahsan N, Rao RSP, et al. Overexpression of TPL2 is linked to imatinib resistance and activation of MEK-ERK and NF- κ B pathways in a model of chronic myeloid leukemia. *Mol Oncol* 2018;12:630-47.
- [3] Lee JH, Lee JH, Lee SH, et al. TPL2 is an oncogenic driver in keratoacanthoma and squamous cell carcinoma. *Cancer Res* 2016;76:6712-22.
- [4] Li X, Liu C, Ip BC, et al. Tumor progression locus 2 ablation suppressed hepatocellular carcinoma development by inhibiting hepatic inflammation and steatosis in mice. *J Exp Clin Cancer Res* 2015;34:138. <https://doi.org/10.1186/s13046-015-0254-2>.
- [5] Gkirtzimanaki K, Gkouskou KK, Oleksiewicz U, et al. TPL2 kinase is a suppressor of lung carcinogenesis. *Proc Natl Acad Sci U S A* 2013;110:e1470-9.
- [6] Boldrini L, Giordano M, Servadio A, et al. Prognostic role of TPL2 in early-stage non-small cell lung cancer. *Mol Med Rep* 2017;15:3451-8.
- [7] Lee HW, Cho HJ, Lee SJ, et al. TPL2 induces castration resistant prostate cancer progression and metastasis. *Int J Cancer* 2015;136:2065-77.