MAP3K8 (TPL2) and Multiple Myeloma

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Abstract

MAP3K8, also known as Tumor Promoting Local 2 (TPL2), is a gene that encodes serine and threonine protein kinase. It is involved in multiple cellular signalling pathways, especially those related to immune response and inflammation. Specifically, it acts as a signaling node downstream for receptors, such as TLRs (Toll-Like Receptors) and TNF receptors, activating downstream MAPK and NF-κB pathways. Meanwhile, TPL2 plays a role in the development of multiple myeloma (MM), particularly in the interaction between myeloma cells and macrophages within the bone marrow microenvironment. MAP3K8 can promote myeloma growth and influence the inflammatory environment of the myeloma. This review paper will discuss the physiology function of MAP3K8 and the role in multiple myeloma bone marrow microenvironment.

Key words: Mitogen-Activated Protein Kinase Kinase Kinase 8 (MAP3K8), Multiple Myeloma, Bone Marrow Microenvironment, Nuclear Factor kappa-light-chain-enhancer of activated B (NF-κB cells), MAPK/ERK

1. What is MAP3K8/TPL2?

MAP3K8, also known as Tumor progression locus 2 (TPL2), is a gene that encodes serine and threonine protein kinase. It is a mitogen-activated protein kinase kinase (MAP3K8) activated downstream of TNFαR, IL1R, TLR, CD40, IL17R, and some GPCRs (Njunge et al., 2020). It is able to be involved in multiple cellular signalling pathways, especially those related to immune response and inflammation (Xu et al., 2018).

2. Function of MAP3K8/TPL2

This gene is an oncogene that is required for lipopolysaccharide (LPS)-induced, activating downstream MAPK/ERK pathway in macrophages, and producing TNF-alpha during immune responses. It is involved in regulating T-helper cells in differentiation and IFNG expression in T-cells. While activating the MAPK/ERK pathway, which responds to IL1, this process leads to an up-regulation of IL8 and CCL4(Xu et al., 2018).Through regulating MEK1/2 and ERK1/2 pathways, TPL2 controls a series of inflammatory responses. Similarly, TPL2 activates p38α and p38δ to promote various inflammatory mediators in neutrophils(Xu et al., 2018).

3. TPL2 and multiple myeloma (MM)development

TPL2 can be directly affecting myeloma cells and indirectly affecting myeloma cells by affecting the surrounding microenvironment.

3.1 Promotes Myeloma Growth:

MAP3K8 can promote myeloma growth and influence the inflammatory environment of the myeloma. Overall, TPL2 directly promotes the proliferation of myeloma cells, and its activity impacts the activation of NF-κB and MEK-ERK pathways (Cippitelli et al., 2023; Roy et al., 2018). Both play crucial roles in cancer cell growth. NF-κB critically affects the survival, proliferation, and drug resistance of myeloma cells. Specifically, both canonical and non-canonical NF-κB pathways are

usually activated by factors in bone marrow microenvironments including TPL2 and genetic mutations in multiple myeloma. Unusual NF-κB activations directly contribute to the occurrence of MM and provide a therapeutic target for its treatment.

The RAS/MEK/ERK pathway, or the MAPK pathway, controls cell proliferation and apoptosis, which significantly affects the growth and survival of myeloma cells. Deregulating this pathway, which is often caused by mutations in the RAS/RAF genes, increases the survival rate of cancer cells through increasing MCL-1 expression in MM cell by preventing MCL-1 degradation and enhancing its stability (Cherla et al., 2018), further more, the activated MEK/ERK phosphorylates pro-apoptotic factors like Bim, blocks its pro-apoptotic functions by weakening its ability to bind to pro-survival Bcl-2 family members, therefore promoting cell survival(Fan et al., 2017). Also, phosphorylation primes Bim for ubiquitination and degradation caused by the proteasome, decreasing the overall levels of the Bim protein(Fan et al., 2017).

3.2 TPL2 and Myeloma Microenvironment

TPL2 plays a role in the development of multiple myeloma (MM), particularly in the interaction between myeloma cells and macrophages within the bone marrow microenvironment. TPL2 controls the inflammatory microenvironment of the myeloma niche by regulating the production of pro-inflammatory cytokines, such as TNFα and IL-1β from the macrophages. It is activated downstream of TNFαR, TLR, CD40, IL1R, IL17R, and certain GPCRs (Hope et al., 2014; Xu et al., 2018). Researchers found TPL-2 controls M2-MΦ function to regulate chronic TH2-associated inflammation and immunopathology (Kannan et al., 2016). TPL2-/- in myeloid cell impair Lipid Metabolism and M2 differentiation, suggested it is necessary for normal lipid metabolism and suitable activation of myeloid cells and macrophages to limit fibrosis (Kannan et al., 2016). Moreover, TPL-2 prevents TH2 cell expansion, downstream immunopathology, and fibrosis by regulating inflammation through supporting lipolysis and M2 macrophage activation (Kannan et al., 2016). Ultimately, TPL2 supports the inflammatory milieu, which can help plasma cell survival and proliferation and tumor progression by controlling M2 polarization. Furthermore, by interacting with other pathways, such as the PI3K-Akt pathway, TPLs impacts the myeloma microenvironment by influencing macrophage chemokine receptor expression and migration.

3.3 Potential Therapeutic Target:

The main reason that TPL2 is considered a potential therapeutic target in MM is because it regulates the myeloma microenvironment by influencing macrophages, thus promoting the survival and progression of cancer cells. By targeting TPL2, to dampen inflammation by blocking this pro-tumorigenic signal, promoting tumoricidal macrophages, such as M1 macrophages, instead. In this way, immunosuppressive and antiapoptotic macrophages can be limited, eventually inhibiting MM progression (Hope et al., 2014). Recently, Yoshifuji et al reported TPL2 as a new potential prognostic factor and therapeutic target in activated B-cell-like diffuse large B-cell lymphoma through NF-κB and Stat3 signaling (Yoshifuji et al., 2025). NF-κB and STAT3 signaling pathways are constitutively activated in multiple myeloma (MM, promoting cancer cell proliferation, survival, and drug resistance(Lu et al., 2024). Targeting TPL2 led to targeting both pathways simultaneously or sequentially is a promising therapeutic strategy. Additionally, targeting TPL2 along with signaling pathways like NF-κB is a therapy that has high hopes for overcoming drug resistance in MM. In chronic myeloid leukemia, overexpression of Tpl2 is linked to imatinib resistance and activation of MEK-ERK and NF-κB pathways (Chorzalska et al., 2018). Meanwhile, interactions between TPL2 and other pathways like the PI3K-Akt pathway can impact the myeloma microenvironment by

influencing the expression and migration of macrophage chemokine(Hope et al., 2014). As a result, inhibiting the TPL2 pathway became immunosupportive and necessary, disrupting signalling pathways that promote myeloma cell growth and survival.

4. Discussion and conclusion:

According to multiple studies, TPL2 deficiency leads to the delay of myeloma's onset in a mouse model, demonstrating its role in disease progression. Specifically in myeloma-related macrophages, TPL2 is constitutively activated, which produces pro-inflammatory cytokines and influences the phosphorylation of STAT3. Moreover, TPL2 promotes the M2-polarized phenotype of tumor-associated macrophages, thus promoting tumor progression. Therefore, inhibiting TPL2 activity can suppress signaling pathways, such as MAPK and NF-κB, reducing myeloma cell growth. In summary, TPL-2 is a kinase that has notable involvements in myeloma cell growth and the inflammatory microenvironment in bone marrow, both greatly boosting myeloma growth. Considering its involvement in pathways such as MAPK, NF-κB, and PI3K-Akt, it is recognized as a potential therapeutic target for further studying.

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