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Commentary

Kinase Action and Function of *TPL2* Gene

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DESCRIPTION

Tumor progression locus 2 (TPL2) gene belongs to the MAP3K family of protein kinases. The rat homologue of Cancer Osaka Thyroid (COT) was named *TPL2*. The two translation initiation sites (M1 and M30) of *TPL2* equalize the molar concentrations of the 58 kDa (p58) and 52 kDa (p52) proteins. TPL2 is a cytoplasmic protein of 467 amino acids (AA) composed of three parts: amino-terminal (N-terminus), kinase domain (138AA-388AA), Carboxy-terminal (C-terminal), and C-dye-terminal cleavage determinants. Degron, 435aa-457aa is very important for the protein stability of *TPL2*. However, removal of the C-terminal domain appears to activate the transforming potential of *TPL2* through two mechanisms. First, it has been suggested that truncation of the C-terminus increases the specific kinase activity of *TPL2*, and that the C-terminus may regulate the catalytic activity of *TPL2* by refolding into the kinase domain. Second, the C-terminal truncation removes the degron sequence (amino acids 435-457) that facilitates proteolytic degradation of TPL-2 by the proteasome. A C-terminally truncated sequence 'degron' (435-457) increases kinase-specific activity, suggesting that this region may inhibit *TPL2* kinase activity.

TPL2 has important innate immunity in regulating signaling in TNF-α, TLR, and G protein-coupled receptor signaling pathways. Previous studies have shown that *TPL2* mediates the production of *IL-12* from T cells, which is essential for production of IFN-γ. Stimulation of *Tpl2*$^{-/-}$ CD4^{+} T cells *in vitro* shows an impaired induction of IFN-γ production and a low rate of differentiation towards a Th1 phenotype. MyD88 is essential for Leishmania eradication. Previous studies have reported that MyD88-deficient mice are more susceptible to Leishmania infection than control mice. These studies also show that lipophosphoglycan, a key parasite molecule, activates innate immune signaling pathways through TLR2. Moreover, in response to infection with the Th1-inducing parasite *Toxoplasma gondii, TPL2*-deficient mice confer a higher pathogen load associated with reduced systemic IFN-γ production, thereby positively regulating both Th1 responses. It has been defined to promote *TPL2* as a factor in both *in vitro* and *in vivo*. Thus, reduced levels of two factors, T-bet and Stat4, in *TPL2*-deficient T cells are essential for their differentiation from Th1 cells. Furthermore, *TPL2* knockout mice exhibited decreased IFN-γ production, resulting in increased susceptibility to *Toxoplasma gondii* infection. Strikingly, *TPL2*$^{-/-}$ mice have an impaired immune response to intracellular *Toxoplasma gondii*. This is thought to result from T cell autonomic neuropathy rather than alterations in the innate immune response. Such responses are associated with host pathologies that defend against the pathogen *Toxoplasma gondii*, where IFN induction is impaired and pathogen load is increased. Cot/*TPL2*$^{-/-}$ mice display Th1-skewed antigen-specific immune responses after *in vivo* immunization and primary infection with leishmaniasis, suggesting that Cot/*TPL2* is a key negative regulator of Th1-type adaptive immunity. It also suggests that Dinucleotide CG (CpG-DNA)-rich bacterial DNA activated ERK in a Cot/*TPL2*-independent manner. Peritoneal macrophages and bone marrow-derived DCs from Cot/*TPL2*$^{-/-}$ mice produced significantly more *IL-12* in response to CpG DNA than those from WT mice. Immunization of Cot/*TPL2*$^{-/-}$ mice with ova and Freund's Complete Adjuvant (CFA or FCA) effectively expanded antigen-specific T cells and increased IFN-γ production. Since Ig class, switching is regulated by cytokines from T cells. These findings are consistent with high *IL-12* production and suggest that systemic responses to exogenous antigens in Cot/*TPL2*$^{-/-}$ mice are Th1 type.

If *TPL2* contributes to the CD28 co-stimulatory signal, *TPL2* deficiency could impair CD28 co-stimulation and thus affect IFN-γ production. Parasite burden was increased in *TPL2*$^{-/-}$ mice that survived parasite infection compared with wild-type mice. These findings suggest that *TPL2* is essential for IFN-γ production in CD4^{+} T cells.

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