MALT1 protease: equilibrating immunity versus tolerance

Arianna Bertossi & Daniel Krappmann

MALT1 paracaspase links signaling cascades emanating from adaptive or innate immune receptors to the canonical NF-κB pathway. Now, Jaworski et al. (2014) investigate the physiological role of MALT1 protease activity in mice. Besides the expected requirement of MALT1 activity for immune activation, the study unveils a novel function for MALT1 activity for the development of peripheral tolerance. Thus, MALT1 protease can act immunogenic or tolerogenic, and this interplay will be highly relevant for the clinical development of MALT1 inhibitors.

See also: M Jaworski et al (December 2014)

The activation of the NF-κB family of transcription factors in immune cells represents a key event during the establishment of an immune response. Stimulation of B- or T-cell antigen receptors (BCR/TCR) or distinct innate immune receptors promotes the assembly of the CBM complex consisting of CARMA1(CARD11)-Bcl10-MALT1 or CARD9-BCL10-MALT1. Within the CBM complex, the MALT1 scaffold serves as a bridging factor to recruit the IκB kinase (IKK) complex and to activate canonical NF-κB signaling (reviewed in Thome, 2008). In addition, MALT1 also contains a very unique paracaspase domain whose proteolytic activity is activated upon TCR stimulation (Coornaert et al., 2008; Rebeaud et al., 2008). Pharmacological inhibition and genetic inactivation revealed that even though MALT1 proteolytic activity is dispensable for canonical NF-κB signaling, it is required for optimal T-cell activation (Rebeaud et al., 2008; Duwel et al., 2009). MALT1 deficiency was shown to protect mice from the induction of experimental autoimmune encephalomyelitis (EAE) in a murine multiple sclerosis model (MS) (Bristle et al., 2012; Mc Guire et al., 2013). Further, constitutive MALT1 activity drives survival of ABC DLBCL, one of the most aggressive B-cell malignancies (Ferch et al., 2009; Hailfinger et al., 2009). Thus, MALT1 protease is a promising drug target to treat distinct lymphomas as well as autoimmune diseases.

To evaluate the contribution of MALT1 protease activity to the physiological role of MALT1, Thome and collaborators generated a mouse model expressing catalytically inactive MALT1 by replacing the active site cysteine with alanine (MALT1C472A/C472A) (Jaworski et al., 2014). As expected, MALT1C472A/C472A mice are characterized by profound defects in both the adaptive and the innate immune responses. Indeed, despite the fact that BCR and TCR-driven activation of IKK/NF-κB and JNK signaling is not relying on MALT1 protease activity, it is necessary for the establishment of effector functions in lymphocytes, natural killer (NK) and dendritic cells (DC). Just like in MALT1 KO mice, IL-2 production and proliferation of T cells are strongly compromised. MALT1 protease is also required for the development of marginal zone and B1 B cells, and T-cell-dependent or T-cell-independent IgM and IgG production upon immunization. Consequently, MALT1 inactivation protects mice in two T-cell-dependent autoimmune models from EAE induction as well as colitis.

Besides these expected phenotypes, MALT1C472A/C472A mice beyond the age of 6 weeks displayed swollen lymph nodes and an increase in the total number of B and T cells that was much more pronounced than in MALT1 deficient mice. T cells have an activated/effector phenotype and secrete higher levels of the Th1 and Th2 cytokines IFN-γ and IL-4. MALT1C472A/C472A mice develop spontaneous autoimmune gastritis, characterized by loss of animal weight and increased serum levels of IgE and IgG1. Thome and collaborators suggest that the autoimmune phenotype is caused by impaired peripheral tolerance (Fig 1). MALT1C472A/C472A mice show a severe cell intrinsic defect in the development of FoxP3 regulatory T cells (Tregs). Further, adoptive transfer of functional Tregs reduced T-cell activation and ameliorated the symptoms of autoimmune gastritis in MALT1C472A/C472A mice. These findings support a model in which the autoimmune phenotype in MALT1 protease defective mice is caused by residual immune activation that relies on the preserved MALT1 scaffolding function and the concomitant severe defect in peripheral tolerance as a result of reduced Treg numbers (Fig 1). In contrast, MALT1 KO mice that are characterized by even a more severe decrease in the number of Tregs are protected from the development of autoimmune gastritis, because they also completely lack immune activation due to the loss of both scaffold and protease functions (Fig 1). Hence, the autoimmune phenotype is caused by a partial TCR signaling defect in MALT1C472A/C472A mice that shifts the balance from tolerance to autoimmune activation.

The reported duality of the MALT1 protease to promote cell intrinsic T-cell effector functions and to suppress activated T cells in a Treg-dependent manner raises a number of interesting questions. Even though the adoptive transfer demonstrates the potential of Tregs to counteract the autoimmunity, it remains open, if the reduced number of
Tregs is indeed sufficient to cause the inflammatory phenotype. In the adoptive transfer experiment, only very few Tregs are sufficient to rescue the autoimmune phenotype raising the possibility that MALT1 protease mutant mice may also indicate that deregulated T-cell effector functions could also be involved in the early onset of gastritis, which is no longer counterbalanced due to the strong accompanying reduction in Tregs. The loss of equilibrium in the T-cell compartments promotes the expansion of activated Teffs, which leads to autoimmunity.

It has been shown that deregulated T-cell effector functions could also be involved in the early onset of gastritis, which is no longer counterbalanced due to the strong accompanying reduction in Tregs. The loss of equilibrium in the T-cell compartments promotes the expansion of activated Teffs, which leads to autoimmunity. This could be achieved, for example, by mutating the ubiquitin-acceptor site K644 that is required for MALT1 proteolytic activation (Pelzer et al., 2013). Third and most important, the mouse model abrogated MALT1 activity already in early embryogenesis before the immune system and peripheral tolerance have developed. Thus, inactivation in adult mice by an inducible system will be more reminiscent to MALT1 inhibitor treatment. Further, generation of conditional transgenic mice will be required to establish the role of MALT1 protease in Treg biology.

Besides its physiological role in the immune system, MALT1 function has been studied in the context of hematological malignancies and especially ABC DLBCL biology. The first small-molecule MALT1 paracaspase inhibitors have been identified that effectively kill ABC DLBCL tumors in a murine xenotransplantation model (Fontan et al., 2012; Nagel et al., 2012). As this tumor model required the usage of immune-deficient mice, effects on the immune compartment were not analyzed. However, higher numbers of Foxp3-positive cells correlated with an adverse clinical outcome in DLBCL cohort enriched for ABC DLBCL.
(Tzankov et al., 2008). Thus, in contrast to autoimmunity, inhibition of peripheral tolerance may even foster immune surveillance in lymphomas.

Taken together, the study by Jaworski et al. underscores that deciphering the exact mechanism of autoimmune protection versus induction will be relevant for therapeutic targeting of the MALT1 protease in the context of autoimmune diseases as well as lymphomas.

References


