Ten-eleven translocation (Tet) demethylases mediate peripheral B cell tolerance

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Break of immunological tolerance results in autoimmunity. Especially, loss of peripheral tolerance is a critical step. 3-10% of B cells at peripheral lymphoid organs has potential to be activated by self-proteins (self-reactive) but are inactivated by a mechanism called peripheral tolerance. In case, the tolerance is broken, it allows self-reactive B cells to attack self, resulting in autoimmunity. However, the molecular mechanism of tolerance has been largely unknown. Ten-eleven translocation (Tet) DNA demethylase play a pleiotropic role in multiple biological events and suggested to be implicated with autoimmune diseases. However, role of Tet in self-tolerance has been unknown. B cell-specific Tet2, Tet3 double knock out mice (here after Tet DKO) showed aberrant activation of immune cells in secondary lymphoid organs and manifestation of autoimmune diseases such as production of autoantibody and cell-infiltration in non-lymphoid organs. Cell-depletion study demonstrated the requirement of T-B interaction for disease induction. The gene expression analysis just before onset of the disease identified CD86 as an only costimulatory molecules whose expression was enhanced in Tet DKO B cells. CD86 blocking partially reversed autoimmune condition, suggesting that CD86 is not sufficient but required for aberrant lymphocyte activation in the DKO mice. Furthermore, in a model for peripheral tolerance (MD4-HEL system), Tet DKO B cells survived efficiently with high expression of CD86, compared to control B cells, suggestive of peripheral tolerance break by loss of Tet in B cells. Mechanistically, DNA methylation does not seem to regulate CD86 expression by global analysis for DNA methylation. In contrast, loss of Tet2/3 caused impaired accumulation of HDAC2 and enhanced acetylated histone on *Cd86* gene promoter. Taken together, Tet2/3 play a crucial role in maintenance of B cell tolerance through the HDAC-mediated epigenetic suppression of CD86 expression and B cell-survival.