Homeostatic Proliferating CD4 T Cells Are Involved in the Pathogenesis of an Omenn Syndrome Murine Model

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MM mouse having a hypomorphic point mutation in *Rag1* gene was discovered from a normal C57BL/10 colony. We found that T cell development in thymus was partially blocked and peripheral T cell numbers decreased in the mutant. It is known that patients with Omenn syndrome also have hypomorphic RAG mutations and develop varying manifestations of severe combined immunodeficiency. MM mouse contains high numbers of memory-phenotype CD4+ and CD8+ T cells and experienced hepatosplenomegaly and eosinophilia, had oligoclonal T cells, and demonstrated elevated levels of IgE, major symptoms of Omenn syndrome. In periphery of MM mouse, T cells are proliferating more compared to control animals by homeostatic proliferation induced by a lymphopenic condition of the mutant. Homeostatic proliferating CD4+ T cells in MM mouse produce various cytokines, including IL-4 and IL-6 etc. Depletion of CD4+ T cells from the MM mouse recovered from a hyper IgE concentration in serum, which is a critical differential diagnosis of Omenn syndrome from non-T/non-B SCID patients. Moreover, all double mutant MM mice that were crossed with IL-4KO, IL-6KO, and CD40KO recovered from the hyper IgE. Thus, these results demonstrated that homeostatically proliferating CD4+ T cells are critically involved in the pathogenesis of the Omenn syndrome.

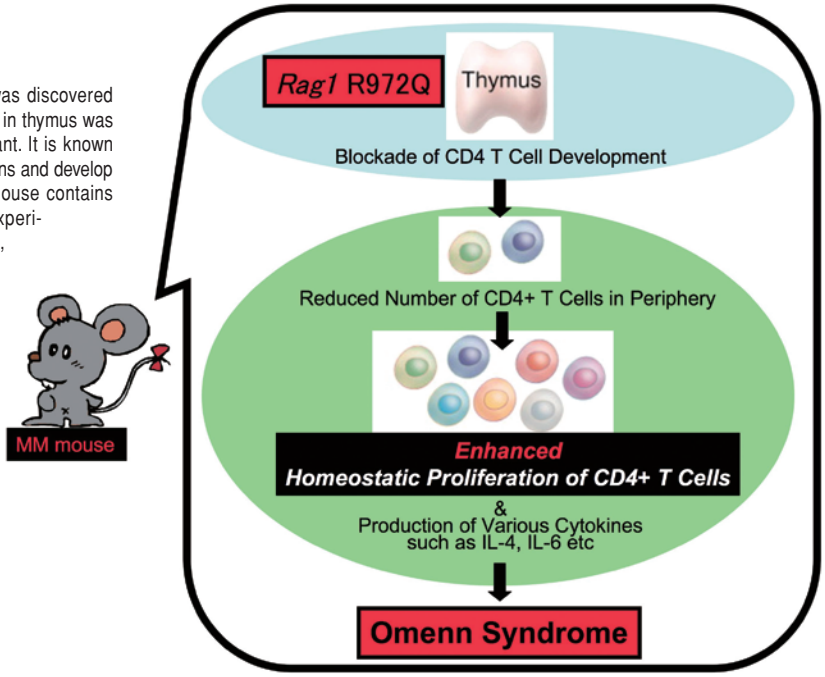

Fig. Schematic for the development of Omenn syndrome by homeostatic proliferating CD4+ T cells.

Crossover assurance And Crossover Interference Are Distinctly Regulated By The ZMM Proteins During Yeast Meiosis.

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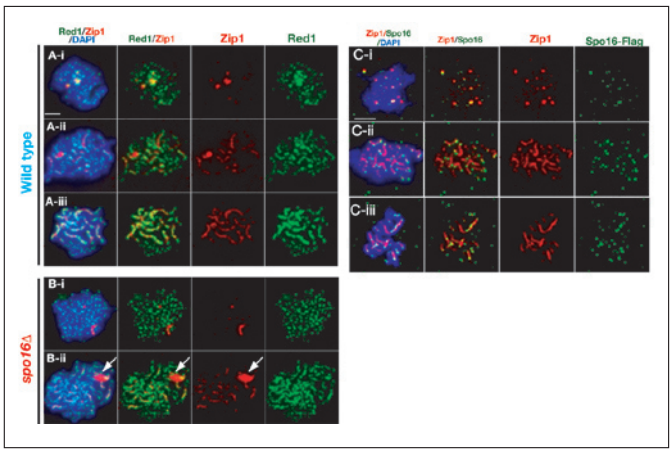

Fig. 1

Meiosis is a specialized cell division, which produces haploid gamates. Recombination, the exchange of genetic materials, plays a critical role in chromosome segregation at meiosis division I as well as in generation of genetic diversity in population. Meiotic crossing-over, reciprocal exchange of paternal and maternal chromosomes (DNAs), is highly regulated such that each homolog pair receives at least one crossover (assurance) and adjacent crossovers are widely spaced (interference). Mutations in the meiosis-specific *ZMM/SIC* genes (Zip1, Zip2, Zip3, Mer3, Msh4 and Msh5) cause coordinate loss of both crossover assurance and interference, suggesting a single underlying mechanism. In this article, we provide evidence that interference and assurance are in fact mechanistically distinct processes that are separated by mutations in a new ZMM/SIC member, Spo16. Like other *zmm/sic* mutants, *spo16* cells are coordinately defective for crossing-over and synaptonemal complex (SC) formation (Fig 1A and B). Unlike *zip1*, *msh4*, *msh5* and *mer3* mutants, however, the residual crossovers in *spo16* cells exhibit wild-type levels of interference. Spo16 binds to meiotic chromosomes at distinct loci (Fig.1 C) and interacts with a second ZMM/SIC protein, Spo22 (a.k.a. Zip4), and *spo22* mutants also show normal interference between residual crossovers. Notably, timely assembly of the MutS homologs, Msh4 and Msh5, into chromosomal immunostaining foci is proficient in both *spo16* and *spo22* cells but not in other *zmm* mutants. We suggest that crossover interference requires the normal assembly of Msh4-Msh5-containing recombination complexes but not Spo16-Spo22 dependent extension of SCs. In contrast, crossover assurance requires all ZMM/SIC proteins and full-length SCs.