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DEVELOPMENT AND PHYSIOLOGICAL SIGNIFICANCE OF T CELLS EXPRESSING $\gamma\delta$ T CELL ANTIGEN RECEPTORS

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Physiological Significance of T Cells Expressing $\gamma\delta$ T Cell Receptors ($\gamma\delta$ T Cells)

T cells with $\alpha\beta$ receptors ($\alpha\beta$ T cells) recognize fragments of foreign antigens associated with MHC molecules, and are engaged in most characterized cell-mediated antigen-specific immune responses. The search for the genes encoding T cell receptor polypeptides, however, led to the identification of a pair of another rearranging genes that were shown to code for the second heterodimeric $\gamma\delta$ receptors ($\gamma\delta$ T cells). In contrast to $\alpha\beta$ T cells, the general rules for $\gamma\delta$ T-cell recognition remain undefined and the biologic role of $\gamma\delta$ T cells in immune responses is not well understood. It has been demonstrated, however, that this distinct class of T cells is abundant in various epithelia such as the epidermis of the mouse and intestinal epithelium of many species. Recent findings indicated a fundamental difference in antigen recognition between $\gamma\delta$ T cells and $\alpha\beta$ T cells, suggesting that $\gamma\delta$ T cells may contribute to the immune system differently than $\alpha\beta$ T cells do.

We have aimed to elucidate the physiological significance of one major $\gamma\delta$ T-cell subset that is localized in the mouse intestinal epithelium. The pool of intestinal intraepithelial T lymphocytes (IELs) of adult mice is comparable in size to the T-cell pool in the spleen. It consists of both $\alpha\beta$ T cells (40–70%) and $\gamma\delta$ T cells (30–60%). The striking fact that IELs interdigitate between the basolateral faces of intestinal epithelial cells (IECs) suggests close functional relationship between IELs and adjacent IECs. We have examined the intestinal epithelia of T-cell-receptor mutant mice, which were deficient in either $\gamma\delta$ T cells or $\alpha\beta$ T cells, and of normal littermates. Our results show that the absence of $\gamma\delta$ T cells is associated with a reduction in epithelial cell turnover and a downregulation of the expression of major histocompatibility complex class II molecules. No such effects are observed in $\alpha\beta$ T-cell-deficient mice. These findings indicate that intraepithelial $\gamma\delta$ T cells regulate the generation and differentiation of intestinal epithelial cells.

We have also aimed to elucidate the physiological function of murine dendritic epidermal cells (dEC) expressing monomorphic $\gamma\delta$ T cell receptors ($\gamma\delta$ dEC). Our previous study demonstrated that the epidermis of mice that had spontaneously recovered from cutaneous graft-vs.-host disease (GVHD) induced by local injection of

$CD4^+$ autoreactive T cells contained unexpectedly large numbers of dEC and became resistant to subsequent attempts to induce GVHD in a site-restricted manner, suggesting that the resistance is mediated by dEC. However, because $\alpha\beta$ dEC as well as $\gamma\delta$ dEC were greatly increased in number in the epidermis, it was unclear whether $\gamma\delta$ dEC are indeed responsible for this protection. The availability of this murine model and mice selectively lacking $\gamma\delta$ T cells as a result of disruption of the T cell receptor C_δ gene segment allowed us to investigate the role of $\gamma\delta$ dEC. In the epidermis of $\gamma\delta$ T cell-deficient mice ($\delta^{-/-}$), a congenital lack of $\gamma\delta$ dEC was substituted for by $\alpha\beta$ dEC of either a $CD4^-8^+$ or a $CD4^-8^-$ phenotype. After intradermal injection of the autoreactive T cells, $\delta^{-/-}$ mice developed significantly enhanced delayed-type hypersensitivity responses and cutaneous GVHD, which persisted longer than in heterozygous littermate controls ($\delta^{+/-}$). Surprisingly, resistance to the cutaneous GVHD was not induced in the epidermis of $\delta^{-/-}$ mice after spontaneous recovery from the GVHD, whereas the "susceptible" epidermis of $\delta^{-/-}$ mice contained large numbers of $\alpha\beta$ dEC comparable to those in the "resistant" epidermis of $\delta^{-/-}$ mice. Injection of day 16 fetal thymocytes from wild-type mice into $\delta^{-/-}$ mice resulted in the appearance of donor-type $\gamma\delta$ dEC in the epidermis, and reconstitution with $\gamma\delta$ dEC restored the protective immune response of the epidermis against the GVHD to nearly normal levels. These results indicate that $\gamma\delta$ dEC are responsible for the site-restricted protection against cutaneous GVHD.

Extrathymic development of intestinal intraepithelial T lymphocytes (IELs)

In the past decade, a substantial number of murine T cells have been shown to develop without passing through the thymus. Among them, IELs constitute the largest group of peripheral extrathymic T cells. Although considerable insights into IELs have been made during the past few years, much remains to be learned about their physiological significance and the precise anatomical nursery where the differentiation of IELs is allowed to proceed. We have recently revealed that about one and a half thousand tiny clusters, filled with one thousand closely packed lymphocytes, can be found throughout the murine small and large intestinal mucosa. They are located in crypt lamina propria (cryptopatches ; CP) and can be first detected at 14–17 day after birth. A large fraction of lymphocytes in CP expresses *c-kit*, IL-7R, Thy 1 and a lymphocyte function-associated antigen, LFA-1, whereas most of them remain $CD3^-$, TCR $\alpha\beta^-$, TCR $\gamma\delta^-$, $sIgM^-$ and $B220^-$. These findings indicate that CP are the first identification of gut-associated murine lymphoid tissues where the generation of IL-7-dependent lymphohematopoietic progenitors for T and/or B cell descendants may start to take place at the age of commencement of weaning. In any event, isolation and subsequent purification of CP lymphocytes, characterization of such lymphocytes, and *in vitro* as well as *in vivo* progeny studies on the purified population are all mandatory before we evaluate the physiological significance of CP and their lymphoid residents. These procedures were found to suffer from several obstacles

imposed by anatomical and numerical restraints, but we are currently trying to overcome all those difficulties.

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