CHARACTERISATION OF T CELLS IN RATS THAT DEVELOP INDEPENDENTLY OF THE THYMUS: LYMPHOCYTES WITH POTENTIAL REGULATORY ROLES

by

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ABSTRACT

It is becoming accepted that there exist sites, other than the thymus, that support T cell differentiation. Proposed sites of thymus-independent T cell differentiation include the liver and the gut epithelium. Previous work in this laboratory has identified a previously uncharacterised structure within the rat small intestine as another candidate site for extra-thymic T cell development. These structures are present in both euthymic and athymic rats and take the form of modified villi that contain closely packed lymphocytes and dendritic cells. It was shown that the majority of the lymphocytes in these lymphocyte-filled villi (LFV) did not express markers of mature B cells and T cells but they did express CD25 and CD43. Furthermore, lymphocytes within LFV were shown to undergo cell division, they were excluded from the recirculating pool and they included a minor population of cells which expressed markers of mature T cells (which include the α/β TCR, CD3, CD2, CD5 and CD4). It is shown herein that the major population of CD25⁺ CD43⁺ cells also express CD44 and CD161, a phenotype similar to that expressed by immature thymocytes at the time of commitment to the T cells lineage. These observations, together with the detection of RAG-1 protein in LFV, indicate that LFV have similarities to the thymus and are likely sites of thymus-independent T cell development. It is shown that with increasing age, cells expressing the α/β TCR increase in number in the tissues of athymic rats. Cells expressing the α/β TCR are detected in the TDL of young adult athymic rats before they are found in significant numbers in lymphoid organs. This suggests that the gut may be the source of these cells and raises the possibility that T cells developing at mucosal sites, in particular in LFV, may seed the peripheral lymphoid organs of athymic rats. Furthermore, the presence of LFV in euthymic rats indicates that they may contribute a corresponding thymus-independent T cell population in normal animals. Previous
studies have shown that the α/β T cells found in athymic rats cannot mediate rejection of allografts and hence are not the functional equivalents of conventional thymus-derived T cells. Phenotypic comparisons presented in this study show that the α/β T cells present in athymic rats are distinct from the majority of α/β T cells found in euthymic littermates. They have a larger mean size, exhibit a lower level of surface TCR expression, a higher proportion express activation markers and the majority express a pattern of adhesion molecules consistent with previous antigenic stimulation. Furthermore, additional work showed that the α/β T cells found in athymic rats share a number of features with NKT cells, a recently described subset of T cells with unique functional properties. These differences may be reflected in the observations reported in this thesis that show that as a whole, the α/β T cells found in athymic rats recirculate in reduced numbers and show a different pattern of tissue distribution following adoptive transfer. Moreover, examination of the cytokines produced by T cells following in vitro stimulation showed that NKT cells and α/β T cells from athymic rats produce large amounts of IFN-γ. Collectively, the information detailed in this thesis show that the NKT cells and the thymus-independent α/β T cells present in athymic rats are phenotypically and functionally related. This raises the possibility that thymus-independent α/β T cells are distinct from conventional T cells and that their functions in normal individuals are regulatory, as has been suggested for NKT cells.
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