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Thymic Nurse Cells and Radiation Leukemia Virus Induced Thymic Lymphomas in C57BL Mice*

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A. Introduction

The selective thymotropism of *radiation leukemia virus* is an interesting example of specific interaction between an oncogenic agent and the differentiation pathway of a well-defined cell lineage. Indeed, the inoculation of RadLV in C57BL/Ka mice leads to the development of thymic lymphomas [4].

Only a few immature thymocytes can act as target cells for productive infection by RadLV [1]. Infection is followed by virus replication which starts in the outer cortex to spread rapidly to the whole cortical thymocyte population [2]. Thymus-dependent preleukemic cells emerge during the first phase of virus replication, although the thymus is still not tumoral. Finally thymus-independent neoplastic cells appear and give rise to lymphomas (Boniver et al., to be published).

The immaturity of target cells and the thymus dependency of the preleukemic process led us to investigate the possible role of *thymic nurse cells* (TNCs) in thymic lymphomagenesis. These lymphoepithelial cell complexes are indeed at a critical stage of the early thymic lymphopoiesis [3, 5, 6].

B. Results

I. TNCs and Virus Replication

Early after the intrathymic inoculation of RadLV, the first virus-producing cells were found preferentially within TNCs: on day 2, their frequency was 200 times higher in the TNC-associated lymphoid cells than in the whole thymocyte population [3]. Later on, virus replication spread to the whole cortex [1, 2].

II. TNCs and Preleukemic Cells

Thymus-dependent preleukemic cells were detected on day 2 after inoculation of RadLV using an in vivo transplantation test. Thymus-independent preleukemic cells, i.e., able to proliferate into thymectomized mice, were found in non-tumoral thymuses between the 75th and the 120th day (Boniver et al., to be published).

The relation of preleukemic cells to TNCs was then investigated. C57BL/Ka (Thy 1.2) mice were killed at various time intervals after inoculation of RadLV. In order to obtain TNCs, thymuses were dissociated with enzymes (S start) and separated in several fractions (S1 . . . S4, TNCs) by 1-g sedimentation [3]. Only S start and TNCs fraction contained TNCs. Samples of each cell suspension obtained with this procedure were injected intrathymically into 400-R irradiated congenic C57BL/Ka (Thy 1.1) mice, which were killed when moribund. The donor, or recipient, origin of lymphomas was scored by Thy 1.1 and Thy 1.2 detection with a FACS. In this transplantation assay, only the donor type tumors indicated the presence of preleukemic cells in the inoculate. Recipient-type tumors were due to transfer of infectious virus particles.

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Table 1. TNCs and preleukemic cells after inoculation of RadLV

Time of killing[a] (days)	Thymocyte number[b] ($\times 10^6$)	TNC number/ thymus[c] ($\times 10^3$)	Preleukemic cells in thymocyte fractions obtained along the TNC isolation procedure[d]					
			S start	S1	S2	S3	S4	TNCs
2	81	13.4	+	–	–	–	–	+
15	97	3.7	–	–	–	–	–	+
30	93	2.1	+	+	+	+	ND[e]	+
45	94	2.3	+	–	+	ND	ND	+
60	113	0.56	+	–	+	ND	ND	+

[a] C57BL/Ka were inoculated with RadLV at 30 days of age
[b] Normal values: 30 days old, 170.10^6; 90 days old, 125.10^6
[c] Normal values: 30 days old, 15.10^3; 90 days old, 10.10^3
[d] Tested by in vivo transplantation assay (see text)
[e] ND; no cells in the fraction

As shown in Table 1, preleukemic cells were found only in TNCs on day 2 and 15. Later on preleukemic cells were detected also in cell suspensions which did not contain TNCs (i.e., S1 to S3). Interestingly the number of TNCs per thymus dropped drastically from day 15 onward to reach very low values on day 60, whereas it decreased very slowly in control mice.

C. Discussion

The intra-TNC localization of early virus replication after inoculation of RadLV can be explained easily: both target cells for productive infection by RadLV and intra-TNC lymphoid cells display an "immature" phenotype and therefore probably belong to an unique subpopulation at the first stage of thymic lymphopoiesis. The first preleukemic cells might derive from the same population. Their selective association with TNCs, for about 2 weeks, suggests that the RadLV-induced preleukemic potential is restricted to a specific (intra-TNC) step of T-cell differentiation. The almost complete disappearance of TNCs and the spread of preleukemic cells to various thymocyte fractions indicate a blockade of the physiological interactions which normally maintain lymphopoiesis.

The observations strongly indicate that the selective thymotropism of RadLV relates to specific interactions with well-defined susceptible target cells; these target cells are at a critical stage of the T-cell differentiation pathway, under control of the thymic microenvironment, and particularly of the epithelial component of TNCs.

References

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