Chapter 10

Mature T-Cell Malignancies

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1. INTRODUCTION

Malignancies of mature, post-thymic T-cells are rare in comparison with their B-cell counterparts and are highly heterogenous. They continue to pose major clinical problems both in terms of diagnosis and management. This is in part due to their rarity, but also to the fact that diagnosis requires detailed immunophenotypic and genotypic analyses to demonstrate lineage, clonality and stage of differentiation. In many cases, these data are not available. More extensive study of the pathogenesis of the various types of malignancy remains hampered by the lack of suitable cell lines.

The purpose of this chapter is to review some of the functions of mature T-cells and advances in our understanding of the different forms of mature T-cell malignancy, to describe some of the derived cell lines and to place these in the current scheme of classification.

2. FUNCTIONS OF MATURE T-CELLS

T-lymphocytes derive from hematopoietic precursor cells within the bone marrow, which initially migrate to the thymus. Here, the T-cell receptor for antigen (TCR) proteins are first expressed following TCR gene rearrangement. A complex process of both positive and negative selection of antigen- and self-reactive T-cells occurs through interaction of the T-cell precursors with thymic stromal and antigen presenting cells. Two different T-cell lineages can be identified on the basis of their expression of TCR proteins composed of either TCRα/β or TCRγ/δ heterodimers. These lineages have different functions and tissue distributions. In clinical specimens, affiliation...
to either lineage can be ascertained either by the use of monoclonal antibodies (MAB) specific for constant epitopes within the TCR proteins or by using DNA methods to detect clonal rearrangements within the TCR genes. The TCRδ gene segments are located entirely within the TCRα complex and rearrangement of TCRα results in complete deletion of the TCRδ sequences. Mature T-cells of the TCRγ/δ lineage comprise about 5% of total peripheral blood T-cells and malignancies of this lineage are uncommon and have some distinct properties, as discussed below.

On emerging from the thymus, mature T-cell subpopulations express a panoply of surface membrane proteins that reflect their functions. The functions of many of these proteins have now been identified. Some of those that have been used clinically are shown in Table 1 (reviewed in Barclay et al. 1998). These molecules can be used to differentiate the malignancies of T-cell precursors (T-cell lymphoblastic leukemias and lymphomas) from the various malignancies of post-thymic T-cells and from malignancies of other related lineages, notably malignancies of natural killer (NK) cells. Some forms of T-cell malignancy may co-express both T-cell and NK lineage markers. Clinically, the most widely utilized of these proteins are the CD4 and CD8 molecules, which broadly divide mature T-cells into those which mediate B-cell “help” and those which mediate T-cell cytolysis respectively. In contrast to thymic malignancies that are often CD4/CD8 double positive, mature post-thymic T-cells usually express only one or other of these molecules, although in some instances, notably in T-cell prolymphocytic leukemia, co-expression of CD4 and CD8 may be observed. Assessment of the expression of the nuclear enzyme terminal deoxynucleotidyl transferase (TdT) may be necessary to distinguish malignancies of T-cell precursors from those of mature T-cells.

Mature T-cells migrate to a number of peripheral lymphoid sites, including spleen and lymph nodes, but also to more “specialized” sites such as the skin and intestinal epithelia; T-cells in these sites may differ from those elsewhere. They are competent to perform a number of different effector functions including mediation of:

- B-cell “help” to produce specific antibodies (predominantly a function of CD4+ subpopulation).
- Cytolysis of virally infected/bacterially infected cells as well as allogeneic and malignant cells (predominantly a function of CD8+ subpopulation).
- Stimulation of monocytes/macrophages in the inflammatory response.

These subjects are discussed in detail in Paul [37].