***Review Article:***

# Role of T Lymphocytes In Chronic Leukemia

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**Abstract**

Functional immune cells are required for the prevention or resolution ofimmune-mediated disease , in particular T cells, including helper (CD4+; Th) or cytotoxic (CD8+; Tc) T cells. Th cells differentiate into Th1 or Th2 type cells, through production of inflammatory (IL-2, IFN-α) or anti-inflammatory (IL-4, TGF-ß) cytokines, respectively. Th cells also can differentiate into a third type of Th cells termeds Th17 type cells that produces IL-17 thereby mimicing the effects of Th1 cells. Th type cells can also differentiate under certain conditions into a regulatory (T-reg) type cell capable of secreting immunosuppressive cytokines such as TGF-ß and IL-10. This mini-review discusses the importance of T cell plasticity in regulating the nature of the immune cell responses seen in inflammatory diseases or cancer.

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## T Lymphocytes:

T lymphocytes are essential for coordinating diverse inflammatory responses via synthesis of of cytokines, essential for the proliferation, differentiation, recruitment and survival of pro-inflammatory cells. Two broad subsets of T lymphocyte have been defined according to their cell markers and distinct roles: the $CD4^+$ (T helper) and the $CD8^+$ (T cytotoxic; Tc) cells. $CD4^+$ cells are further subdivided into Th1 and Th2 cells, subject to the type of cytokines = they produce. Th1 responses are characterized by the release of cytokines to enhance macrophage phagocytosis and synthesis of IgG opsonising antibodies by B cells. Th2 cellset respond principally to extracellular antigens and a subsequent Th2 pattern of inflammation involves T cell directed B cell production of IgM and IgE immunoglobulins through production of cytokines including: IL-4, IL-5, IL-9, or IL-13.

Induction of Th1 type cells is associated with strong T cell cellular responses, in contrast induction of a Th2 cells is associated with antibody-mediated or humoral immune responses[1]. Th1 and Th2 type cells express mutual inhibitory effects that Th1 type responses can downregulate a Th2 type response and vice versa[2-3]. Several distinct transcription factors, including STAT4 and T-bet (for Th1 cells) and STAT6 and GATA3 (for Th2) are responsible for the differentiation of Th cells to Th1 or Th2 subtypes The Tc1 and Tc2 CD8 subsets are the only specific effector cells with the ability to kill intracellular pathogens or cancer cells. Although Th cells are do not have the ability to kill target cells, they are critical for the cytolytic function of Tc cells. (Fig1).

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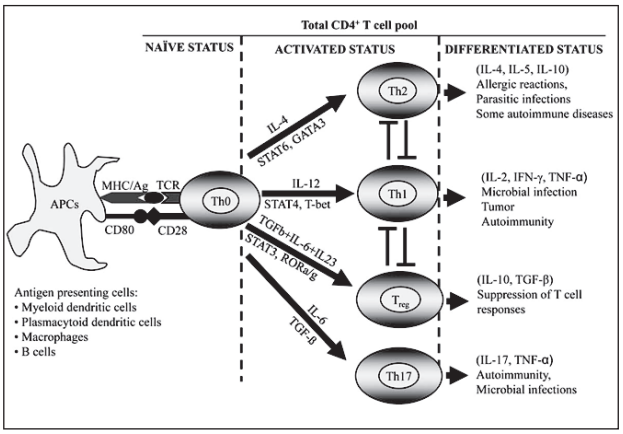


Fig. 1: Schematic layout of CD4+ T cell differentiation

**Leukemia:**

Leukemia is a malignant leukocyte disease characterized by uncontrolled cell proliferation, reduced apoptosis and, in certain types of leukemia, insufficient differentiation that results in normal leukocyte displacement and increased numbers of malignant cells found in the bone marrow and in peripheral blood. Research into chronic myeloid leukemia (CML) is a classical instance of how discoveries in the field of cancer genetics may in due course provide targeted therapy for the treatment of malignant diseases. An important initial finding was of a consistent chromosomal abnormality in CML patients i.e., translocation t(9;22)(q34;q11.2, that was followed by the identification of the chromosomal translocation responsible for this abnormality. CML (also termed chronic myelogenous or granulocytic leukaemia) is classified by the World Health Organization as a myeloproliferative disorder belonging to a group of conditions that includes essential thrombocythaemia, polycythaemia vera and chronic idiopathic myelofibrosis[4]. The myeloproliferative diseases are clonal disorders of the HSC characterized by aberrant proliferation of granulocyte, erythroid and megakaryocytic cells. CML presents with a definitive molecular biological profile and is now more correctly considered as a separate entity[5].

***Role of T cells in leukemia: paradigm for anti-tumour immunity.***

$CD4^+CD25^+$ T cells might have an important role in facilitating immune tolerance through regulation of those T cells responsible for autoimmune disease[6]. Evidence from murine models provides evidence suggesting that T cells can downregulate immune responses against a number of hematological malignancies[7]. We investigated this hypothesis by examining the role of T cells in the chronic phase and/or blast crisis phase of CML relapse following either bone marrow transplantation and/or chemotherapeutic treatment. CML patients were selected for this project with immunophenotypic performed to test for the occurrence of these cells. This approach might show that a relapse after chemotherapeutic treatment might result from an increase in the regulatory T cell population which in turn may lead to an enhanced inhibition of the graft versus leukemia effect. $CD4^+CD25^+$ regulatory cells have been demonstrated to regulate tumour immunity and tolerance of alloantigens. These cells are present in the population of donor T cells in CML and may contribute to a relapse by suppression of the graft versus leukemia response. Therefore, several lines of evidence suggest an important role for regulatory cells in the suppression of the graft versus leukemia response thereby contributing to CML relapse following treatment[8-9].

$CD4^+CD25^+$ regulatory T cells can be activated via the TCR but remain hyporesponsive in terms of proliferation[10]. However, this regulatory role can be overcome by a strong signal to the TCR e.g. CD28 co-stimulation or stimulation with IL-2[11]. This important observation provides evidence that the regulatory role of T cells has to be viewed in the context of TCR signal strength. Furthermore, $CD25^+$ cells make up 5-10% of the $CD4^+$ T cell population in normal mice and these cells comprise 6-12% of $CD4^+$ T cells in humans[12]. In humans, these regulatory properties may be restricted to the $CD25^{high}$ population that comprises 1-2% of $CD4^+$ T cells. Human $CD4^+$ $CD25^{high}$ rather than $CD25^{low}$ T cells show suppressive and non-proliferative properties following TCR cross-linking. This observation suggests that human CD4+CD25+ T cells may be a heterogeneous population consisting of primed and regulatory components. In addition to CD25, other associated markers such as HLA DR, CD45RO and CD122 signify an activated memory phenotype with a high affinity for IL-2R[13].

Immune tolerance includes the facility for regulation of leukocytes that can recognize self-antigens, such mechanisms of tolerance originate centrally in the thymus and are complemented by peripheral

tolerance. Thymic tolerance comprises the specific positive selection of T cells that express TCR with low affinity ligand and clonal deletion of high avidity ligand. In the periphery, tolerance is preserved by the mechanisms of anergy, naïve status and the counterweight provided by cytokines. Among the mechanisms used to for immune system regulation, the notion of a specific regulatory T cell population has found prominence. Early work on thymectomised neonatal mice found that suppressor cells originating via the thymus influenced immune responses to self antigens and in their absence, gave rise to organ specific autoimmune disease[14]. Later characterization revealed a coexistence in the $CD4^+$ population of both self reactive cells that can result in autoimmunity or regulatory cells capable of abrogating autoimmune responses[15]. These $CD4^+$ regulatory cells also co-expressed CD25 that forms the alpha subcomponent of IL-2 receptor[14]. CD25 represents an early activation marker that together with CD122 forms a high affinity IL-2 receptor, while $CD45RB^{low}$ was identified as another activation marker .

SCID mice instilled with $CD4CD45RB^{high}$ developed colitis and a wasting syndrome whilst $CD4^+CD45RB^{low}$ was found to be protective (16), more recently this regulatory property has been shown to be limited to the CD25 expressing subset of $CD4^+CD45RB^{low}$ (17). The role of CTLA-4 in the role played by regulatory cells has been shown in murine $CD4^+CD45RB^{low}$ T cells as abolishing regulation with blocking anti-CTLA-4 Mab and transfer to SCID mice may result in colitis similar to that given by $CD45RB^{high}$ alone (17).

Additionally, $CD4^+CD25^+$ T cells have been suggested to have a modulating effect on the APC costimulatory ligand by downregulating dendritic cell CD80 and CD86 expression (18). However, findings from in vitro models have demonstrated that suppression is APC independent and does not affect expression of costimulatory molecules including. CD86, CD40 or adhesion molecules such as ICAM. The ability of $CD4^+CD25^+$ T cells isolated from TCR transgenic mice to suppress antigen specific responses of $CD4^+CD25^+$ T cells from multiple TCR transgenic mice suggests that suppression is not antigen specific (19). In addition, regulation spans allogeneic disparity with the suppressive capacity of $CD4^+CD25^+$ T cells including reduced IL-2 production by $CD4^+CD25^+$ T cells (19). The mechanism of suppression remains to be fully eluciated. However, several lines of evidence from experiments designed around murine autoimmune disorders including adoptive transfer of cloned autoantigen specific effector cells or transfer of $CD4^+CD25^+$ T cells have confirmed a role of these cells in abolishing autoimmune disease (20-21). Further supportive findings derive from the study of CD25 knockout mice and humans with a defect in CD25 who lack $CD4^+CD25^+$ T cells, manifesting autoimmune disease including widespread lympho-adenopathy (22).

The role of the donor T cells is facilitated by the allogeneic recognition of recipient antigens that include the major histocompatibility antigens with ensuing T cell activation (23). These antigens encompass both tumour and healthy tissues. T cell responses focused on tumour antigens might result in a graft versus leukemia (GVL) response that might contribute to reducing leukemia. The success of donor lymphocyte infusion (DLI) is ascribed to the advantage conferred by GVL[24]. However, such benefits are countered by graft versus host disease (GVHD) directed at normal tissue. Thus an unwanted side-effect of the immunosuppressive treatment used to decrease GVHD may include a suppression of the GVL effect thereby contributing to leukemia relapse. $CD4^+CD25^+$ T cells can protect against GVHD by preserving tolerance to alloantigens[25], but detrimentally this might be at the expense of GVL as experiments in mice suggest $CD4^+$ $CD25^+$ T cells can have inhibitory effects on GVL. Tumour immunity is exposed by the deletion of CD25+ cells as shown in BALB/c athymic nude mice inoculated with syngeneic leukemia cells and reconstituted with syngeneic CD25-splenocytes. In contrast, non-depleted splenocytes or a mixture of $CD25^-$ with $CD4^+$ T cells did not avert tumour mortality. The same workers removed $CD4^+CD25^+$ T cells with anti-CD25 Mab to demonstrate regression of 6/8 syngeneic mouse tumours [26]. One important feature of regulation by $CD4^+CD25^+$ T cells is their ability to inhibit $CD8^+$ T cells[27]. Tumour immunity is classically linked to he activity of cytotoxic T cells although the prominence of the T helper cell is increasingly recognised. $CD8^+$ T cell suppression is facilitated by a T cell to T cell interaction that is independent of APC. These observations are supported by the phenotypic findings in lung or ovarian carcinoma,

where there is a greater proportion of $CD4^{+}CD25^{+}$ tumour infiltrating leukocytes (TIL) in tandem with lower expression of $CD25^{+}$ by CD8+ cells[28].

***Conclusion:-***

Preclinical studies have significantly increased our understanding of the mechanisms governing different disease states and led to potential relevant applications. However, a number of cytokines with potential adjuvant effects, in particular those produced by Th17 cells, are currently under evaluation in preclinical studies, and may provide promising applications in clinical settings in near future. Findings generated from these studies might lead to significant improvements in the treatment of cancer.

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