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Review Article

An Update - Chronic Myeloid Leukemia: An Interaction Between in Cells, Genes and Molecules

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Abstract

In chronic myeloid leukemia (CML) proliferation is increased and resistance to apoptosis has been proposed as a mechanism accounting for myeloid cell expansion. Anti-apoptotic effects, high levels of proliferation, insensitivity to negative regulators and defects in the adhesion mechanism between primitive progenitor cells and stromal cells are considered to result from expression of the p210BCR-AB fusion protein. These defects are therefore likely to be responsible for myeloid expansion. These mini-review update recent insights into cells, genes and molecules pathways employ to regulate immune responses as well as to correlate the presence and molecular profile of CML

Keywords: Leukemia; Therapy; T cells; $CD4^+CD25^+$; Exosomes

Introduction

Chronic myeloid leukemia (CML), effectively a cancer of white blood cells, involves an unregulated increase in the growth of myeloid cells in the bone marrow that leads to an accumulation of these cells in the blood. It represents 15-20% of all leukemia's in humans. Even though the use of tyrokine kinase inhibitors, and multi-modal treatments, in CML have led to recent improvements in patient survival over the past decade, leukemic relapse remains a formidable clinical challenge meaning that that the quality of life of CML patients is often compromised, and that survival rates remain low, principally due to disease relapse [1]. One hurdle to effective treatment is that tumors are known to exert suppressive effects on the immune system, and that tumor progression is linked to functional impairments of immune cells [2-3]. The failure of conventional therapies to control disease relapse has stimulated the search for novel more effective approaches, including immune therapies. Immunotherapy may be an especially attractive option both in acute and chronic myeloid leukemia because immune cells are functionally disabled [4]. How can immunotherapy best be configured to treat CML? How can a better understanding of the abnormal cellular processes involved CML lead to necessary improvements on current therapeutic approaches?

Role of $CD4^+CD25^+$ Regulatory T in CML

It is known that $CD4^+CD25^+$ regulatory T cells can be activated via T cell receptors (TCR) but they remain hypo-responsive in terms of proliferation [5]. Despite this, the regulatory function can nevertheless be overcome by strong TCR and this can be achieved using either CD28 co-stimulation or IL-2 addition [6]. This represents an important observation because it means that regulatory function needs to be considered in the context of TCR signal strength. Also, whilst $CD25^+$ cells comprise 5-10% of the $CD4^+$ T cell population in the normal mice [5], in humans this figure is approximately 6-12% [7]. It should also be noted that human regulatory properties may be restricted to the $CD25^{high}$ population which represents 1-2% of $CD4^+$ T cells [6]. Human $CD4^+$ $CD25^{high}$ rather than CD25 low is far more important here in the sense that it exhibits suppressive and non-proliferative properties in response to TCR cross-linking. This means that human $CD4^+CD25^+$ T cells may well be heterogeneous populations which comprise both of primed and regulatory components. It is also worth noting that, in addition to CD25, various other associated markers (such as HLA DR, CD45RO and CD122) also indicate activated memory phenotypes which demonstrate a high affinity to IL-2R [6-8].

Whilst it has been shown that $CD4^+CD25^+$ T cells may exert a modulating effect on the antigen presenting cells (APC) co-stimulatory ligand through the down regulation both of CD80 and CD86 on dendritic cells, others do not agree and have reported that suppression is APC independent and does not affect expression of co-stimulatory molecules such as CD86, CD40 or adhesion molecules such as intracellular adhesion molecules (ICAMs) [6-8]. It is clear that suppression is not antigen specific because $CD4^+CD25^+$ T cells isolated from TCR transgenic mice suppress antigen specific responses of $CD4^+CD25^+$ T cells from multiple TCR transgenics [5], and also that this regulation straddles allogeneic variation [9].

IL-2 production by $CD4^+CD25^+$ T cells can be reduced by the suppressive capabilities of $CD4^+CD25^+$ T cells [5,6] although the precise mechanism for this is unclear. Work from several laboratories either using clone auto antigen specific effector cells or adaptor transfer of $CD4^+CD25^+$ T cells have established the role of these cells in reducing autoimmune disease [10,11]. In addition, research in murine CD25 knockout mice and humans (with a defect in CD25 which lacks $CD4^+CD25^+$ T cells and manifests autoimmune disease including extensive lymphoadenopathy) adds further support [12,13].

The role of cytotoxic T lymphocyte antigen-4 (CTLA-4) in regulatory cell function has been shown in murine $CD4^+CD45$ R Blow T cells. When regulation is blocked with anti-CTLA-4 monoclonal antibody (Mab) and then transferred to severe combined immunodeficiency (SCID) mice this may give rise to a colitis similar to $CD45RB^{high}$ alone [14]. The role of CTLA-4 here therefore suggests involvement of the antigen presenting cell (APC). However, it seems that actual cell contact is required (as opposed to soluble factors e.g. cytokines [6,7]. Whilst $CD4^+CD25^+$ T cells do secrete IL-10 and TGFb, work with cytokine blocking antibodies indicates that suppression may

be independent of these factors, at least in vitro [6,7]. In addition, $CD4^+CD25^+$ T cells from IL-4 and IL-10 knockout mice retain their suppressive nature [5]. For the human experiments it is possible that a heterogeneous population was utilized for co-culture; however, levels of $CD4^+CD25^{+high}$ did not correlate suppression with the production of IL-10 [6]. However, murine experiments suggest that $CD4^+$ $CD25^+$ T cells can exert inhibit graft versus leukemia (GVL), which could be clinically relevant here. Tumor immunity may be revealed by the removal of $CD25^+$ cells (as shown in BALB/c a thymic nude mice inoculated with syngeneic leukemia cells and then reconstituted with syngeneic CD25-splenocytes). But in contrast, non-depleted splenocytes (or a mixture of $CD25^-$ and $CD4^+$ T cells) do not prevent tumor mortality, whilst depleted $CD4^+CD25^+$ T cells with anti-CD25 Mab showed regression in 6 of 8 syngeneic murine tumors [15].

$CD4^+CD25^+$ T cells inhibit $CD8^+$ T cells, a process thought to represent an important aspect of regulation [16]. Whilst tumor immunity has long been linked to cytotoxic T cell activity, understanding of the relevance of T helper cells continues to grow. It is known that $CD8^+$ T cell suppression is mediated by T cell-T cell interaction, and that this is independent of APC. Downstream effects of this include inhibition of the production of IL-2 as well as an increasing threshold for IL-2 activation; the end result of this is an inhibition of $CD8^+$ T cell proliferation, IFNg production and CD25 expression [17]. This conclusion is further supported by several phenotypic findings in ovarian and lung cancer, where an increased proportion of $CD4^+$ $CD25^+$ tumor infiltrating lymphocyte (TIL) in association with lower expression of $CD25^+$ on $CD8^+$ cells has been noted [18].

Additionally, two groups showed an increase in $CD4^+$ $CD25^+$ F T-reg cells in CML patients, indicating an immune mechanism that may be important in the control of CML [19,20].

Role of Cell Cycle Genes in CML

In haemopoiesis, stem and progenitor cell proliferation and differentiation are normally tightly 'coupled' meaning that the haemopoietic cell mass is unchanged (i.e. neither expands nor contracts) under steady-state conditions. However, in CML, cell proliferation and differentiation become dysregulated and the consequent expansion of haemopoiesis eventually leads to cellular transformation. We hypothesize that CML stem and progenitor cells are unable to modify the balance between self-renewal and differentiation. This is because (unlike normal stem cells) they are unable to return to the G0 phase of the cell cycle between divisions.

The pRB pathway (involving cyclin D, CDKs, CKIs, and E2F), whose components are central to restriction point control; link the positive and negative proliferative signals to the machinery of the cell cycle. Inactivation of this pathway (which commonly occurs in cancer in humans) may alter growth factor dependence in cells. After passing the restriction point at mediated GI phase of the cell cycle, mammalian cells then become growth factor independent. The two families of GI cyclins, namely D-type cyclins (cyclin Dl, D2, and D3) and E-type cyclins (cyclin El and E2), and also their dependent kinases (CDKs) control the transition through the restriction point. The principal cellular targets of the GI cyclin-dependent CDKs and the retinoblastoma protein (pRB) family of pocket proteins, is consisting of pRB, p107 and p130. When hypophosphorylated, these pRB-related pocket proteins associate with members of the E2F family of transcription factors and thus negatively regulate the transcription activity of E2F-regulated genes, a crucial process for entry into the S phase of the cell cycle. Evidence supporting this hypothesis is robust [21], and further, using cycloheximide, our laboratories have also demonstrated that the probability of self-renewal by cultured haemopoetic progenitor cells can be enhanced by prolonging the G0/G1 phase of the cell cycle [22,23]. In addition, others have demonstrated that some haemopoietic growth factors can vary the proportions of cells in different phases of the cell cycle [24]. These findings come together to represent strong evidence that the mechanism 'coupling' proliferation and differentiation is located within the cell cycle machinery, particularly in the control of G0/Gl phase of the cell cycle.

Three classes of molecules (cyclin-dependent kinases (CDKs), cyclins and CDK inhibitors), by their mutual expression and interaction, dominate the control of the timing of events in the cell cycle.

CDKs are activated by the cyclins, and are inhibited by a number of proteins (such as p15, p16, p21, p27). The CDKs phosphorylate target molecules which then control the processes which lead to DNA replication and mitosis. That the cell division cycle is altered in malignant cells is supported by a large number of publications, and suggests that investigation of molecules that regulate the cell cycle in CML is likely to represent a fruitful line of clinically-relevant research.

Cyclin Dl is a regulator of GI-phase progression which, in cell culture, acts synergistically with the ABL oncogene to transform fibroblasts and haemopoietic cell lines [25], whilst in addition; cytokines that induce proliferation also regulate cyclin expression [26]. Furthermore, levels both of CDKs and cyclins can be altered by some antineoplastic agents and immunomodulators [27], and therefore may represent targets for new therapeutic strategies which focus on exerting control over chronic phase haemopoiesis in CML. Consistent with this, Mahon et al found that exposure of CML cells to BCR-ABL junction-specific antisense oligonucleotides changed their distribution within the cell cycle.

The activities of the cyclin-dependent kinases are negatively regulated by CDK-inhibitors (CKIs) (particularly p21, p27 and p57), and these target a wide spectrum of CDKs. The CKIs p15, p16, p18 and p19 specifically inhibit cyclin D-CDK4/6 interaction. In addition, results from our laboratories have shown that cyclin D2 and p27 each have a role in regulating survival and apoptosis; however, cyclin D2 deletion does not affect T cell proliferation. These findings demonstrate that, in B and T cells, the function of cyclin D2 cannot be compensated by other D cyclins. Furthermore, we have shown that B cells from Btk-I do not up regulate cyclin D2 expression in response to BCR cross-linking. Consequently, we believe that the pRB pathway, and in particular cyclin D2, plays an important role in B and T cell proliferation and development (personal data; unpublished).

Moreover, at least two groups showed that an increase in the expression level of cyclin D in BM cells is tightly linked to high proliferation rate of leukemic cells (i.e. blast crisis phase in CML) and therefore may be helpful in treatment decision-making [28,29].

Involved in a variety of cellular responses (such as cell growth, survival, metabolism, differentiation, cytoskeletal organization, and membrane trafficking), the PI3-K signal transduction cascade phosphoinositide 3-kinases (PI3-Ks) are a group of lipid kinases that catalyze the specific phosphorylation of the inositol ring of phosphoinositides at position 3. Our laboratory previously demonstrated that, in B lymphocytes, cyclin D2 is responsible for the

phosphorylation and inactivation of p130 and represents a process which releases E2F activity and entry into the cell cycle. Using primary and tissue culture B cell systems, we showed that p27 functions downstream of cyclin D2 in B cells in response to B cell receptor (BCR) stimulation (personal data; unpublished). Previous studies using pro-B cells and embryo fibroblasts, demonstrated that p27 is a target of the PI3-K pathway, and also that inhibition of P13-K (by LY294002 or Wortmannin) induces an increase in levels of p27 (which binds to and inhibits the cyclin/KDK2 complexes). Furthermore, we demonstrated that these inhibitors arrest cell growth via inhibition of P13-K and activation by PKB/Akt for proteins AFX, FKHR, and FKHR-L1, and by up regulation of p27 expression [26].

Additionally, there has been a promising early clinical activity in chronic lymphocytic leukemia (CLL), CML and NHL, after the development of inhibitors of the B-cell BCR signaling pathway antagonists [30]. Askmyr's groups reported for the first time that the BCR-ABL1-induced block in B-cell development occurs at the pre-B-cell stage in CML CP patients. They also showed a close link between an increase in the activation of STAT5 caused by BCR-ABL1 and blockage of the differentiation of cells in pre-B stage [31].

Role of Exosomes in CML

Exosomes are derived from endosomes by a fusion process to form multi vesicular bodies (MVB) [32]. Via inward budding of the MVB membrane, intraluminal vesicles are formed which, through invagination, enclose a number of endoplasmic components [33]. Once there is MVB fusion with the cell membrane, an ATP-dependent process generates the release of exosomes into the extracellular space as double-membrane, viral-size vesicles. These exosomes contain proteins and glycoproteins that are present in the cytosol of the parental cells [34]. The exosome fractions that are obtained from plasma of cancer patients are highly enriched in several immunosuppressive molecules (and these include death receptor ligands such as FasL, TRAIL, and also the inhibitory cytokines, IL-10 and TGF) [35]. Unlike exosomes in normal cells, exosomes from human tumors also generate apoptosis of activated $CD8^+$ T cells, as well as differentiation (and altered function) of T Reg cells, and they also alter dendritic cell differentiation, and these are all processes which promote the expansion of myeloid-derived suppressor cells [36].

Whiteside' laboratory has demonstrated an up regulation of T Reg cells in the peripheral circulation of AML patients, and we also found higher suppressor activity these cells relative to T Reg cells in the peripheral blood of normal donors [37]. In addition, they demonstrated that blast-derived exosomes from AML patients contain an immunosuppressive payload [38]. In these de novo AML patients, they found higher ($p<0.001$) levels of exosomes compared to normal controls [38]. They also found that exosomes isolated from plasma from patients with CML, and exosomes isolated from patients with AML each had a very distinct molecular profile from control subjects. These findings demonstrated that these exosomes had originated from leukemic blasts [39].

Therefore, it is believed that these exosomes potentially reduce the ability of a patient to produce effective anti-tumor responses (i.e. Immunosuppressive exosomes present in AML plasma suppresses the host immune system to promote AML relapse, this mechanism is also highly relevant in CML.

Tumor-derived exosomes now clearly seem to be one of the key immunosuppressive mechanisms involved in cancer [8,39]. Despite this, relatively little is currently known about the origin and properties of exosomes present in the plasma of cancer patients, including those produced by AML and CML blasts. Since, we now know that AML blast-derived exosomes exert suppressive effects on anti-tumor immune cells, it has become essential for future therapeutic advancement to identify the molecular mechanisms responsible for this suppression. Evaluation of the impact of exosome-mediated immune suppression on the disease process in CML patients, and its responses to therapy, is therefore now of critical importance.

Conclusion

Although advances in CML therapy have considerably improved initial response rates and the patients' quality of life, the survival rates remain low, largely due to disease relapse; therefore, immunotherapy may be an especially attractive option in CML.

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