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Review

The duality of macrophage function in chronic lymphocytic leukaemia

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ABSTRACT

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia and, in some patients, is accompanied by resistance to both chemotherapeutics and immunotherapeutics. In this review we will discuss the role of tumour associated macrophages (TAMs) in promoting CLL cell survival and resistance to immunotherapeutics. In addition, we will discuss mechanisms by which TAMs suppress T-cell mediated antitumour responses. Thus, targeting macrophages could be used to i) reduce the leukaemic burden *via* the induction of T-cell-mediated antitumour responses, ii) to reduce pro-survival signalling and enhance response to conventional chemotherapeutics or iii) enhance the response to therapeutic antibodies in current clinical use.

1. Chronic lymphocytic leukaemia (CLL)

Chronic lymphocytic leukaemia is a B cell lineage-derived blood cancer characterised by an accumulation of leukaemic cells within the blood, bone marrow and lymphoid tissues [1]. Whilst the clinical course of CLL is varied, it usually presents as indolent disease which endures for a variable length of time. Conversion of CLL from the quiescent (stable disease) phase to disease requiring treatment (progressing disease) occurs in approximately 70% of patients and is often associated with reduced lymphocyte doubling time, del(17p), TP53 and IKZF3 mutations [2,3]. Whilst we often refer to CLL as being stable or progressive it may be more realistic to view CLL as a disease that exists on a spectrum spanning “stable” through to disease requiring treatment. We know that CLL development, progression and relapse are accompanied by multiple mutational events [2,3], but it is also clear that the microenvironment contributes to disease progression and responses to chemo-immunotherapeutic regimes. Of central importance to CLL are interactions between the leukaemic cells and the microenvironment within the bone marrow, lymphoid tissues and the circulation. The CLL microenvironment is shaped by a complex network of cytokines and chemokines, as well as direct interactions of malignant B cells with CD4 + and CD8 + T-cells, NK T-cells, and specialised macrophages often referred to as nurse like cells (NLCs) or tumour associated macrophages (TAMs). A better understanding of the role of the microenvironment and its relationship with leukaemic CLL cells has identified several events with considerable potential for translation into patient treatments. In particular, tumour associated macrophages (TAM) are important contributors to CLL development and progression as well as effectors of antibody-based immunotherapy. In this review we focus on the duality of the roles of TAMs, in particular their pro-tumourigenic and immune-suppressive role in CLL as well as their role as immune effectors of therapeutic antibodies.

2. Macrophage lineage

Macrophages are an essential component of the innate immune system and are comprised of resident tissue macrophages as well as monocyte-derived macrophages. Many tissue macrophages are derived from the early embryonic yolk sac or liver [4]. Post-partum, tissue macrophages are either derived *via* self-renewal of resident tissue macrophages or through the attraction and subsequent differentiation of monocytes. In the latter instance, haemopoietic stem cells differentiate into two progenitor cell lineages namely myeloid progenitor cells (myelopoiesis) and lymphoid progenitor cells (lymphopoiesis) [5]. Lymphopoiesis gives rise to B-cells, T-cells and NK-cells whereas myelopoiesis gives rise to erythrocytes, monocytes, granulocytes and platelets [5–7]. Progenitor cells of both lineages give rise to differentiated cells that are released into the bloodstream where they remain or can be induced to undergo further differentiation within specific tissue sites [8–10]. In the post-partum setting, monocytes are derived from macrophage and dendritic cell (DC) progenitor cells (MDPs), which can differentiate into dendritic cells or macrophages in periph-

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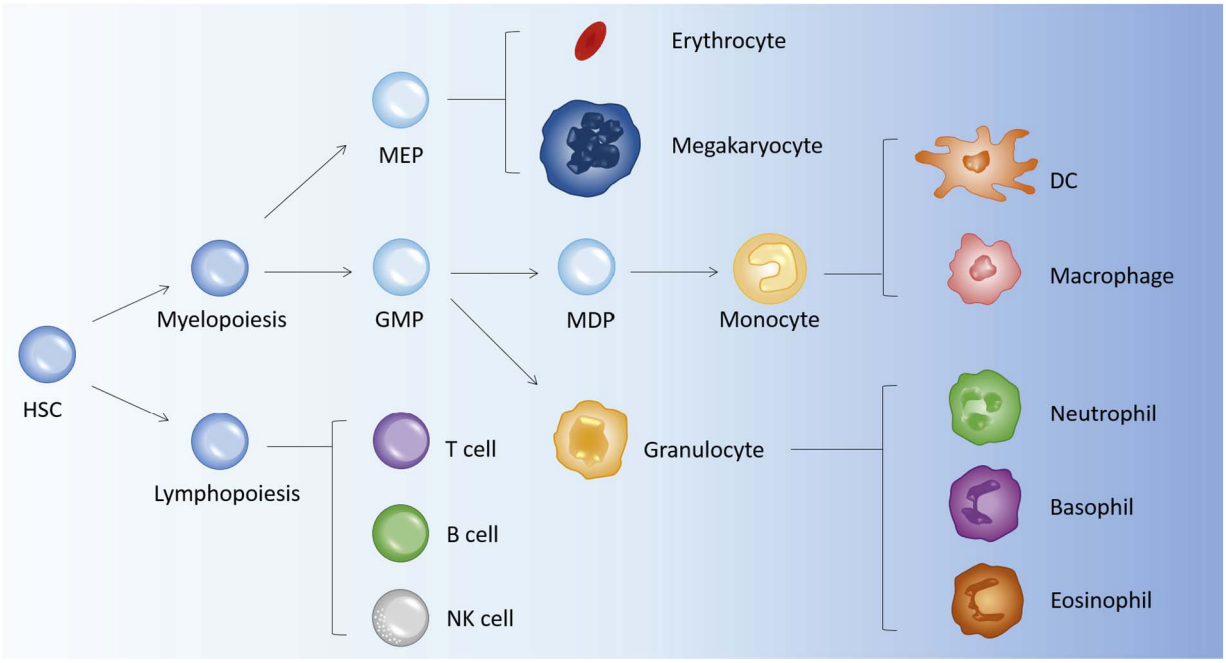

Fig. 1. Haematopoietic lineage of macrophages. The haematopoietic cells in bone marrow differentiate into myeloid (myelopoiesis) or lymphoid progenitor cells (lymphopoiesis). Lymphopoiesis gives rise to B-cells, T-cells and NK-cells whereas myelopoiesis involves two progenitors namely granulocyte–monocyte progenitors (GMPs) and megakaryocyte-erythrocyte progenitors (MEPs). Macrophage and dendritic cell progenitor cells (MDPs) give rise to monocytes which in turn differentiate into dendritic cells (DCs) and macrophages after recruitment to peripheral tissue sites.

eral tissue sites, (Fig. 1) [11–13]. Activated dendritic cells migrate to secondary lymphoid organs and present antigen to lymphocytes such as T-cells [14,15], a key event in the initiation of adaptive immune responses. In contrast, macrophages have tissue-specific functions [11,12,16–18] and largely remain within the peripheral tissue after activation [9]. Macrophages present antigens and are effectors of Fc gamma receptor (FcγR)-dependent cell elimination *via* antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADP). More recently, it has emerged that TAMs can suppress T-cell mediated antitumour responses *via* PI3Kγ mediated immune response [19,20]. In addition, macrophages regulate tissue homeostasis through the modulation of metabolism, tissue damage sensing, and tissue remodelling [11,16].

Whilst macrophages are traditionally thought as phagocytes with activity against infectious particles and cancer cells, it has become evident that multiple macrophage phenotypes exist that display a wide repertoire of functional capabilities [21]. Macrophages are classified by the expression of cell surface markers and their functional activation status. Classically, macrophages activated by IFNγ or microbial components were referred to as M1 macrophages [22], which release pro-inflammatory cytokines (TNF-a, IL-12) and activate T-cells. On the other hand, M2 macrophage-phenotypes were induced by IL-4/IL-13 and characterised by anti-inflammatory effector molecules (IL-10, TGF-beta, HO-1, and arginase) that modulate inflammatory responses, and control wound healing and tissue regeneration [22]. More recently, it has become accepted that macrophages display considerable phenotypic plasticity where the experimentally induced “M1”-like and “M2”-like phenotypes are the extreme ends of the spectrum [21]. Macrophages phenotypically adapt to suit the microenvironment in response to various stimuli and cytokines. For example, within an infectious microenvironment macrophages may acquire an “M1” state whereas within cancerous tissue there are different cues that induce “M2”-like properties [23–25]. Multiple studies have shown that the diversity and nature of the macrophage infiltrate in tumours may have either negative or positive prognostic implications depending on the tumour type [26–28]. This suggests that the infiltration of macrophages into a tumour is not only dependent on the tumour type but is dependent on, and may in turn modify, the behaviour of the tumour. These observations suggest that macrophages can potentially both promote the survival of tumour cells (pro-tumourogenesis) whilst also being mediators of tumour cell killing. Indeed, recent studies have shown that the pro-tumourigenic and immunosuppressive properties of tumour associated macrophages can be modulated by the PI3K/mTOR pathway which is actionable using clinically available agents [29,30]. Thus, tracking macrophage phenotypes in the context of malignancy will be informative since it can provide an assessment of whether the malignant cells exist within the context of a pro- or anti-tumourigenic environment which may guide targeted therapies [31,32]. It is this paradox that makes macrophages such a compelling target for anticancer therapies [31,33].

3. The role of macrophages in CLL pathogenesis

Macrophages both support the functioning of normal tissue-specific parenchymal cells and malignant cells, and are dependent on the signals generated by the parenchymal cells in the local environment [11,22,34,35] for their differentiation. In CLL, evidence supports a “symbiotic” relationship between the malignant CLL cells and tumour associated macrophages, (Fig. 2). For example, TAMs are required to maintain the survival of the malignant B cells within the bone marrow [36–39].

During conversion from the normal to neoplastic state, B cells start to secrete factors that attract circulating monocytes into the developing tumour niche [40] and induce them to differentiate into macrophages, which are characterised by high expression of surface markers such as CD14 +, CD68, CD163 and CD206 [37,41], consistent with an “M2”-like phenotype and functionality [27]. These macrophages have been shown to be functionally and transcriptomically indistinguishable from NLCs [42–45]. The term NLC specifically refers to *in vitro* cultures of monocyte-derived M2-like macrophages isolated from PBMCs and are the functional equivalent of TAMs located *in vivo* within CLL tissues (i.e. NLCs = CLL-specific TAMs) [36]. NLCs are generated following the *in vitro* co-culture of CD14 + monocytes from either healthy donors or CLL patients with CD19 + CLL cells. In these cultures, the CLL cells induce