OncoImmunology 1:3, 387–388; May/June 2012; © 2012 Landes Bioscience

Under one roof

The bone marrow survival niche for multiple myeloma and normal plasma cells

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Keywords: multiple myeloma, plasma cells, CD80, CD86, CD28, dendritic cell, IL-6, IDO

Abbreviations: MM, multiple myeloma; BM, bone marrow; PC, plasma cell; BMSC, bone marrow stromal cells; APC, antigen presenting cells; DC, dendritic cell; IDO, indoleamine 2,3, dioxygenase; LLPC, long lived plasma cell

Our recently published data demonstrate significant similarities between normal and malignant plasma cells in the cellular and molecular interactions that support their survival in the bone marrow microenvironment, and suggest that the biology of multiple myeloma may largely reflect that of their normal counterparts.

Introduction

Multiple myeloma (MM) is a clonal neoplasm of the normal bone marrow-resident long lived plasma cells. Like normal plasma cells, MM depend on their interactions with bone marrow stromal cells (BMSC) for survival and production of essential growth factors.[1] But it remains largely unclear which specific stromal cell types or molecules are involved in these interactions. Our recent studies have shown that activation of CD28, a prototypical co-stimulatory molecule on T-cells, (overexpression of which is a poor prognostic marker in myeloma patients)[2] protects myeloma cells against apoptosis in vitro.[3] Antigen presenting cells (APC) such as dendritic cells (DC) and other myeloid cells that provide the ligands CD80/CD86 for CD28 activation on T-cells are also found to be closely associated with myeloma cells in the BM. Our recently published work[4] extend these observations and define similarities in the role for CD28 and DC in supporting normal PC as well as myeloma by inducing pro-survival signals and modulating the BM microenvironment in vitro and in vivo.[5]

Dendritic Cells Support Myeloma and Plasma Cell Survival

Our findings[4] that BM from MM patients have a higher percentage of $CD11b^+$ myeloid cells compared with normal controls, and that myeloid DC protect MM in vitro against cell death[3] and that DC produce both IL-6 (an essential MM cytokine[6]) as well as the immunosuppressive enzyme indoleamine 2,3 dioxygenase [IDO,[7] induces anergy in activated T-cells by depleting the essential amino acid tryptophan or induce them to become T-regs (known to accumulate in the BM of MM patients)[8]] in co-cultures with MM; all suggest that DC have the potential to modulate the BM microenvironment.

Expanding on recent studies on the role of DC in B-cell and PC survival,[9] our work[5] demonstrates that direct interactions between DC and PC in murine BM is important for their long-term survival and function. Despite the complexity of the PC-DC cellular interaction, PC survival, Ig production and induction of DC IL-6 production were completely dependent on the interaction between CD28 on the MM/PC and CD80/CD86 on the stromal DC.

CD28: A Cell Intrinsic Survival Receptor for Normal and Malignant Plasma Cells

CD28 activation by antibodies or by co-culture with $CD80/CD86^+$ DC protected both myeloma cells[4] and normal BM plasma cells[5] from death induced by serum starvation or chemotherapeutic agents in vitro and this was abrogated when agents that block CD80/CD86 or CD28 were included in the co-cultures. Similar to myeloma, loss of CD28 specifically in the B-cell lineage significantly reduced normal BM PC survival and prevented the generation of long-term antigen specific antibody titers.[5] These findings support a central role for CD28 function in the maintenance of normal PC survival within BM and show that CD28 plays a key pro-survival role for normal BM resident plasma cells and multiple myeloma cells.

Similar to T-cell models,[7,10] not only does blocking CD28 in MM-DC co-cultures abrogate the protective effect of DC on MM survival, but also reduces DC ability to produce IL-6 or IDO thus suggesting that CD28 might be a molecular bridge by which MM/PC modulate the microenvironment. Moreover, IDO activity in these co-cultures

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Submitted: 10/13/11; Revised: 11/09/11; Accepted: 11/11/11
http://dx.doi.org/10.4161/onci.18746

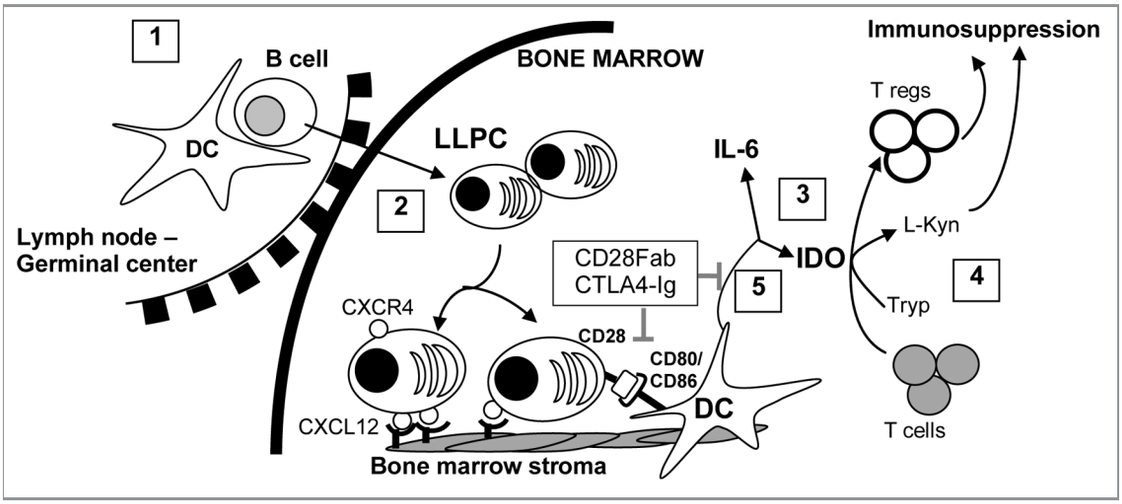

Figure 1. Model of the microenvironment niche interactions for plasma cells/myeloma cells in the bone marrow.

was sufficient to induce activated T-cells to become T-regs and could play a potential role in suppressing anti-myeloma T-cell responses in patients (T-regs are known to accumulate in the BM of MM patients[8]). IDO may also create a nutritionally-depleted niche within the highly proliferative BM that is more favorable for the survival of myeloma cells, which have a lower proliferative index and are less susceptible to tryptophan depletion. Based on these findings, a model of DC and CD28 interactions in the MM pro-survival niche is proposed in **Figure 1**. Newly differentiated normal PC or myeloma cells from germinal centers in the lymph node (1) traffic to the BM via CXCR4 expressed by MM/PC and CXCL12 expressed by BMSC (2), where they interact with myeloid dendritic cells (DC) through CD28 on MM/PC and CD80/CD86 on DC. Ligation of CD28 delivers pro-survival signals to the MM/PC and simultaneously, ligation of CD80/CD86 induces the DC to make IL-6 and IDO (3). While the IL-6 promotes survival in MM/PC, IDO depletes the essential amino acid tryptophan by converting it into its metabolite L-kynurenine. This directly suppresses T cell activation and also induces the generation of T-regs (4), and both contribute to the immunosuppressive environment characteristic of multiple myeloma. Blocking the CD28-CD80/CD86 interaction (5) with agents such as CTLA4-Ig or CD28(Fab) downregulates IL-6 and IDO production, and also blocks DC-mediated survival in myeloma cells.

Just like in MM, we also found that CD28-CD80/CD86 interactions are critical for the in vivo survival of normal BM PC and production of antibody titers in murine models and induced DC production of IL-6 in co-cultures, which was completely (CD80) or largely (CD86) lost when CD80 or CD86 were blocked.[5] Significantly diminished antigen-specific antibody titers following vaccination in $CD80^{-/-}$ or $CD86^{-/-}$ mice compared with fewer BM resident PC suggest that CD28 expressed on PC and their interaction with CD80/CD86 play an essential role in the survival of normal PC just like that observed in myeloma.

Targeting the myeloma microenvironment offers a rational direction toward developing novel anti-myeloma drugs. Studies by others[9] and by us[4,5] show common elements in the pro-survival niches of both normal PC and MM, indicating that therapeutics developed to target PC in autoimmune diseases or organ graft rejection may have significant efficacy in the treatment of multiple myeloma.

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