Mechanisms of Immune Resistance

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61.1 Introduction

It is widely accepted that the curative potential of allo-HSCT for malignant diseases relies on the transfer of healthy donor immune cells capable of recognizing transplantation antigens on residual tumor cells (graft versus leukemia, GvL) and eliminating them. However, as extensively documented in solid cancers, if tumor eradication is incomplete, the prolonged immune pressure selectively allows immune-resistant subclones to survive (Schreiber et al. 2011). There is growing evidence that such an "immunoediting" also accounts for relapse after HSCT. Malignant cells evade GvL either by reducing their immunogenicity and conveying inhibitory signals to the donor immune system (intrinsic evasion) or through the microenvironment (extrinsic evasion).

61.2 Mechanisms of Immune Evasion

61.2.1 Mechanisms Intrinsic to the Malignant Clone

A remarkable example of tumor-intrinsic mechanism of immune evasion is the *genomic loss of the mismatched HLA haplotype* frequently documented in leukemia relapses after T-cell-replete HSCT from HLA haploidentical family donors (Vago et al. 2009). In this setting, donor T cells mount a vigorous alloreactive response against the incompatible HLA molecules, and this reaction is not only responsible for a significant risk of severe GvHD but also a major contributor to the GvL effect. Yet, this strong and selective immune pressure is easily overturned by tumor cells which, by losing the allogeneic HLA haplotype, find a means to avoid recognition and re-emerge. "HLA-loss" variants account for up to one third of relapses after HLA-haplo-HSCT (Crucitti et al. 2015) and have been described also in the setting of HSCT from partially HLA-incompatible URD, although their actual frequency in this setting is yet to be determined (Waterhouse et al. 2011). The documentation of HLA loss at relapse has an important clinical impact, because IS withdrawal or administration of DLI would be much less effective against these diseases variants (Tsirigotis et al. 2016).

Another evidence that supports "leukemia immunoediting" is the occurrence of *isolated*

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extramedullary relapses after allo-HSCT or even more frequently after DLI. These relapses may occur, but not necessarily, in immunological sanctuaries, including the CNS. Although to date the biological drivers of extramedullary relapses remain unknown, some studies have suggested a link with immune-related factors such as chronic GvHD (Solh et al. 2012; Harris et al. 2013).

A number of studies have highlighted a further strategy by which hematological cancers can evade immune control, whereby they express large numbers of *molecules capable of dampening immune responses* such as programmed death-ligand (PD-L)1. The expression of these inhibitory ligands significantly increases at relapses after allo-HSCT. This observation provides a rationale for the use of "checkpoint blockade" to restore immune control at relapse. Initial experience in patients with relapsed lymphoma or extramedullary leukemia with anti-PD1 and anti-cytotoxic T-lymphocyte-associated antigen (CTLA)-4 MOAb is very promising (Davids et al. 2016; Herbaux et al. 2017). However, the risks of triggering life-threatening GvHD remain to be quantified.

61.2.2 Mechanisms Extrinsic to the Leukemic Cells

The alternative, but not mutually exclusive, strategy by which malignant cells enact evasion from immune cell recognition relies on hijacking the stem cell niches in which normal HSC self-renew and differentiate. By doing this, malignant cells create a *tumor microenvironment* (TME) that has profound consequences on disease progression and relapse. The initial studies conducted on solid tumors have shown that the TME consists of two major cellular populations that alone or in combination drive resistance to conventional therapies and suppress antitumor immune responses. The first group comprises a diverse and heterogeneous group of myeloid-derived cells which, according to a yet unresolved debate on their nomenclature, can be generally classified as tumor-associated monocytes/macrophages

(TAM) and myeloid-derived suppressor cells (MDSC) (Bronte et al. 2016). The IS activity of these cells is mediated by factors that include nitric oxide synthase-2 (NOS-2), arginase-1, heme oxygenase-1 (HO-1), interleukin (IL)-10, transforming growth factor (TGF)-β, and prostaglandin E2 (PGE2). All these molecules also favor the recruitment of regulatory T cell (Tregs) that eventually contribute to the inhibition of antitumor CD8^{+} T-cell and natural killer cell effector function (Ostuni et al. 2015). Although most of these mechanisms have been initially demonstrated in solid tumors, there is consistent evidence that they are also involved in hematological malignancies. High-risk AML can actually behave as MDSC by upregulating NOS and suppressing T-cell responses (Mussai et al. 2013). The presence of MDSC in AML has later been confirmed and also identified in multiple myeloma whereby they protect malignant cells through MUC1 oncoprotein (Bar-Natan et al. 2017; Pyzer et al. 2017).

The second cellular group consists of an equally heterogeneous population of mesenchymal origin, variously referred to as *mesenchymal stromal cells* (MSC) or *cancer-associated fibroblasts* (CAF) (Raffaghello and Dazzi 2015). Regardless of their developmental heterogeneity, they all play a similar role by protecting the malignant cells from cytotoxic agents and immune responses. In the bone marrow, MSC protect CML and AML cells from imatinib and Ara-C via the CXCR4-CXCL12 axis (Vianello et al. 2010).

Much information has been provided about the *IS activity of MSC* that is exerted in a non-antigen-specific fashion (Jones et al. 2007). One of the primary direct mechanisms responsible for this involves the expression of indoleamine 2-3 dioxygenase-1 (IDO-1), which consumes the essential amino acid tryptophan. Additional IS mechanisms include the release of suppressive factors such as TGF-β1, hepatocyte growth factor, PGE2, soluble human leukocyte antigen G, and TNF-α stimulated gene 6 protein (TSG-6). However, more recent data have highlighted the important contribution of tissue-resident monocytes/macrophages in delivering a more sustainable IS effect (Cheung and Dazzi 2018).

Finally, the role of *Tregs* in generating immune resistance has been much discussed. While there is plenty of data indicating how these cells exert a very negative impact on the outcome of solid tumors, data in preclinical models of allogeneic HSCT have suggested that Tregs may selectively inhibit GvHD without compromising GvL (Edinger et al. 2003). In contrast, clinical data suggest to consider Treg levels post transplant with caution (Nadal et al. 2007).

> **Key Points**
> - Leukemia can counteract the beneficial graft-versus-leukemia effects post transplant.
> - This is effected either by changes in the tumor cells which make them evade immune recognition or by instructing different components of the microenvironment to deliver in situ immunosuppression.

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