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Harnessing the immune system in acute myeloid leukaemia

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ABSTRACT

Acute myeloid leukaemia (AML) is an aggressive blood cancer caused by the proliferation of immature myeloid cells. The genetic abnormalities underlying AML affect signal transduction pathways, transcription factors and epigenetic modifiers. In solid tumours, it is emerging that the genetic landscape of the

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tumour has a direct effect on the anti-tumour immune responses and response to immunotherapeutic treatment. However, there remains little information as to whether genetic abnormalities affect anti-leukemic immune responses. This review discusses current knowledge of AML antigens and immune responses to AML with a particular focus on the role of T cells and natural killer cells. Understanding immune responses to AML has implications for the development and use of immunotherapies to treat AML patients with distinct genetic abnormalities.

1. Introduction

The recent success of immune checkpoint inhibitors such as ipilimumab, anti-CTLA-4 and nivolumab and pembrolizumab, anti-PD-1, in improving survival of metastatic melanoma patients highlights that the immune system can be successfully harnessed to target and eliminate cancer cells more broadly for clinical benefit (Robert et al., 2015, 2014; Hamid et al., 2013; Hodi et al., 2010). An emerging paradigm for understanding cancer immunosurveillance and patient responses to immunotherapies is that genetic mutational quality directly correlates with tumour cell's immunogenicity and is thus fundamental to driving patients' clinical outcomes. Much of the evidence to support this paradigm has been generated from solid tumour patients such as melanoma, however less is known about the correlation of mutational quality and immune responses in haematological malignancies. This review will focus on acute myeloid leukaemia (AML) and discuss evidence for heterogeneous genetic abnormalities driving endogenous differential anti-leukemic immune responses. In particular, novel immunotherapeutic strategies will be discussed for treatment of AML patients.

The ability of the innate and adaptive immune cells to attack the tumour before it becomes clinically detectable is known as cancer immunosurveillance (Smyth et al., 2006; Swann and Smyth, 2007). However, cancers are able to avoid the immune response by a variety of mechanisms. Recently, "evasion of immune destruction" has been included as one of the emerging hallmarks of cancer (Hanahan and Weinberg, 2011). Thus, the important role of the immune response in cancer control and progression warrants a brief summary of the current theories. The term "cancer immunoediting" was coined to describe the phases of the immune response to cancer (Smyth et al., 2006; Schreiber et al., 2011; Dunn et al., 2004; Mittal et al., 2014). The elimination phase describes the initial recognition, targeting and killing of cancer by the innate and adaptive immune cells. The immune system and tumour cells may then enter an equilibrium phase where the immune system prevents the tumour from expanding. This phase is one of genetic instability in the tumour that eventually leads to the sculpting and escape of less immunogenic tumour cells from the immune system. The tumour cells facilitate escape either through employing mechanisms to suppress the immune response or by down-regulating (editing) immunogenic molecules. The next sections will discuss the evidence for the critical role of genetic mutations in cancer immunosurveillance.

2. Connecting oncogenesis and cancer immunosurveillance

The core feature of cancer cells that separates them from normal cells is the underlying genetic mutations that drive cancer progression (Vogelstein et al., 2013). Recently, a study identified 20 mutational signatures in 30 different types of cancer and found a varying prevalence of somatic mutations (Alexandrov et al., 2013). These mutational signatures may influence the ability of the immune system to recognise and attack the cancer. Proteins derived from mutated genes are known as neo-antigens. Interestingly, AML was found to have one of the lowest mutational burdens (somatic mutations per megabase of DNA) implicating AML cells as having low immunogenicity, study found an average of only 13 mutations in genes of de novo AML patients (The Cancer Genome Atlas Research Network, 2013). However, as will be discussed, the mutational quality rather than the mutational burden may be more important. A number of studies have used sequencing data from solid tumours to investigate the relationship between genetic mutations and endogenous immune responses and have found correlations between certain genetic signatures and clinical outcomes (Cescon et al., 2015; Rutledge et al., 2013; Rooney et al., 2015; Brown et al., 2014).

It is necessary for neo-antigen peptides to bind to major histocompatibility complex (MHC) Class I and be presented at the tumour cell surface in order to be immunogenic. In addition, the peptides have to be recognised as non-self by T cells through binding T cell receptors (TCRs). This is reflected in the finding that patients with mutations predicted to bind antigen presentation machinery, MHC Class I have higher CD8+ tumour infiltrating lymphocytes and elevated expression of immune checkpoint markers, CTLA-4 and PD-1, indicating an elevated immune response and possible survival advantage (Brown et al., 2014). Furthermore, investigation of the relationship between cytolytic activity and specific cancer mutations links higher cytolytic activity to neo-antigen expression and also suggests that cytolytic activity results in immunoediting of tumours cells with higher neo-antigen expression (Rooney et al., 2015). It follows that patients who exhibit high cytolytic activity and have immunogenic neo-antigens may benefit more from treatment with immunotherapies.

The importance of a patient's neo-antigen signature has been demonstrated by differential responses of melanoma patients to treatment with ipilimumab. A recent study showed that patients who responded to ipilimumab treatment had a specific neo-antigen signature derived from mutant proteins predicted to bind MHC Class I (Snyder et al., 2014). There has been less focus on neo-antigen burden in blood cancers compared to solid tumours, however, a study investigating the neo-antigen burden of 13 different cancer types by combining massive parallel sequencing and HLA-binding prediction algorithms showed that chronic lymphocytic leukaemia and AML had the lowest burden of neo-antigens generated from missense and frameshift mutations (Rajasagi et al., 2014). These data implicate leukaemias as potentially having low immunogenicity and thus difficult for antigen specific cytotoxic immune cells such as T cells to recognise.

Nevertheless, successful treatment of patients with haematological malignancies by allogeneic haematopoietic stem cell transplantation (allo-HSCT) shows that blood cancer cells can be eradicated by the immune system. Allo-HSCT was the most potent immunotherapeutic treatment available for decades. The anti-leukemic response in allo-HSCT transplant patients is mediated by a graft-versus-leukaemia (GVL) effect in which donor T cells and NK cells are able to eliminate cancer cells. The mechanisms of GVL effect have been extensively reviewed elsewhere (Bleakley and Riddell, 2004; Kolb, 2008; Robb et al., 2011). While allo-HSCT