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Review article

Epigenetics and immunotherapy: The current state of play

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ABSTRACT

Cancer cells employ a number of mechanisms to escape immunosurveillance and facilitate tumour progression. The recent explosion of interest in immunotherapy, especially immune checkpoint blockade, is a result of discoveries about the fundamental ligand-receptor interactions that occur between immune and cancer cells within the tumour microenvironment. Distinct ligands expressed by cancer cells engage with cell surface receptors on immune cells, triggering inhibitory pathways (such as PD-1/PD-L1) that render immune cells immunologically tolerant. Importantly, recent studies on the role of epigenetics in immune evasion have exposed a key role for epigenetic modulators in augmenting the tumour microenvironment and restoring immune recognition and immunogenicity. Epigenetic drugs such as DNA methyltransferase and histone deacetylase inhibitors can reverse immune suppression via several mechanisms such as enhancing expression of tumour-associated antigens, components of the antigen processing and presenting machinery pathways, immune checkpoint inhibitors, chemokines, and other immune-related genes. These discoveries have established a highly promising basis for studies using combined epigenetic and immunotherapeutic agents as anti-cancer therapies. In this review, we discuss the exciting role of epigenetic immunomodulation in tumour immune escape, emphasising its significance in priming and sensitising the host immune system to immunotherapies through mechanisms such as the activation of the viral defence pathway. With this background in mind, we highlight the promise of combined epigenetic therapy and immunotherapy, focusing on immune checkpoint blockade, to improve outcomes for patients with many different cancer types.

1. Introduction

The recent clinical success of immunotherapy in cancer patients, particularly immune checkpoint blockade, is at least in part due to elegant studies that have led to fundamental discoveries about ligand-receptor interactions between immune and cancer cells within the tumour microenvironment (TME). Distinct ligands expressed by cancer cells engage with cell surface receptors on immune cells, triggering inhibitory pathways that render immune cells immunologically inert or "tolerant". For example, binding of the key T cell surface receptor programmed cell death 1 (PD-1) to the co-inhibitory receptors programmed death ligand 1 (PD-L1) or programmed death ligand 2 (PD-L2) on cancer cells inhibits T cell proliferation, cytokine production, and ultimately results in T cell dysfunction or apoptosis (Dong et al., 2002; Sheppard et al., 2004; Parry et al., 2005). Under normal conditions, these immune checkpoints temper or fine-tune the host immune response to pathogens. However, in the context of cancer, immune checkpoints can be dysregulated or hijacked as a mechanism of immune resistance.

An improved understanding of these molecular mechanisms underlying immune regulation has resurrected the concept of targeting cancer immunologically (Pardoll, 2012; Dolan and Gupta, 2014). Consequently, immunotherapeutic strategies designed to re-activate anti-tumour immune responses and reverse the immunologically tolerant state are now at the forefront of anti-cancer therapy. Similarly, recent elucidation of the role of epigenetics in immune evasion has

Abbreviations: TME, tumour microenvironment; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; PTMs, post-translational histone modifications; DNMTi, DNA methyltransferase inhibitor; HDACi, histone deacetylase inhibitor; TAA, tumour-associated antigens; APM, antigen processing and presentation machinery; NK, natural killer; NKG2D, NK group 2D; MICA/B, MHC class I-related chain A/B; ULBPs, ULB16-binding proteins; TRAIL, TNF-related-apoptosis inducing ligand; FASL, FAS ligand; DC, dendritic cell; APC, antigen presenting cells; TFH, T follicular helper; Treg, regulatory T cell; CTL, cytotoxic T lymphocyte; TCR, T cell receptor; HLA, human leukocyte antigen; TAP, transporter associated with antigen presenting; ICAM-1, intercellular adhesion molecule 1; TILs, tumour-infiltrating lymphocytes; CTLA-4, cytotoxic T lymphocyte antigen 4; TNBC, :triple-negative breast cancer; NSCLC, non-small cell lung cancer; AML, acute myeloid leukaemia; CCL, chronic lymphatic leukaemia; mAb, monoclonal antibody; FDA, Food and Drug administration; Ig, immunoglobin; PI3K, phosphoinositide 3-kinase; MDSC, myeloid-derived suppressor cell; CAF, cancer-associated fibroblast; CSC, cancer stem cell; HGF, hepatocyte grown factor; CTAs, cancer testis antigens; HMW-MAA, high molecular weight melanoma-associated protein; Th1, T helper 1; EZH2, enhancer of zeste homologue 2; H3K27, me3: histone 3 lysing 27 trimethylation; DNMT1, DNA methyltransferase 1; ERVs, endogenous retroviral sequences; 5-AZA-dC, 5-aza-2′-deoxycytidine

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uncovered a role for epigenetic drugs in modulating immune pathways to restore and/or improve immune recognition and immunogenicity. In this way, epigenetic targeting may 'prime' the host immune response for subsequent immunotherapy (Sigalotti et al., 2014; Heninger et al., 2015; Terranova-Barberio et al., 2016). Several studies have demonstrated the efficacy this combined strategy in both clinical studies (Bao et al., 2011; Ishibashi et al., 2016; Krishnadas et al., 2015; Xu et al., 2016) and animal models (Mikyskova et al., 2014; Terracina et al., 2016; Lucarini et al., 2017; Covre et al., 2015; Tellez et al., 2014). Furthermore, immune priming using different epigenetics agents has been observed in combinations with several immunotherapy types such as adoptive cellular immunotherapy (Ishibashi et al., 2016; Terracina et al., 2016), cytokine-based therapy (Lucarini et al., 2017; Gollob and Sciambi, 2007), vaccines (Krishnadas et al., 2015), and immune checkpoint inhibitors (Jazirehi et al., 2014; Yao et al., 2013). Together, these discoveries establish a highly promising basis for combination studies using epigenetic and immunotherapeutic agents in cancer patients.

Even though the concept of partnering epigenetic therapy with immune re-activating strategies such as immune checkpoint therapy is recent, a wave of translational research highlights the potential for this approach in many different cancer types (Terranova-Barberio et al., 2016; Maio et al., 2015; Weintraub, 2016; Chiappinelli et al., 2016a). Furthermore, a number of on-going clinical trials are currently exploring the efficacy of this combined approach (Table 1). This review summarises our current understanding of the key mechanisms of immune evasion in cancer and emphasises the significance of epigenetic immunomodulation of these components in priming the host immune system to immunotherapies. In addition, we highlight the promise of combination epigenetic and immunotherapy regimens, particularly immune checkpoint blockade, for improving outcomes in patients with cancer.

2. Epigenetic therapy

Epigenetic dysregulation is a central mechanism in cancer development and progression (Jones and Baylin, 2002; Esteller, 2008). Epigenetic regulation is defined as heritable modifications to DNA that alter gene expression and chromatin structure without changes to the underlying nucleotide sequence (Esteller, 2008; Jones and Takai, 2001). These epigenetic changes (or marks) include DNA methylation and post-translational histone modifications (PTMs) (Jones and Takai, 2001; Kouzarides, 2007). Epigenetic marks are interdependent, switching genes 'on' and 'off' in response to extracellular signals. With regard to transcriptional regulation, chromatin predominantly exists in two interchangeable states: closed (heterchromatin) or open (euchromatin), which are regulated by a balance between distinct active and repressive epigenetic marks (Fig. 1). Establishing a repressive chromatin structure can preclude access and/or function of transcriptional activators such as RNA polymerases and DNA-binding transcription factors to target genes, and this state is generally associated with transcriptional silencing. In contrast, an open chromatin state is accessible to transcriptional machinery and facilitates active transcription (Li et al., 2007).

Chromatin remodelling regulates a gene's transcriptional state via a number of mechanisms: (1) post-translational modifications of histone proteins; (2) DNA methylation; (3) ATP-dependent chromatin remodelling complexes; (4) histone variant exchange; and (5) the action of non-coding RNAs (such as miRNAs). The most abundant histone modifications are acetylation, methylation, phosphorylation, and ubiquitylation; however, many other modifications have been reported (Kouzarides, 2007). In this way, epigenetic modifications to DNA and histone proteins dynamically shape the chromatin landscape to regulate gene transcription.

Several epigenetic marks have been identified in association with specific chromatin states and transcription levels. DNA methylation predominately occurs at cytosine residues in CpG dinucleotides that are enriched in regions known as CpG islands and is associated with the closed heterochromatin state and transcriptional repression/silencing. Epigenetic modifications to the amino-terminal tails of histone proteins have also been shown to regulate chromatin state and transcription. Histone acetylation of lysine residues (e.g., acetylation of H3K9, H3K14, H4K5, and H4K16) is predominately associated with open chromatin states and active gene transcription. In contrast, histone methylation is more complex and results in different chromatin and transcription states depending on the extent of methylation (e.g., mono-, di-, or tri-methylation). For example, monomethylation of H3K9, H3K27, and H3K79 histone proteins is associated with euchromatin (active transcription), whereas trimethylation of these histones results in a heterochromatin conformation and transcriptional repression.

In addition to the local chromatin state, the 3D nuclear architecture also contributes to transcriptional regulation (Espada and Esteller, 2007; Fedorova and Zink, 2008; Bartova et al., 2008; Schneider and Grosschedl, 2007). Chromatin is spatially organised into higher-order structures that ultimately exhibit a non-random 3D organisation within cell nuclei. The nucleus is an extremely dynamic structure in which many components rapidly and transiently interact, and these dynamic interactions have functional consequences for regulation of gene expression. For example, chromatin domains containing transcriptionally active genes can form chromatin loops that extend away from compact chromosome territories to reposition near transcriptional factories at the center of the nucleus. However, perinuclear repositioning has also been shown to establish transcriptionally silent chromatin. The organisation of the nuclear architecture is thought to mediate gene transcription by controlling accessibility of regulatory DNA elements to transcription factors and RNA polymerases through subnuclear gene positioning and intra-/inter-chromosomal interactions. The impact of nuclear architecture and gene activity is closely related to epigenetic modifications (such as DNA methylation and histone modifications) of individual chromatin domains. For example, it is well established that changes in nuclear organisation are associated with DNA methylation patterns during mammalian pre-implantation development (Bartova et al., 2008; Schneider and Grosschedl, 2007). Furthermore, several inhibitors of histone deacetylase activity have been shown to induce reorganisation of chromatin and histone modifications (Taddei et al., 2001; Bartova et al., 2005). Moreover, chromosome instability and disrupted nuclear morphology is commonly associated with DNA hypomethylation of discrete nuclear regions in cancer cells (Bartova et al., 2008). However, the precise interplay between epigenetic modifications and nuclear architecture remains unclear. In this way, the nuclear architecture is able to contribute, in part, to regulation of gene expression.

Due to the dynamic and reversible nature of epigenetic marks, these alterations represent attractive and therapeutically relevant targets in many diseases including cancer. Current epigenetic therapies are primarily directed towards two functional categories of epigenetic regulators: those that target the "writers", enzymes that establish epigenetic marks, and those that target the "erasers", enzymes that remove epigenetic marks. Specifically, DNA methyltransferase inhibitors (DNMTi; writers) and histone deacetylase inhibitors (HDACis; erasers) are the main epigenetic therapy drug classes. DNMT and HDAC inhibitors exhibit anti-tumour functions by inducing differentiation, apoptosis, growth inhibition, cell cycle arrest, and cell death. DNMTis reactivate gene transcription by inhibiting the action of DNA methyltransferases (which add methyl groups to DNA) by directly incorporating into the DNA and trapping DNMTs for proteosomal degradation. The loss of DNMT is DNA replication dependent, and results in passive hypomethylation of DNA in daughter cells after cell division. Similarly, HDACis block the action of HDACs, which remove acetyl marks from tagged histones to increase global histone acetylation. These inhibitors might also work, at least in part, to re-activate