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Review

Local tumour ablative therapies: Opportunities for maximising immune engagement and activation

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ABSTRACT

The relationship between cancer and the immune system is a complex one. The immune system can prevent tumour growth by eliminating cancer cells but this editing process ultimately results in poorly immunogenic cells remaining allowing for unchallenged tumour growth. In light of this, the focus of cancer treatment should be to maximise cancer elimination and the prevention of escape mechanisms. In this review we will examine current and emerging ablative treatment modalities that induce Immunogenic Cell Death (ICD), a special type of cell death that allows for immune cell involvement and the generation of an anti-tumour specific immune response. When paired with immune modulating agents, capable of potentiating the immune response and reversing the immune-suppressive environment created by tumours, we may be looking at the future of anti-cancer therapy.

Contents

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1. Introduction

Cancer can be defined as the rapid and uncontrolled growth of malignant cells in the body and even with recent advances in the areas of detection and treatment, there were 8.2 million cancer related deaths worldwide in 2012 [1]. With an estimated 14.1 million new cases of cancer in 2012 and projections predicting a substantial increase to 19.3 million cases per year by 2025 [1], the need for more effective treatments has never been higher. With this is mind there has been renewed interest in the immune system, its relationship with cancer and the ability to harness its potential for fighting the disease.

The main function of the immune system is to protect us against invading pathogens; it detects these pathogens via a set of pattern recognition receptors (PRRs) that bind pathogen-associated molecular patterns (PAMPs) [2]. PAMPs include viral RNA, the components of bacterial cell walls and, when detected trigger the activation of the innate immune system to protect the host [3]. However not all threats come in the form of invading bacterial/viral organisms and so the immune system has developed the ability to identify and eliminate cancerous/transformed cells. Two landmark murine studies demonstrated the importance of a functional immune system in preventing carcinogenesis; mice lacking IFN-γ responsiveness or specific immune cells (T cells, B cells and NK cells) were more susceptible to chemically induced tumour formation [4,5]. Lung and kidney transplant patients are put on immunosuppressive drugs (cyclosporine A, corticosteroids, azathioprine, etc.) to prevent against transplant rejection, and the fact that these patients have been shown to have a higher chance of developing neoplastic malignancies, reinforces the protective importance of the immune system [6–11]. Human immunodeficiency virus (HIV) and the subsequent acquired immunodeficiency syndrome (AIDs) result in depletion of $CD4^+$ T cells and leave patients severely immunocompromised [12]. It is no coincidence that HIV/AIDs sufferers have increased incidences of cancer [13–15] and in fact several cancers (Kaposi's sarcomas, cervical cancer and non-Hodgkin's lymphoma) are now commonly deemed AIDs defining malignancies [16–18]. Subsequent work in the field has shown that 'immuno-surveillance' is only one aspect of the complex relationship between the immune system and cancer [19] and has led to formation of the 'cancer immuno-editing' hypothesis.

2. Cancer immuno-editing

Cancer immuno-editing is a refinement on the original 'immuno-surveillance' idea and suggests that the immune system not only protects the host against cancer, but also shapes tumour immunogenicity (the ability for the tumour to provoke an immune response). Murine studies have shown that tumours that develop in immune-competent mice (deemed 'edited' tumours) often grow more easily than tumours that originate from immunocompromised mice ('unedited'), when transplanted into syngeneic immune-competent mice [5]. Therefore the immune system not only protects the host against tumour formation but also applies selection pressure favouring the development of less immunogenic tumours, which escape recognition by a functioning immune system. Immuno-editing is deemed to have 3 phases, each of which we will examine further.

2.1. Elimination

The innate immune system acts as our body's first line of defence and its main components are dendritic cells (DCs), macrophages and monocytes, neutrophils, natural killer (NK) cells, and natural killer T (NKT) cells. NK cells are important in the early stages of cancer elimination; they have the ability to recognize stress induced ligands such as NKG2D-L, through their NKG2D receptors. The NKG2D ligands can be induced on tumour cells through DNA damage [20] and other stimuli, alerting NK cells to unwanted transformation [21]. NK cells' ability to eliminate tumour cells is dependent on the expression of tumour cell p53, a consequence of the cellular DNA damage response [22], which leads to the secretion of various interleukins and cytokines that recruit NK cells to the tumour site [23]. Tumours lacking p53 expression can evade NK mediated clearance but when p53 activity is restored, the tumour cells are gradually cleared by NK cells and other infiltrating cells [24]. Upon activation, NK cells secrete interferon-γ (IFN-γ), a type II cytokine critical to the initial immune response. IFN-γ up-regulates production of the cytolytic protein perforin [25] as well as the apoptotic inducing Fas ligand [26] and TNF-related apoptosis-inducing ligand (TRAIL) [27]. IFN-γ has also been shown to protect against the growth of transplanted tumours [28], to activate dendritic cells and promote the generation of tumour-specific $CD4^+$ T and $CD8^+$ T cells [29], and to augment major histocompatibility complex (MHC) expression on tumour cells [30]. These functions are crucial in improving tumour immunogenicity and potentiating the activity of both the innate and adaptive immune responses. Type I interferons (IFN-α/β) have an important role in the immune-editing process; in fact IFN-α is the most used cytokine in patients, used to treat a wide range of cancerous malignancies [31]. IFN-α/β can up-regulate the p53 mediated response of tumour cells to DNA damage [32] but it seems that their major contribution to anti-cancer immunity is their actions on haematopoietic cells. Type I IFNs are important for the in vivo proliferation and long-term survival of anti-TAA (tumour specific antigens) specific CD8 + T cells [33] and they also enhance the expression of anti-apoptotic genes in human T cells [34]. Dendritic cells (DCs) are often regarded as the most effective of the antigen presenting cells (APCs) and type I IFNs have important effects on DC differentiation and maturation [35,36]. As such type I IFNs are often thought of as an important link between the innate and adaptive arms of the immune system.

Adaptive immunity consists of T and B lymphocytes and their respective mediators (cytokines and antibodies) and its ability to generate an immune 'memory'. It is the interplay and communication between both arms of the immune system that make it effective against cancer functional cytotoxic CD8 + (CTL) and helper CD4 + T (T_H1) cells are critical for the eradication of cancerous cells. The T cell receptor (TCR) of cytotoxic CD8 + T cells is capable of binding with the MHC-1 molecule of harmful/cancerous cells or antigen presenting cells (APC) and causes subsequent cellular lysis through the release of perforin, granzymes and granulysin. Once activated, the CD8 + T cells undergo rapid clonal expansion, aided by the MHC-II/TCR mediated secretion of IL-2 from the CD4 + T helper cells, which is a potent growth and differentiating factor. Higher numbers of total circulating and tumour infiltrating CD8 + and CD4 + T cells are associated with improved prognosis/survival in patients with various cancer types [37–39]. T