Immuno-oncology of Dormant Tumours

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Abstract Cancer is a complex, often aggressive disease. As such, cancer treatment requires a diverse approach that often includes surgery, chemotherapy, radiotherapy, targeted therapy, or immunotherapy. Despite the potency of these treatments, cancer cells adapt to escape killing and survive either in their original microenvironmental niche, or as disseminated cancer cells in distant organs. Depending on tumour type and treatment modality, tumours display a variety of growth patterns, from rapid proliferation and invasion to a more controlled dormant phenotype. This dormant phenotype is characterized clinically as the asymptomatic period post therapy before relapse, and biologically by an enrichment in cancer cells that are not dividing but survive in a quiescent state, arrested in G0-G1 phase of cell cycle. Dormancy is a tumour intrinsic characteristic that corresponds to the equilibrium phase of the immune-editing hypothesis, in which tumour cells neither proliferate nor are eliminated by the immune response. In this chapter we provide an overview of anti-tumour immunity and ways in which the immune response may shape tumour dormancy.

Keywords Cancer immunoediting • Immunosurveillance • Immunotherapy • Microenvironment • Cancer-immune system interactions • Immune evasion • Tumour dormancy • Therapy induced dormancy • Immune checkpoint • Checkpoint blockade

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Anti-cancer Immunity: An Overview

The immune system is an intricate and organized system of cells and organs that functions to protect the body from pathogens. Healthy immunity is achieved when cells of both the innate and adaptive arms of the immune system are able to prevent disease while avoiding destruction of host tissue, or auto-immunity. This "tolerance" of self is essential in a properly functioning immune system, yet it also poses a significant challenge to mounting an immune response against cancer, which arises from self-tissues.

Despite sharing many characteristics of normal tissue, tumour cells do express and produce antigens that are recognized as foreign by the immune response. In the 1950s, Burnet and Thomas were the first to propose that the immune system is able to detect and prevent the growth of tumours; this was the cancer immunosurveillance hypothesis [1]. It took almost 50 years and the development of highly sophisticated transgenic mouse models, where select components of the immune response could be manipulated, to prove that both innate and adaptive immunity are essential to prevent a variety of tumour types. In the early 2000s, the cancer immunosurveillance hypothesis was refined and concept of cancer immunoediting emerged. This process includes three distinct phases; i) elimination, in which cancer cells are recognized and destroyed by immune cells, ii) equilibrium, in which cancer cells survive and may be recognized by the immune response but are not eliminated by them, and iii) escape, in which the immune response is no longer able to prevent cancer cell proliferation or metastasis [2], (also depicted in Fig. 1). In the equilibrium phase, a tumour microenvironment (TME) consisting of tumour cells, immune and non-immune stromal cells, and their secreted products, is established that plays a large role in dictating whether tumours will eventually escape the immune response.

Many components of the immune system contribute to an effective anti-cancer immune response, however $CD8^+$ cytotoxic T cells have emerged as a major driver of tumour rejection, through the direct killing of tumour cells. Induction of an effective $CD8^+$ T cell response is a multistep process that requires coordinated interactions between numerous cell types [3, 4]. This process begins with the expression of tumour antigens that can be taken up by antigen presenting cells (APC) such as dendritic cells (DCs) and presented in the context of major histocompatibility complex (MHC). These APCs then migrate to draining lymph nodes and present the antigen to a T cell that expresses a T cell receptor (TCR) specific for that antigen-MHC complex. Effective T cell priming and activation depends on the presentation of antigen with concomitant co-stimulatory and cytokine signals, and leads to the proliferation and clonal expansion of tumour-antigen specific effector T cells. Activated T cells then travel via the bloodstream and infiltrate vascularized tumours where they recognize and kill tumour cells.

Each of these steps is carefully controlled by multiple mechanisms of immune-regulation [1, 2, 5–9], many of which may be co-opted by tumours enabling immune escape. Escape from equilibrium depends on both tumour intrinsic mechanisms of immune evasion and mechanisms of immunological tolerance [10, 11]. For example, tumours secrete multiple factors that have pleiotropic suppressive effects on

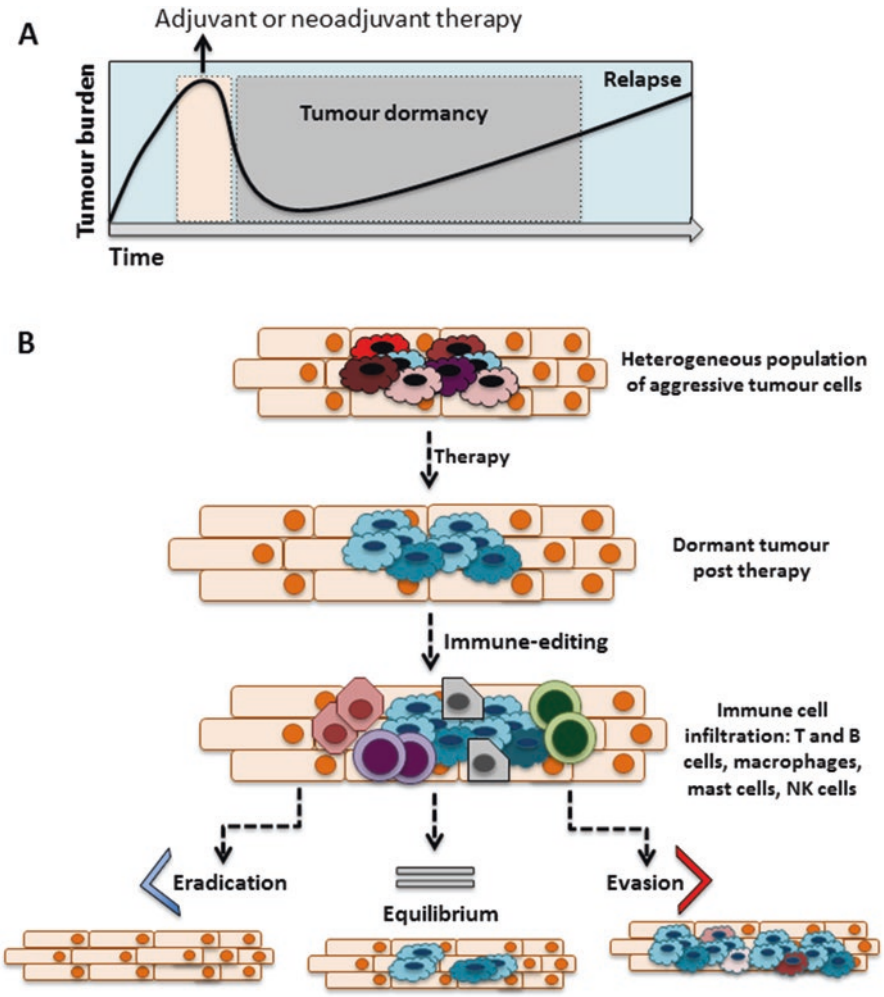

Fig. 1 (**a**) Tumour burden and volume decreases following adjuvant or neoadjuvant therapy prior to tumour recurrence, a period signified as tumour dormancy. (**b**) Cancer stem cell like interactions with immune system. The three stages of cancer immunoediting involved in growth of clinical tumours describe the intricate relationship between a tumour mass and its infiltrating immune cells. The three phases of editing consist of eradication, equilibrium, and escape. Eradication: Highly immunogenic tumour cells are eradicated by an armamentaria of immune cells. Equilibrium: Moderately immunogenic tumour cells are partially eradicated by immune cells and some remain dormant. Evasion: Poorly immunogenic tumour cells evade immunosurveillance and invade their microenvironment

immune cells in the TME. While cytokines and growth factors like IL-1β, GM-CSF, and VEGF have been implicated in driving the expansion of myeloid derived suppressor cells (MDSCs) within the TME that promote tumour growth [12], others like TGF-β [13] and IDO [14] secreted by DCs play important roles in the conversion

of effector $CD4^+$ T cells towards a T regulatory (Treg) cell phenotype. The accumulation of MDSCs and Treg cells within the TME is a poor prognostic indicator across multiple cancer types [15–18].

Tumour intrinsic mechanisms of immune escape also include the expression of surface molecules that interact directly with infiltrating immune cells, thereby preventing their activation or anti-tumour effector functions. The most well studied are Ig family molecules such as programmed death ligand-1 (PD-L1), which acts as an inhibitory signal when bound to its receptor, programmed cell death 1 (PD-1), expressed on activated T cells, natural killer (NK) cells, B cells and some myeloid subsets. Overall, immune escape occurs as a result of induction of potent immunosuppressive mechanisms, or through immune editing, in which the immune system kills immunogenic tumour clones effectively selecting for cancer cells that are non-immunogenic and fall "under the radar" of immune surveillance.

The clinical significance of the tumour immunosurveillance is highlighted by the increased incidence of cancer in patients undergoing immunosuppressive therapy [19, 20]. Furthermore, the effective use of immunotherapies targeting inhibitory receptors, so called checkpoint molecules, that limit T cell effector activity, have now re-established the capacity of the immune system to effectively eradicate tumours. The use of checkpoint inhibitors has led to dramatic and long-lasting clinical responses in a subset of patients with a variety of cancers, including metastatic melanoma and bladder cancer [21]. Indeed, anti-cytotoxic T lymphocyte associated protein 4 (CTLA-4) monoclonal antibodies (mAb) (ipilimumab), and anti-PD-1 mAb (pembrolizumab and nivolumab) have been approved by the FDA for use in metastatic melanoma, while the anti-PD-L1 mAb (atezolizumab) has been approved for use in metastatic bladder cancer, and numerous clinical trials are currently ongoing [11, 21]. This, together with numerous studies identifying positive associations between tumour immune infiltrates with better prognosis, highlight the importance of the immune system in regulating cancer progression [22, 23].

Dormant Tumour-Immune System Interactions

Tumour dormancy can exist as either a state in which rates of cell proliferation match those of cell death, or when tumour cells themselves are in a state of quiescence [10]. Dormant tumour cells are by default in a state of equilibrium with the immune response. In the context of the immune-editing hypothesis, tumour cells exiting dormancy will therefore be either eliminated by, or escape anti-tumour immunity. The length of the dormancy equilibrium period, signified with minimal residual diseased-state, depends on the patient and cancer type [24, 25]. Prostate [26], breast [27], melanoma [28], and non-hodgkin's lymphoma [29] patients show relatively longer disease free periods post therapy prior to recurrence compared to higher mortality cancers of pancreas [30], brain [31], lung [32] and esophagus [33]. Importantly, although dormant tumours are in equilibrium with immune responses and tumour cells exiting dormancy must evade or trigger immune responses, the variability in dormancy periods across cancers cannot be explained by one

"immune-phenotype". Indeed, how dormant tumour cells specifically interact with immune cells at this stage remains unclear.

The value of immunity directed against cancer stem cells (CSCs) however, is an area of rapidly expanding research that may provide insight as to how dormant cells, which share many features of CSCs in terms of their microenvironmental niche and survival mechanisms [34, 35], induce or prevent immune responses. CSCs across multiple tumour types alter cell surface molecules known to inhibit both innate and adaptive anti-tumour immunity, including the anti-phagocytosis receptor CD47 [36], MHC I [37], MHC II [38], and PD-L1 [39–42]. In certain CSC types, tumour neoantigens are also expressed at lower levels compared to non-CSCs, and induce expansion of Treg cells [43]. CSCs in renal cell carcinoma have also been shown to prevent the differentiation of mature DCs [44].

Despite these immune evasion strategies, CSCs express multiple tumour associated antigens, which have been exploited as efficacious vaccine strategies in models of ovarian [45], metastatic melanoma [46, 47] and pancreatic [48] cancers. The latter study was recently expanded to a phase I clinical trial (NCI-2010-01868 and NCI-2013-02238) exploring safety and tolerability for a pancreatic cancer CSC vaccine [49]. These studies show selective depletion of CSCs in tumours after pulsing DCs with CSC-derived material, indicating that a specific T cell response can be generated against CSCs in vivo and is efficacious in reducing tumour burden. In addition to cytotoxic T cells, NK cells have also been shown to have preferential killing ability towards CSCs, which upregulate the NK cell recognition ligands MICA/B as well as the death receptors FAS and DR5 [50].

Immunotherapy for Dormant Tumours

While it remains unclear whether dormant tumour cells may share similar immune-modulatory properties as CSCs, if they do, these reports suggest that common immunotherapeutic strategies may target dormant tumour cells [51–53]. Certainly, reports of high expression of PD-L1 on CSCs [54] suggests that these cells could be targets of monoclonal antibody immunotherapies directed against the PD-1/PD-L1 checkpoint pathway, such as nivolumab, pembrolizumab and atezolizumab [55–57]. Across many solid tumour types, defining checkpoint molecule expression and immune cells in the tumour and circulation predict response to immunotherapy and/or correlate with prognosis. Multiple studies have shown greater objective responses to immunotherapies where targets, such as PD-L1, are present on tumour [58–62] cells. However, this is not an absolute requirement for response, and mounting evidence indicates the importance of tumour infiltrating lymphocytes (TIL) and circulating immune cell correlates in disease progression. For example, expression of PD-L1/PD-1 by circulating innate immune and T cells is a prognostic indicator for glioblastoma, pancreatic, hepatocellular and lung cancer [5, 6, 8, 9] as well as responses to checkpoint blockade with Ipilimumab [7]. Furthermore, in a study that looked at seven different tumour types, PD-L1$^+$ TILs were strongly associated with response to anti-PD-L1 therapy [63]. Importantly however, these studies have all

been conducted using sections from primary, or relapsed metastatic tumours, which cannot be defined as dormant tumours. It thus remains highly unclear whether in a dormant setting, the presence of checkpoint molecules on tumour or immune cells are similarly prognostic.

By definition, dormant tumour cells are in equilibrium with the immune response; therefore a rationally designed immunotherapeutic strategy against dormant tumours must either initiate their exit from dormancy or specifically target the unique elements of dormant tumours. Classical interventions like chemotherapy or radiation may provide the initial trigger causing tumour cells to exit the dormant phase, after which an immune response can be mounted. For example, dendritic cells increase tumour antigen presentation at low chemotherapeutic doses [64] and the abscopal effect that is observed after radiotherapy to localized tumours has been attributed to immune-mediated clearance of distant metastases [65, 66]. Chemotherapy can also have direct effects on immune cells; immunogenic drugs, such as oxaliplatin combined with cyclophosphamide, increase sensitivity of tumours to checkpoint blockade therapy [67]. Similarly, epigenetic targeting therapies are associated with upregulation of immune checkpoints. In leukemia [68, 69] and NSCLC [70], treatment with the DNA hypomethylating agent Azacitidine increases PD-1 or PD-L1 promoter demethylation and their expression. Importantly, the exit from dormancy initiated by chemo or radiotherapy is most likely associated with the release of neoantigens and other damage-associated molecules from the tumour that trigger immune responses [71]. The importance of increasing immunogenicity of tumours is underscored by the widespread efforts to design anti-cancer vaccines [72–74]. These may be especially relevant in the context of more dormant tumours such as Prostate, for which the first and only cancer vaccine has been approved [75, 76].

Thus, combining immunotherapies with therapies such as chemotherapies, radiation or epigenetic therapies, that alter the neo-antigen repertoire or checkpoint expression pattern of dormant tumour cells, is a potentially promising treatment strategy.

Ultimately, anticancer immunity is a prerequisite for the successful outcome of conventional cancer therapies [65, 66, 77–79]. While the immune response against tumour associated antigens can be elicited by either the innate or adaptive immune systems [78, 80], the goal of active immunotherapy is to achieve anti-tumour immunity. Therefore, apart from designing comprehensive studies related to phenotyping and genotyping of dormant tumours, it is important to consider therapies or combinatorial therapies that are designed for the specific dormant cancer phenotype.

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