Turning up the heat on non-immunoreactive tumours: opportunities for clinical development

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Notable advances have been achieved in the treatment of cancer since the advent of immunotherapy, and immune checkpoint inhibitors have shown clinical benefit across a wide variety of tumour types. Nevertheless, most patients still progress on these treatments, highlighting the importance of unravelling the underlying mechanisms of primary resistance to immunotherapy. A well described biomarker of non-responsiveness to immune checkpoint inhibitors is the absence or low presence of lymphocytes in the tumour microenvironment, so-called cold tumours. There are five mechanisms of action that have the potential to turn cold tumours into so-called hot and inflamed tumours, hence increasing the tumour's responsiveness to immunotherapy—increasing local inflammation, neutralising immunosuppression at the tumour site, modifying the tumour vasculature, targeting the tumour cells themselves, or increasing the frequency of tumour-specific T cells. In this Review, we discuss preclinical data that serves as the basis for ongoing immunotherapy clinical trials for the treatment of non-immunoreactive tumours, as well as reviewing clinical and translational data where available. We explain how improving our understanding of the underlying mechanisms of primary resistance to immunotherapy will help elucidate an increasingly granular view of the tumour microenvironment cellular composition, functional status, and cellular localisation, with the goal of further therapy refinement.

Introduction

Cancer treatment has evolved in the past 10 years from a strategy mainly focused on targeting tumour cells, to a broader therapeutic strategy encompassing targeted activation of immune cells to help fight tumour cells. Notable advances have been made in cancer immunotherapy, with the development of immune checkpoint inhibitors (ICIs) approved to treat various tumour types. However, despite their efficacy, many patients go on to have progressive disease. Initial response likely depends on the tumour immune phenotype at baseline.[1] Consequently, tumour immune classification systems (based on the type of immune-cell infiltrate, density, and location) have been proposed to characterise the immunological tumour status and predicted responses to ICIs.[1,2] These classifications offer clues for the development of therapeutic approaches to overcome primary therapeutic failures.

In this Review, we outline the main tumour immune phenotypes that have been described in the literature thus far, and the underlying tumour features that probably affect the efficacy of immunotherapy. We then offer a conceptual therapeutic framework based on five main strategies that aim to enhance ICI efficacy. These include increasing inflammation in the tumour microenvironment of non-inflamed tumours; neutralising immunosuppressive factors at the tumour site; normalising tumour vasculature; targeting tumour-cell-intrinsic pathways; and increasing tumour-specific T cells. We recognise that, as with any tumour classification, the one offered in this Review might be an oversimplification, considering the complex interplay between the tumour and the immune system. Furthermore, we recognise that the conceptual framework in which we organised our thinking is, by default, arbitrary, given that the proposed therapeutic strategies can be approached from different perspectives. Moreover, although at the surface these therapeutic strategies could appear orthogonal, the strategies discussed can induce multiple effects on immune cells, as well as tumour cells. Thus, individual therapeutic interventions can in fact have overlapping mechanisms of action and thus be assigned to more than one of the main strategies listed above. Understanding these limitations, we will attempt to provide a concise overview of the field based on our current understanding of the mechanisms underlying T-cell exclusion and immune desertification of tumours, and available opportunities for rational interventions, with the aim of reprogramming tumours to enhance T-cell infiltration, engraftment, and function, to ultimately improve patient response to ICIs.

Immune phenotypes determine immunotherapy outcomes

Tumours can be spontaneously populated by T cells, which can succeed in infiltrating tumour nests.[3] Careful assessment of tumour-infiltrating lymphocytes (TILs) has helped distinguish three dominant immune phenotypes: immune-inflamed, immune-excluded, and immune-desert, which roughly correlate with response to PD-1 blockade.[2] Tumours with an immune-inflamed phenotype, also known as hot tumours, are characterised by an increased infiltration of CD4 T cells and CD8 T cells to the stroma, the tumour parenchyma, and tumour cell nests (or tumour islets). These highly infiltrated tumours are presumed to be immunogenic and immunoreactive (figure 1), and clinical responses to anti-PD-1 and anti-PD-L1 ICIs occur frequently in this histological subtype.[2,4] Factors that can contribute to immunoreactivity include a high mutational burden[5–7] and certain inflammatory or chemokine networks, among others.[8]

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