The fight against cancer: is harnessing the immune system the ultimate strategy?

ABSTRACT

Malignancy is a micro-evolutionary phenomenon shaped by selection pressures. Chief among these is the adaptive immune system, which recognizes malignant cells as a threat and attempts to eradicate them. The task is not easily achieved – if it were, cancer would not be a part of our human experience. The field of immunotherapy has rapidly expanded over the last two decades. It has produced some of the most exciting results of 21st century medicine, and has deepened clinicians' understanding of the relationship between malignancy and the immune response. This review discusses this relationship and analyses key tools in the immunotherapy arsenal.

The statement 'behind every cancer survival story is the immune system' is just a hypothesis, but it is gaining credence: the 2019 Annual Meeting of the American Society for Clinical Oncology was dominated by advances in immunotherapy – treatments that manipulate or deliver an immune response against malignancy.

Plausibility of the anti-cancer immune response

It makes sense that the immune response might be central to surviving cancer: malignancy is an inevitability of human existence and can occur during a person's reproductive lifespan. It has therefore exerted a selective pressure during human evolution. Cellular mechanisms exist for preventing the development of neoplastic change, but these are not foolproof, and the immune system must step in when needed.

The immune system need not destroy all cancer cells to effect a cure. Rather, it must simply stop proliferation to the point that cancer is detectable by current methods of assessment. To illustrate: a woman was diagnosed with malignant melanoma (MacKie et al, 2003). She underwent local excision of the tumour and, after 15 years of follow up, was discharged with the 'all clear'; she died a year later following a presumed subarachnoid haemorrhage. Her kidneys were donated, but within 2 years, each recipient had been diagnosed with invasive melanoma. One explanation is that microscopic melanoma deposits in the donor's kidneys were kept in check by her immune system, but the recipients' immune systems were unable to do the same owing to the immunosuppressive drugs they had to take to prevent rejection.

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Cancer *vs* immune system: the normal way of things

A glaring paradox requires explanation: if the immune system has such powerful anti-cancer properties, why is cancer so common?

The immune response to malignancy

The transition from healthy cell to tumour cell marks a change in cell behaviour and this is often also associated with a change in molecular appearance. Perhaps a mutation in a protein-coding gene leads to an altered protein structure (creating a so-called 'neo-antigen'), or tissue-specific markers are inappropriately switched on in the tumour cell (for instance, the 'cancer/testis antigens' and other specialisation proteins), maybe the tumour cell expresses a supra-physiologically high concentration of a certain antigen, or perhaps oncogenic change is driven by a viral protein. However it happens, a cancer cell becomes distinct from neighbouring healthy cells (Schreiber et al, 2011).

Phenotypic changes are detected by the immune system, via antigen presentation in the major histocompatibility complex (MHC) molecules. Peptides belonging to the cancer cell are sampled by tissue-resident dendritic cells, which return to local lymph nodes and present aberrant peptide signals on MHC molecules to T lymphocytes, including CD8-positive, cytotoxic T cells. If a dendritic cell bears a tumour antigen–MHC combination that is specific for the T cell it encounters, that T cell could be activated – becoming highly proliferative and upregulating its cytotoxic functions. It migrates to the cancer cells in the peripheral tissue and attempts to destroy them (*Figure 1*).

The immunoediting hypothesis

This is the elimination process, proposed by Robert Schreiber as an expanded form of the immunosurveillance hypothesis that originated in Paul Ehrlich's work of the early 20th century (Schreiber et al, 2011). If elimination is not complete and cancer cells remain, an equilibrium phase is entered and after that tumour cells escape and undergo unchecked growth.

These three phases – elimination, equilibrium and escape – are sculpted by interactions between the cancer and immune cells, referred to as immunoediting and demonstrated in seminal studies by Schreiber's group (Shankaran et al, 2010). Two particularly pertinent findings were:

1. Mice lacking an adaptive immune response develop tumours more frequently and quickly than wild-type mice following carcinogen insult
2. Cancers that develop in immunodeficient mice are more likely to be eliminated when grafted into immunocompetent mice than are cancers that develop in immunocompetent mice (*Figure 2*).

This second finding suggests that, in an immunodeficient mouse, the cancer cells have not been subject to selective pressure and so have not evolved the mechanisms to escape an immune response. Therefore, when they are grafted into a normal immune context, they prompt an aggressive response: they are immunogenic, and easily destroyed.

A broad outline of immunotherapy

The aim of immunotherapy is to re-establish the immunogenicity of malignancy so that it becomes a target for immune control. *Figure 1* describes the interactions between cancer and the immune system, and the points at which clinicians may intervene.

Helping the immune system 'see' malignancy

The malignancy has escaped the immune system – maybe by downregulating its MHC molecules or corrupting the machine that prepares peptides for MHC expression – so how do we make it visible once again?

Coley's toxins

Dr William Coley, an American surgeon from the turn of the 20th century, was an immunotherapy pioneer (Hoption Cann et al, 2003). He directly injected dead bacteria, *Streptococcus pyogenes* and *Serratia marcescens*, into sarcomas. 'Coley's toxins' successfully treated a number of 'incurable' cases. He believed that a febrile response was key to a good outcome.

Most likely, the presence of Coley's toxins in the cancer milieu triggered an innate immune response against the whole mass (Hoption Cann et al, 2003). Essentially, Coley's 'vaccine' exposed the malignancy by providing a proxy target in the form of the bacteria. While his technique was abandoned, the biology he elucidated is now the focus of modern immunotherapy efforts.

Vaccinating against malignancy

Cancer vaccines, in their simplest form, involve administration of peptides isolated from cancers to help the immune system learn a tumour's signature and so recognize it – analogous to vaccines for infectious disease. Unfortunately, such vaccines are associated with disappointing results – to the extent that at one point, the whole field of immunotherapy lost credibility (Rosenberg et al, 2004; Zappasodi et al, 2018).

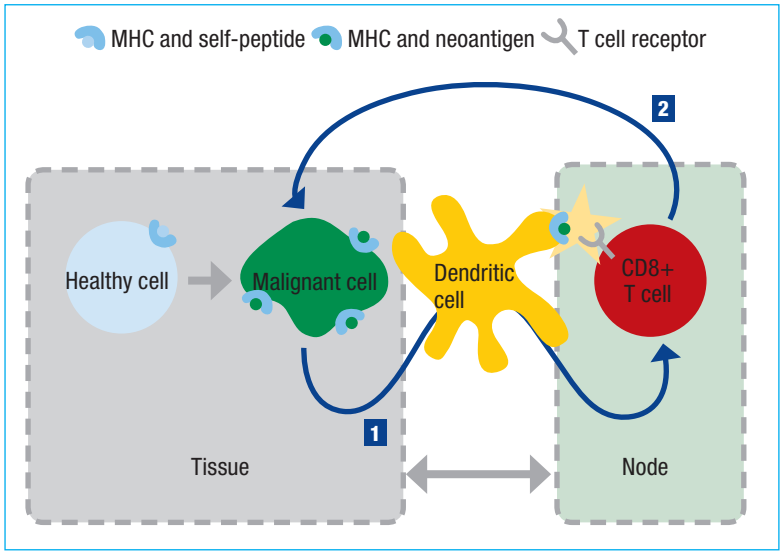

Figure 1. A malignant cell appears different to the immune system following a genetic (or epigenetic) change. Here, a neoantigen arises by non-synonymous mutation and expression of a neoantigen peptide. 1. This neoantigen peptide is presented by the malignant cell on a major histocompatibility complex (MHC) 1 molecule, which is sampled by the dendritic cell and brought to the local lymph node. 2. The dendritic cell then activates a CD8+ cell that carries a T cell receptor specific for the MHC–neoantigen combination. The activated CD8+ cell seeks out the malignant cell and attempts to destroy it.

An updated understanding of cancer immunobiology drove development of dendritic cell vaccines – for instance, to combat glioblastoma (Liau et al, 2018). Patients' dendritic cells are stimulated ex vivo in the presence of glioblastoma lysate and then returned to the patient. Inside the body, these stimulated dendritic cells directly present tumour peptide–MHC complexes to cognate CD8+ T cells. This is a far more potent approach than simple peptide vaccination, because:

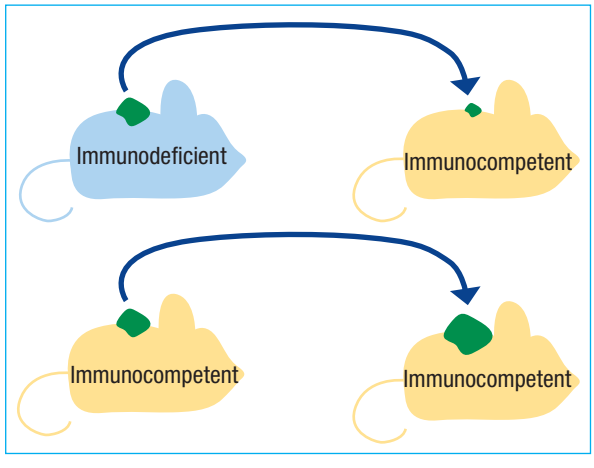

Figure 2. In the studies performed in Robert Schreiber's lab, tumours that grew in immunodeficient mice were usually eliminated when grafted onto immunocompetent mice. Conversely, where a tumour had developed in an immunocompetent mouse, it continued to grow when grafted onto another immunocompetent mouse. This finding led to the suggestion of immunoediting.

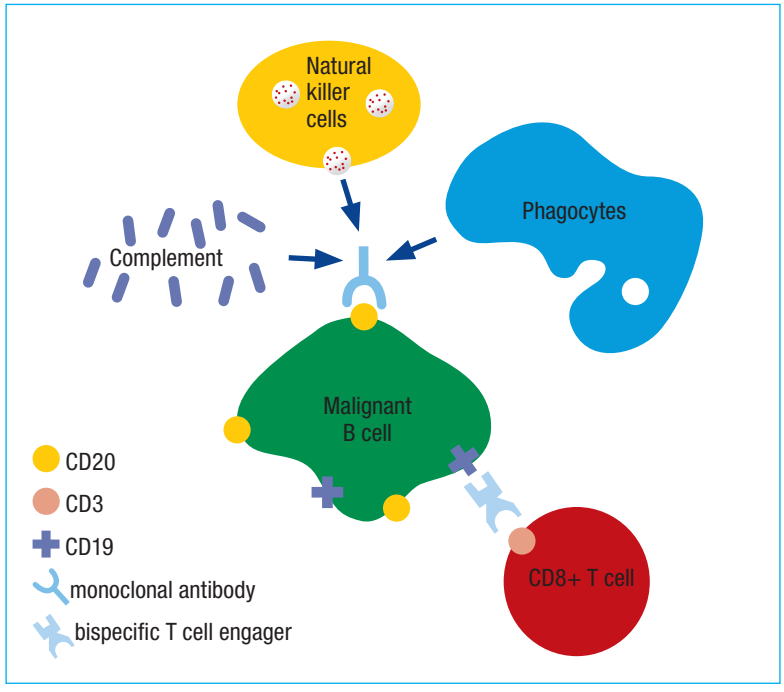

Figure 3. Rituximab, a monoclonal antibody, binds CD20 antigen present on B cells. In so doing, it opsonises the cell and recruits multiple cell-killing mechanisms, such as complement, natural killer cells and phagocytes. Conversely, blinatumomab, a bispecific T cell engager, binds CD19 on the B cell and CD3 on a nearby T cell, thus bringing effector and target cell into close proximity and triggering T cell-mediated killing.

1. Between them, dendritic cells present a host of glioblastoma peptides
2. The peptides are presented appropriately, in MHC complexes
3. The dendritic cells are pre-activated, representing a far greater T cell stimulus.

Complete analysis of this trial is awaited, but results published thus far are encouraging (Liau et al, 2018).

Turning innocuous signals into danger signals

Malignant cells evolve to downregulate presentation of peptide on MHC molecules. Vaccination strategies rely upon the MHC system, and so failure of such strategies is conceivable.

An alternative approach is exemplified by rituximab, a human–mouse monoclonal antibody that binds the CD20 cell surface protein expressed by healthy B lymphocytes and lymphoma cells. CD20 is not an immune target, but the cell bearing it becomes one when it is bound by rituximab (*Figure 3*). Rituximab is now a standard treatment for a range of high- and low-grade B cell disorders (Salles et al, 2017). When added to traditional chemotherapy in the treatment of elderly patients with diffuse large B cell lymphoma, overall survival at 2 years improved from 57% to 70% (Coiffier et al, 2002).

The rituximab concept has been developed with bispecific T cell engagers (BiTEs). BiTEs are cell–cell coupling molecules that connect the CD3 antigen present on all T cells to a chosen antigen on a malignant cell. BiTE binding brings the T cell and the malignant cell into very close proximity (helping the T cell 'see' its target) and activates the T cell through CD3 binding (*Figure 3*). Furthermore, since CD3 is a generic T cell antigen, a BiTE can activate any nearby T cell – unlike in vaccination, where only cognate T cells are activated. Blinatumomab is a BiTE designed for relapsed or refractory acute lymphoblastic leukaemia, a notoriously difficult-to-treat malignancy. It generated remission rates of 44% compared to 25% with standard-of-care chemotherapy (Kantarjian et al, 2017).

Cell–cell coupling molecules analogous to BiTEs have been generated to harness the anti-cancer activity of a subtype of lymphocyte called natural killer cells. Natural killer cells have their own role to play in immunoediting (especially when tumour cells downregulate their MHC class I molecules; Davis et al, 2017) but can be activated by bi- and tri-specific killer engagers (BiKEs and TriKEs). BiKEs form connections between natural killer and target cells; TriKEs can do the same, and can also be adapted to carry cytokine molecules. Mouse work with these molecules has proven promising, and an acute myeloid leukaemia-specific TriKE has been taken through to a phase 1 clinical trial (Davis et al, 2017).

Enhancing the immune system's effector activity

Cancer cells undergo an evolutionary battle with the adaptive immune system. Some acquired traits help the neoplasm to avoid detection, others attenuate the immune cells' attack.

Exhausted T cells

Effector T cells can and do reach the tumour microenvironment, but are often ineffective and exhibit an exhaustion phenotype (Baitsch et al, 2011), with reduced proliferative potential, impaired cytokine production, and a metabolism that is maladapted to the hypoxic and acidotic tumour microenvironment (Wherry and Kurachi, 2015; Thommen and Schumacher, 2018).

Why does this happen? The neoplastic cells co-opt several legitimate immunosuppressive mechanisms that normally promote self-tolerance and prevent autoimmune disease. These include elaboration of immunosuppressive cytokines such as IL10 and TGF-β, recruitment of regulatory cells such as T regulatory cells and myeloid-derived suppressor cells, and adoption of the immune checkpoint system (*Figure 4*).

Checkpoint inhibitors

Immune checkpoints exist as T cell membrane receptors which, when activated, trigger intracellular changes that contribute to exhaustion. Mice that are knockouts for immune checkpoints suffer aggressive autoimmune reactions (Catakovic et al, 2017). The interaction between the programmed cell death-1 receptor and its ligand (PD-1 and PD-L1 respectively) is active primarily in the peripheral tissue, while the axis involving cytotoxic

lymphocyte-associated protein 4 and its ligand (CTLA-4 and B7) operates in the lymph node (Zappasodi et al, 2018). Other immune checkpoints exist, but currently the term checkpoint inhibitor refers to a monoclonal antibody blocking either PD-1/PD-L1 or CTLA-4.

Checkpoint inhibitors are responsible for some extraordinary success stories: for instance, a case of metastatic, refractory melanoma masses disappearing on cross-sectional imaging (Chapman et al, 2015). They have activity against a variety of malignancies, including melanoma, breast cancer, non-small cell lung cancer and Hodgkin's lymphoma. A randomized controlled trial comparing ipilimumab (an anti-CTLA4 antibody) with nivolumab (anti-PD1) against standard-of-care chemotherapy in advanced or metastatic non-small cell lung cancer with high mutation burden demonstrated a 1-year progression-free survival of 42.6% *vs* 13.2% (Hellmann et al, 2018).

Not out of the woods yet

Checkpoint inhibition is not always successful. Some patients' disease is resistant to the therapy from the beginning – called primary resistance – perhaps suggesting that PD-1/PD-L1 or CTLA-4/B7 are not used by the malignancy, or are only 'bit players' within a network possessing significant redundancy. Other cancers may show an initial response, followed by loss of control; so-called acquired resistance, reflecting the effect of immunoediting interactions (Sharma et al, 2017).

Supplying cancer recognition and cancer destruction in one therapy

The immunotherapies hitherto discussed shift the balance in favour of the resident immune response. A different approach is to supply primed CD8+ T cells directly to the patient.

Allografts

The archetype for this is allogeneic haematopoietic stem cell transplantation (or allograft), the gold standard treatment for high-risk haematological diseases. Allografts are associated with high morbidity and mortality but are used because the malignancies they treat cannot be brought into durable remission by current therapies.

Patients undergo conventional therapy to induce and consolidate temporary remission of their disease, then receive a conditioning regimen of chemotherapy (and sometimes radiotherapy) that both empties the bone marrow and prevents rejection of incoming cells. These donor cells 'rescue' the bone marrow from the toxicity of the conditioning regimen (this was the indication for the first ever human allograft, in 1959; Copelan, 2006) and, crucially, provide a graft *vs* tumour effect.

This is the ultimate immunotherapy: wholesale importation of an immune system that will perform both recognition and destruction roles with a vigour that the patient's own immune system lacked.

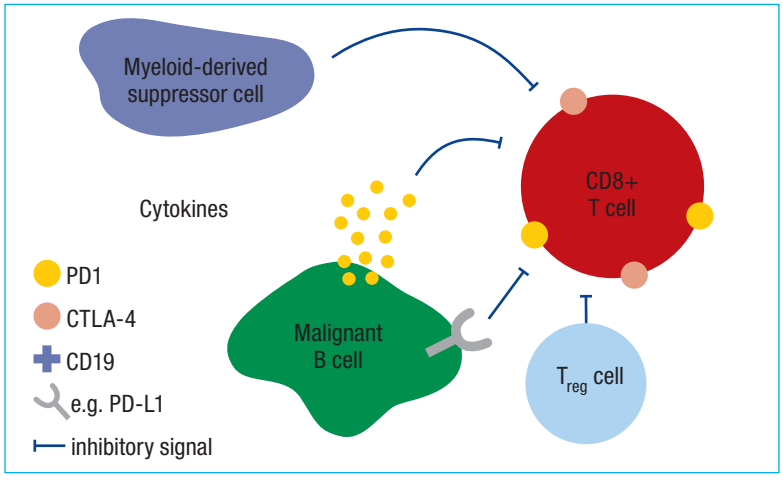

Figure 4. Malignant cells are often able to co-opt numerous immunosuppressive mechanisms that naturally exist in the body to ensure immune tolerance (and so prevent autoimmune disease). These include cellular activity, inhibitory cytokine activity (such as IL10) and checkpoint inhibitors (such as PD-1, CTLA-4 and their ligands, PD-L1 and B7 respectively).

A retrospective study of over 2000 allografts demonstrated a significant variety of relapse risks post-allograft (Horowitz et al, 1990). The highest risk of relapse was among patients whose allograft was from an identical twin – where donor and recipient cells are genetically identical; their 5-year relapse risk was approximately 60%. Contrast this with patients whose donor was unrelated and who experienced acute and chronic graft *vs* host disease, whose chance of relapse was 10%.

There are two fundamental differences between these two patient groups:

1. The low-risk group derived their grafts from genetically different individuals (matched, unrelated donors)
2. The low-risk group experienced demonstrable donor immune activity in the form of both acute and chronic graft *vs* host disease.

The protection associated with graft *vs* host disease was noted as early as 1979 (Weiden et al, 1979). It co-exists with the graft *vs* tumour effect because they both reflect the same phenomenon: incompatibility of minor histocompatibility antigens (Bleakley and Riddell, 2004). The recipient's cells – including their leukaemia cells – are recognized as foreign by the donor immune system, which triggers activation and proliferation of recipient-specific donor T cells that attack and destroy residual leukaemic cells (Marijt et al, 2003) as well as healthy bystander tissue. Identical twins do not have any mismatch so there is no substrate for any graft *vs* tumour effect. Similarly, grafts where T cells were removed (to reduce the harmful effects of graft *vs* host disease) had a higher risk of relapse (Horowitz et al, 1990).

An adjunct to allograft is donor lymphocyte infusion, developed in the 1990s as a salvage option in relapsed chronic myeloid leukemia post-allograft. Originally, buffy coats from the original donor's blood were infused into patients to induce a durable remission (Kolb et al, 1990). Currently, a more selected T cell product is acquired by

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leucopharesis and is used in a variety of types of disease relapse post-allograft. Response rates are variable – relapsed acute myeloid leukaemia remits in about a third of cases (Schmid et al, 2007).

Adoptive T cell transfer

Allografts and donor lymphocyte infusions are effective, but relapse still occurs. It is currently not possible to predict which minor MHC incompatibilities confer effective anti-cancer activity, let alone deliberately achieve those mismatches.

Adoptive T cell transfer is a possible solution. In its infancy, this involved isolating exhausted anti-cancer T cells from fresh tumour biopsies, activating and proliferating them ex vivo and then re-infusing them (Dudley et al, 2002). Techniques are now being developed to identify cancer antigens and their cognate T cells more readily, so that such T cells can be extracted from the bloodstream rather than from biopsy tissue (Baruch et al, 2017), and then perhaps be manipulated ex vivo to improve their anti-cancer effect.

Chimeric antigen receptor T cells

Chimeric antigen receptor T cells, or CAR-Ts, are T lymphocytes that have been taken from a patient (or, more increasingly, an unrelated donor) and then transfected such that their T cell receptor is replaced by a hybrid molecule. The antigen-facing moiety is derived from an antibody, and so is not MHC-restricted; the intracellular moiety is bundled in a complex that increases the potency of downstream signalling (*Figure 5*).

The antigen recognized by a CAR-T cell is chosen by clinicians rather than being the result of an in vivo immune selection process. Thus far, efforts have focussed primarily on CD19, an acute lymphoblastic leukaemia marker. In one landmark publication, complete remission was seen in 27 of 30 cases of relapsed/refractory acute lymphoblastic leukaemia (Maude et al, 2014).

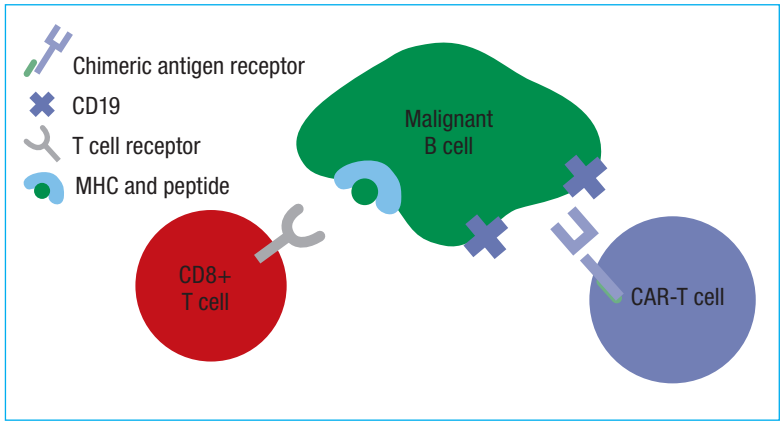

Figure 5. Chimeric antigen receptor T cell (CAR-T) cells use a synthetic, chimeric receptor that detects a chosen antigen (in this case, CD19 on a malignant B cell). The chimeric receptor is complexed with an intracellular domain that enhances the activating signal. In comparison is a normal CD8+ cell, which recognizes malignant peptide–major histocompatibility complexes (MHC).

It is difficult to overstate the excitement that CAR-T therapy has generated. Haematological malignancies are an obvious target because infused CAR-T lymphocytes naturally circulate through haematopoietic tissues, encountering neoplastic cells. The therapy has provided sustained remissions in refractory cases of acute lymphoblastic leukaemia (Maude et al, 2014), chronic lymphocytic leukaemia (Porter et al, 2015), high- and low-grade lymphoma (Kochenderfer et al, 2015) and multiple myeloma (Garfall et al, 2015). Solid organ malignancies represent their own challenges, but more than 60 early phase trials were recruiting as of late 2018 (Filley et al, 2018).

Significant issues remain: the genetic manipulation and culture processes required for autologous CAR-T cells can take longer than the patient can afford, a treatment costs a few hundred thousand pounds, and the side-effect profile can be deadly owing to cytokine release syndrome, neurological sequelae and, in the case of anti-CD19 CAR-T, long-term B lymphocyte depletion. Efforts are being made to mitigate some of these concerns, for instance, 'off-the-shelf' CAR-natural killer cells which are immediately available with less off-target toxicity (Li et al, 2018).

Adapting to the threat

Immunotherapy offers an unprecedented degree of hope. Such optimism is rooted in the philosophy that the immune system is our strongest weapon against malignancy, and pockets of evidence more and more point towards this being the case.

Our understanding is incomplete. Primary and acquired resistance is an issue not just in checkpoint inhibition but in immunotherapy generally. Resistance reflects the redundancy of tumour escape mechanisms and the variability between individual cancers, and ultimately, the extraordinary ability of evolutionary change to allow malignant cells to persist.

Hopefully, as we better characterize each patient's cancer and how it changes in response to immunotherapeutic pressure, we can create a scenario where the immune system truly does triumph and is proven to be the ultimate strategy in the fight against cancer. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The immune response might be critical to overcoming malignancy; at its core are tumour antigen-specific CD8+ T cells that respond to signals presented by dendritic cells.
- The immunoediting hypothesis describes the interactions that exist between cancer and the immune system, and comprise elimination, equilibrium and escape.
- Tumours escape by myriad mechanisms, for instance by avoiding immune detection or undermining the immune attack once detected. All these mechanisms result from selective pressures.
- Immunotherapy tackles these mechanisms in turn or all at once: cancer vaccines, monoclonal antibodies and bispecific T cell engagers assist the immune system in 'seeing' the malignancy; checkpoint inhibitors help the immune system's effector response regain its potency; and allografts and chimeric antigen receptor T cell (CAR-T) cells provide both an identification mechanism and a means for destruction of tumour cells.
- Resistance to immunotherapy is a major hurdle, and requires a personalized, longitudinal understanding of every cancer.