Cancer immunotherapy: T cells and neutrophils working together to attack cancers

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Abstract/Summary

The discovery of immune checkpoint inhibitors that boost T cell activity has revolutionised cancer treatment. However, these therapies do not work in all patients and the quest is on to understand why. Two new studies reveal the surprising finding that activated T cells can recruit neutrophils to kill cancer cells.

Main text

Conventional cancer therapies aim to completely remove and/or kill cancer cells. The immune system can also kill cancer cells, but cancers evolve immunosuppressive mechanisms that enable them to avoid being wiped out, thus to present clinically (Joyce and Fearon, 2015). Myeloid cells such as neutrophils are most often associated with an immunosuppressive tumour microenvironment (Hedrick and Malanchi, 2022) where killer T cells become exhausted by chronic stimulation and are unable to kill cancer cells (McLane et al., 2019). However, in two new papers evidence is presented that instead of promoting immunosuppression, neutrophils are recruited by activated T cells to kill cancer cells directly (Gungabeesoon, 2023; Merghoub, 2023). These novel findings pave the way for a new understanding of the mechanisms of effective cancer immunotherapy and its potential clinical application.

A major breakthrough in our understanding of cancer-induced immunosuppression came in early 2000s with the discovery that cancers co-opt immune checkpoint pathways to evade the immune system. Immune checkpoints are upregulated on activated T cells and restrain ongoing immune responses, thereby protecting the body from unnecessary bystander damage, helping return tissues to homeostasis and maintaining tolerance to self. Monoclonal antibodies that block CTL-4 (ipilumimab), PD-1 (pembrolizumab) or its cognate ligand PDL-1 (atezolizumab) break tolerance, allowing the endogenous immune system to unleash the power of the patient's own killer T cells. The importance of this was duly recognised by the 2018 Nobel Prize for Medicine being awarded jointly to James Allison and Tasuku Honjo (Ledford et al., 2018).

Checkpoint blockade inhibitors catapulted cancer immunotherapy into the clinic, and they are now being used widely. Cytotoxic (killer) T cells of the CD8 lineage have emerged as important players in successful cancer immunotherapy, as they are able to 'see' inside cancer cells and use their T cell receptors (TCR) to detect mutant proteins presented on cancer cell surfaces as short peptides bound to MHC complexes. As a consequence, CD8 T cells directly kill cancer cells because they see them as foreign or non-self, much like they kill virus infected cells. However, these monoclonals, like all effective therapies, have side effects - by

unleashing all T cells self-tolerance can break down resulting in immune-related adverse effects (IrAE) due to systemic autoimmunity.

Another type of cancer immunotherapy depends on taking patients' own T-cells and retargeting them to cancer cells by genetic modification with a chimeric antigen receptor (CAR), hence CAR-T cell therapy. The CAR extracellular domain comprises an antibody fragment that binds to an intact antigen on cancer cells and the intracellular domain comprises TCR-associated signalling motifs. For B cell leukaemias and lymphomas, CAR-T therapy targeting CD19 represents the most promising breakthrough with 40-50 % of patients with a poor prognosis having a complete remission. However, the response rate of CD19-CAR-T therapy in other blood cancers is lower, and in solid cancers such as pancreatic cancer, CAR-T response rates in early phase clinical trials are <17%.

Other approaches to boost endogenous T cell-dependent therapies are being explored, particularly for solid cancers. Next-generation checkpoint inhibitors targeting TIM-3, LAG-3, VISTA amongst others are currently being tested (Marin-Acevedo et al., 2021). An alternative approach is to use agonist (activating) antibodies to so-called costimulatory molecules such as OX40, 4-1BB, ICOS and GITR on T cells or CD40 on antigen presenting cells which leads to expansion and persistence of T cells(Choi et al., 2020). Interestingly, a key correlate of CAR T cell success is long-term persistence of CAR T cells promoted by a particular TCR costimulatory motif (Philipson et al., 2020).

These new studies using different ways to boost T cell immunity show an expected role for neutrophils in bringing about cancer killing. Gunngabeesoon et al use activating antibodies to CD40 and anti-PD1 to boost endogenous CD8 T cells and show that the recruitment of neutrophils to the tumour is critical for successful immunotherapy (Gungabeesoon, 2023). An immature *sell*/L-selectin^{hi} neutrophil subset with a gene signature linked to type I IFN signalling is preferentially recruited. The efficacy of neutrophils is dependent on type 1 cross-presenting Batf3+ dendritic cells (cDC1) which are known to take up and present cancer antigens to CD8 T cells. Interestingly, preclinical studies have already highlighted the role of type 1 IFN signalling in overcoming immunosuppression by activating cDC1 in the tumour microenvironment and strategies to induce IFN signalling in the TME are being developed (Zitvogel et al., 2015).

In Merghoub et al, agonist antibodies to OX40 or anti-CTLA-4 were used in a clinically relevant mouse model of adoptive T cell therapy using CD4 T helper cells expressing a cancer specific TCR (Merghoub, 2023). In this model, the recruitment and activation of neutrophils is T cell-dependent, however, in contrast to Gunnabeeson et al, it is dependent on CD4 T helper cells. What is surprising and unexpected is that T cell activated neutrophils also kill cancer cells that do not express the cognate antigen recognised by transferred CD4 T cells. Interestingly, mature neutrophils were active in these studies and iNOS was shown to be required for killing.

Both studies looked for clinical evidence of neutrophil involvement in cancer therapeutic outcomes. Intriguingly, in non-small cell lung cancer patients undergoing conventional therapy, improved outcomes correlated with an increased blood neutrophil:lymphocyte ratio and in melanoma patients receiving checkpoint blockade therapies, gene signatures associated with cytotoxic neutrophils correlated with patient benefit. Further studies are required to identify "cytotoxic" neutrophils, distinguish them from cytoprotective neutrophils

which protect cancers from T cell attack (Teijeira et al., 2020) and understand how different types of T cell therapies harness cytotoxic neutrophils.

There were 17 million new cases of cancer worldwide in 2018, predicted to rise to 27.5 million cases pa by 2040. The immune system and cancers have a complex relationship, but we have come a long way in understanding how to boost T cells to treat cancers and that there are many other immune evasion mechanisms operating in the tumour microenvironment that need to be overcome. These latest papers highlighting a role for neutrophils in cancer cell killing may provide another avenue to successful cancer immunotherapy.

Figure legend

T cell dependent activation of cancer killing neutrophils. A. Administration of checkpoint inhibitors or T cell agonists promotes pre-existing cancer specific CD8 T cells to recruit immature neutrophils which are activated by interferon signalling to kill cancer cells. B. Adoptive transfer of engineered cancer specific CD4 T cells are stimulated by antigen presenting cells in the tumour microenvironment to recruit mature neutrophils are able to kill cancer cells by releasing nitric oxide.

Key: Blue cell: CD8 T cell; green cell: CD4 T cell; pink cell: neutrophil; purple cell: cDC1 antigen presenting cell; pale orange and yellow cells: cancer cells with and without cancer antigens; IFN: type I interferons; NO: nitric oxide.

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