Title:
Overcoming resistance to cancer immunotherapy

Cancer immunotherapy has significantly improved the prognosis of cancer patients, but the majority experience limited benefit, evidencing the need for new therapeutic approaches. Resistance to cancer immunotherapy can be explained by tumor cell intrinsic factors and obstacles in the tumor microenvironment. The different mechanisms of resistance to current cancer immunotherapies will be explained and approaches to overcome resistance will be discussed, focusing on emerging therapy modalities including targeting cancer-associated glycosylation and cellular therapies for solid cancers.

Immunotherapy: an introduction

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Nowadays, immunotherapy is an exploding way to treat cancer. The terms immunotherapy includes several strategies. **Immune checkpoint inhibitors**, are drugs that block immune checkpoints which are a normal part of the immune system controlling the immune response. Checkpoint proteins, such as PD-L1 on tumour cells and PD-1 on T cells, help keep immune responses in check. By blocking them, these drugs, such as nivolumab, pembrolizumab or durvalumab, stimulate immune cells against cancer cells. **T-cell transfer therapy** (also called adoptive cell therapy, adoptive immunotherapy, immune cell therapy or Car-T cells) boosts the natural ability of T cells to fight cancer. Competent immune cells are selected from patient's tumour, modified and multiplied. **Monoclonal antibodies,** such as trastuzumab, rituximab or cetuximab, are designed to bind, by their Fab fragment, to cancer cells exhibiting the corresponding specific antigen (HER-2, CD-20) or to block growing factors (EGFR, VEGF). This binding induces destruction of cancer cells by several mechanisms such as CDC or ADCC. **Treatment vaccines**, work by boosting immune system response to cancer cells. **Immune system modulators**, which enhance the body's immune response against cancer. Some of these agents affect specific parts of the immune system, whereas others affect the immune system in a more general way.