Immunotherapy – new insights into how CD8+ T cells become unresponsive to treatment

In only 35% of non–small cell lung cancer (NSCLC) cases, the most common type of lung cancer in humans, individuals have responded and are sensitive to immune checkpoint blockade (ICB) (Interesting read – Immune Checkpoint Blockade- Approach to Cancer Therapy). However, in many patients with NSCLC they do not respond to ICB, *which may relate to the lack of infiltration of $CD8^+$ T cells*. ICB is therapy aimed at reinvigorating a subset of immune cells (T cells) which have become exhausted through overstimulation and fighting the tumour for too long and lose function. Successful *response to immune checkpoint blockade (ICB) is associated with programmed cell death ligand 1 expression that is induced by interferon-γ–producing, tumour-infiltrating $CD8^+$ T cells.*

In a recent paper published in *Science Immunology*, Horten, et al., have revealed potential causes for T cells exhaustion and how this subset may become non-responsive to ICB. In addition, they suggest a possible solution to overcome this problem. The study highlighted that some ICB-resistant T cells stop functioning before entering the tumour environment. These cells are not exhausted but rather dysfunctional because of differential gene expression during early T cell activation within the mediastinal lymph node. This remains to be a novel finding and provides new insights into ICB resistance

mechanisms. As a result of these findings it can be said that ICB therapies which work by reinvigorating exhausted T cells within the tumour are less likely to be effective. Therefore, suggesting that it would be more effective in combining ICB with other forms of immunotherapy that target T cells differently in order to help the immune system combat this form of lung cancer

The researchers studied T cells in murine models of NSCLC. These orthotopic mouse models of flank and lung tumours showed that *$CD8^+$ T cells from lung tumours, not flank tumours, had a dysfunctional phenotype distinct from conventional T cell exhaustion that was established in the draining lymph node and correlated to ICB resistance*. The researchers sequenced messenger RNA from the responsive and non-responsive T cells in order to identify any differences between the T cells. Using the Seq-Well technique, allowing for rapid gene expression profiling of single cells whereby Horton, et al., investigated the gene expression patterns the T cells of interest. The results revealed distinct patterns of gene expression between the responsive and non-responsive T cells. *These differences, which are determined when the T cells assume their specialised functional states, may be the underlying cause of ICB resistance.*

To further the study, the researchers wanted to see if they could help the ICB-resistant T cells kill the tumour cells. Through analysis of gene expression patterns of non-responsive T cells, it was seen that T cells had a lower expression of receptors for certain cytokines, most importantly IL-2 and IL-12. To counteract this, the researchers treated lung tumours with the aforementioned cytokines. Based off of the reintroduced response of the T cells, the results suggested that cytokine therapy *might be able to rescue a specific subset of dysfunctional T cells found in lung tumours* based off of the ability of Interleukin (IL)-2 and IL-12 being reported to reinvigorate T cells within lung tumours.

Much work is still needed to be done in this field as the administration of cytokines in cytokine therapy to human patients is not currently safe due to serious side effects (For more: Anti-cytokines Therapies).

In their own words:

"These findings imply that a $CD8^+$ T cell differentiation trajectory, activated during T cell priming in the mediastinal lymph node, limits the response of $CD8^+$ T cells to ICB and thereby may contribute to failure of ICB in a subset T cell–infiltrated NSCLC."

Journal Article: Horton, et al., 2021. Lack of CD8+ T cell effector differentiation during priming mediates checkpoint blockade resistance in non–small cell lung cancer. *Science Immunology.*

Summary by Stefan Botha