BCL-2 Confirmed to Be an Immune Checkpoint for the First Time

Recently, the French Gustave Roussy Cancer Institute team published a new research result in *Cancer Discovery*, revealing for the first time that BCL-2 is an [immune checkpoint](https://immune-checkpoints.creativebiomart.net/) that restricts the function of type I DCs (cDC1) in humans. Knocking out BCL-2 or using BCL-2 inhibitors can improve the activation and antigen presentation function of cDC1, achieve synergy with PD-1 inhibitors, and is expected to be used in the treatment of solid tumors.

French researchers were able to screen out BCL-2 with the help of CRISPR/Cas9 technology, but the screening object was not mature DCs in a terminally differentiated state, but immortalized immature DCs that could expand infinitely. The overall transcriptomic characteristics of cells are similar to those of mature DCs, and allow researchers to accurately screen out genes that affect key functions of DCs, or cell cycle and apoptosis.

BCL-2 stands out in the screening of genes related to antigen presentation function by researchers. At the same time, it is also related to the apoptosis of DCs. In addition, it is an "off-the-shelf" target with drugs, so it will naturally become the focus of exploration.

Preliminary experiments have shown that the use of venetoclax or other highly selective BCL-2 inhibitors under development can enhance the antigen presentation function of immortalized immature DCs or bone marrow-derived DCs. However, the effect of BCL-2 inhibitors depends on the autophagy of DCs, and it is ineffective for autophagy-deficient DCs (knockout of Atg5/Atg7 gene).

Most (82%) of the genes upregulated in immortalized immature DCs after BCL-2 knockout or BCL-2 inhibitors were associated with type I interferon responses, [chemokines](https://www.creativebiomart.net/gene-family-9-chemokines.htm) (such as [CCR2](https://www.creativebiomart.net/symbolsearch_ccr2.htm)/CXCR3) and the expression of co-stimulatory molecules (such as CD80/83/86) receptors was significantly increased, and the ability of DCs to secrete interleukins such as IL-1β and IL-6 was also enhanced. These are "good news" for enhancing the immune activation of DCs.

Experiments on fibrosarcoma and non-small cell lung cancer (NSCLC) model mice also showed that BCL-2 inhibitors can synergize with PD-1 inhibitors, inhibit tumor growth more effectively. Moreover, the analysis of changes in cell surface markers showed that the DCs subpopulation activated by BCL-2 inhibitors was basically limited to cDC1 (shown by upregulation of the expression of CCR7, XCR1, CD86 and MHC-II molecules).

Targeted elimination of cDC1 or T cells, or inhibition of DCs and other myeloid cells from tumor-draining lymph nodes into the tumor site, will make the immunostimulatory effect of BCL-2 inhibitors disappear, which proves the indispensable role of cDC1 in the onset of BCL-2 inhibitors.

In addition, the transfer of a large number of immortalized immature DCs knocked out of [BCL-2](https://www.creativebiomart.net/symbolsearch_bcl2.htm) into tumor-bearing mice can also enhance T cell and type I interferon response-dependent cancer immune surveillance, effectively inhibit tumor growth, and knockout BCL-2, or the use of BCL-2 inhibitors, does not significantly affect the survival of DCs, which provides the possibility of potential "adoptive DCs therapy".

Although the research team classified the effect of BCL-2 inhibitors on enhancing the function of DCs and improving the anti-tumor immune response as "off-target effects", compared with various side effects, of course, the more positive off-target effects of this kind, the better.

Moreover, previous studies have shown that BCL-2 inhibitor treatment can improve the infiltration of effector T cells into colorectal cancer. Perhaps under the stimulation of BCL-2 inhibitors, DCs and T cells can have a two-pronged approach? There are already some early clinical studies evaluating the combined use of BCL-2 inhibitors and PD-1/L1 inhibitors. Hope these studies can also get positive results soon.