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TUMOUR IMMUNOLOGY

Cell cycle inhibitors boost tumour immunogenicity

Pharmacological inhibitors of cyclin-dependent kinase 4 (CDK4) and CDK6, which are key drivers of the cell cycle, are used for the treatment of individuals with metastatic breast cancer. In some patients, these inhibitors not only stop further tumour growth, but can also result in tumour regression. Goel, DeCristo *et al.* provide a mechanistic explanation for this observation by showing that CDK4 and CDK6 inhibitors (referred to here as CDK4/6 inhibitors) increase the immunogenicity of tumours through independent effects on antigen presentation and regulatory T (T_{reg}) cells.

In a transgenic mouse model of mammary carcinoma (*MMTV-rtTA/tetO-HER2* mice), the CDK4/6 inhibitor abemaciclib caused an ~40% reduction in tumour volume by day 12 of treatment. In addition to the expected downregulation of cell cycle-related genes in abemaciclib-treated mice, the authors observed the upregulation of a set of genes associated with antigen processing and presentation, leading to increased cell surface expression of MHC class I proteins. Similar patterns of gene expression were seen in human breast cancer cell lines and when using another CDK4/6 inhibitor, palbociclib. The functional relevance of increased MHC class I expression was shown using ovalbumin (OVA)-expressing mouse tumour cell lines; pretreatment with abemaciclib increased surface expression of MHC class I-bound OVA peptide by these cell lines and increased the proliferation of, and cytokine production by, co-cultured OVA-specific T cells.

> “CDK4/6 inhibition stimulates the production of type III IFNs by tumour cells”

Transcriptomic analysis of human breast cancer cells and mouse mammary tumours showed that abemaciclib upregulates the expression of interferon (IFN)-stimulated genes (ISGs), which have a known role in regulating MHC class I-restricted antigen presentation. Further experiments showed that CDK4/6 inhibition stimulates the production of type III IFNs by tumour cells, which drives ISG expression in an autocrine manner.

Previous work in colorectal cancer has shown that type III IFN production and ISG expression can be induced by the inhibition of DNA methyltransferases (DNMTs), which reduces the methylation of endogenous retroviral (ERV) genes, increases their expression and leads to an immune response to the increased intracellular levels of ERV double-stranded RNA (dsRNA). In line with this, abemaciclib treatment decreased the levels of DNMT1 in tumour cells, decreased DNA methylation of *ERV3-1*, increased levels of dsRNA and increased expression of dsRNA sensors. Thus, DNMT1 inhibition downstream of CDK4/6 inhibition leads to a type III IFN response that enhances antigen presentation by tumour cells.

In a second line of study, the authors showed that inhibition of DNMT1 by abemaciclib and palbociclib significantly reduces the number of circulating T_{reg} cells in a tumour-independent manner. CDK4/6 inhibitors reduced DNMT1 expression in T_{reg} cells, which was associated with increased expression of the cell cycle inhibitor CDKN1A. These changes were not observed in other $CD4^+$ T cells or $CD8^+$ T cells, which might explain a preferential effect of CDK4/6 inhibitors on the proliferation of T_{reg} cells.

Tumour regression in response to CDK4/6 inhibition depends on the activity of $CD8^+$ T cells. Therefore, increased MHC class I-restricted antigen presentation by tumour cells and decreased numbers of T_{reg} cells after CDK4/6 inhibition should promote tumour regression by enhancing the tumour-specific $CD8^+$ T cell response. Indeed, $CD8^+$ T cells in abemaciclib-treated mice had decreased expression of exhaustion markers and increased expression of the effector cytokine IFNγ. This ability of CDK4/6 inhibitors to boost antitumour immunity suggests that they might have a synergistic effect with immune checkpoint blockade; promising results in this regard from the mouse model warrant further trials in humans.

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ORIGINAL ARTICLE Goel, S. *et al.* CDK4/6 inhibition triggers anti-tumour immunity. *Nature* http://dx.doi.org/10.1038/nature23465 (2017)