SIGNAL TRANSDUCTION

The old dog's new tricks

Chemotherapy has a direct cytotoxic effect on tumor cells but can also have an indirect effect by boosting the immune system. For example, anthracyclines induce immunogenic cancer cell death and cyclophosphamide depletes regulatory suppressive T cells (which allow tumor cells to evade the immune system). Less is known about the effects of chemotherapy on dendritic cells (DC)—the midfielders of the immune response—and so Lesterhuis and colleagues wondered whether platinum-based drugs could regulate the stimulating activity of DCs on T cells.

They found that when DCs were activated in the presence of platinum drugs, they had an increased T-cell stimulatory capacity. Interestingly, platinum drugs also downregulated programmed death receptor-ligand 2 (PDL2), a molecule involved in inhibiting the immune response. This effect was caused by direct dephosphorylation of STAT6, a key regulator of PDL2 activity. The researchers found that platinum drugs also dephosphorylated STAT6 in tumor

cells, leading to downregulation of PDL2 and enhanced recognition of T cells.

The clinical relevance of these findings was analyzed in a retrospective study ($n = 58$) in which 80% patients with head and neck cancer expressing STAT6 and receiving cisplatin-based chemoradiation treatment had a 3-year recurrence-free survival compared with 48% of patients who did not express STAT6. This improved recurrence-free survival for STAT6 expressing tumors was not observed in a matched cohort of patients ($n = 48$) who were treated with radiotherapy alone.

“This novel action of platinum compounds may extend their application and provide a rationale for combining them with other immunostimulatory agents to increase the efficacy of cancer treatment” concludes Lesterhuis.

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