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New methods to control neuroblastoma growth

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Downstream of growth factor receptors, signaling by the phosphoinositide 3 kinase (PI3K) pathway is known to play an important role in the growth and survival of many tumor types. The PI3K pathway simplistically comprises PI3K itself, followed by PDK-1, then AKT and finally glycogen synthase kinase 3 (GSK3).[1] PI3K/AKT signaling promotes increased GSK3 phosphorylation, that is associated with reduced GSK3 activity. There are two isoforms of GSK3, GSK3α and GSK3β, which have a high degree of sequence homology.[2] GSK3 plays a role not only in the regulation of glycogen synthase activity but in the expression of multiple other proteins that play a role in cancer biology, including cyclins and anti-apoptotic proteins.[3,4]

Neuroblastoma is a pediatric tumor that occurs in cells of the sympathetic nervous system.[5] Although localized forms of neuroblastoma can successfully be treated with surgery, individuals often present with metastatic disease which is more difficult to treat, resulting in much lower levels of survival.[6] As the PI3K pathway has been validated as a potential target in neuroendocrine tumors, the studies by Carter et al. determined whether a GSK3α/β specific inhibitor could slow the proliferation of neuroblastoma cells.[7]

Treatment of neuroblastoma cells with increasing doses of the GSK3α/β specific inhibitor AR-A014418 caused a dose-dependent reduction in growth and in colony formation ability. This reduction in growth was associated with reduced expression of β-catenin in neuroblastoma cells and reduced expression of the neuroendocrine tumor markers ASCL1 and CgA. AR-A014418 also has anti-proliferative effects in other tumor cell types, including melanoma and renal carcinoma.[8,9] Although AR-A014418 treatment only modestly enhanced the cleavage of PARP in neuroblastoma cells (arguing that apoptosis was not strongly induced), drug treatment did reduce expression of cyclin D1 (cell growth) and more interestingly the cyto-protective proteins MCL-1 and survivin.

The studies by Carter et al. did not go on to determine whether AR-A014418 effects on GSK3 signaling, through reduced MCL-1 and survivin levels, could lead to a greater anti-tumor response in cells treated with chemotherapy or ionizing radiation. As noted by the authors, targeting GSK3 is a more specific and limited approach than targeting PI3K/AKT, though from a tumor biology perspective inhibition of AKT may result in a greater level of single agent tumor cell killing. It is also of note that activation of GSK3 is considered to be a toxic effect, caused by in part by inactivation of PI3K/AKT. In this regard, AR-A014418 has been shown to protect neurons in vivo.[10] As another example, the PI3K/mTOR inhibitor BEZ235 enhances doxorubicin toxicity in neuroblastoma that was linked to GSK3 mediated modulation of the mitochondrial pore protein VDAC1.[11] Clearly future studies in multiple cell systems will be required to define the usefulness of AR-A014418 as a cancer therapeutic.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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