Novel Flavonoid Didymin Inhibits Neuroblastomas—Letter

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The article recently published in the journal Cancer Prevention Research entitled, "Didymin induces apoptosis by inhibiting N-Myc and upregulating RKIP in neuroblastoma" (1), highlights a potentially useful drug for the treatment of neuroblastoma. Didymin appears to inhibit neuroblastoma growth in vivo and in vitro, induces apoptosis, and reduces vimentin expression, a marker of epithelial-to-mesenchymal transition. The authors show that didymin induced the expression of Raf kinase inhibitory protein (RKIP or PEBP1) and that didymin effects were abolished by RKIP silencing. These data suggest that didymin may influence cellular growth, apoptosis, and their regulators, cyclin D1, N-MYC, vimentin, among others, partly through RKIP.

Using HEK-293 cells, we have shown previously that RKIP modulation influences the expression and stability of many molecules including cyclin D1, vimentin, p21 (a molecule downstream of p53; ref. 2), which the authors may not have been aware of. Moreover, RKIP has been shown to stabilize GSK3β. We have found that RKIP induction/overexpression increased GSK3β inhibition of onco- genic substrates, resulting in the destabilization of cyclin D1 (3). On the other hand, RKIP silencing induced the degradation of GSK3β and stabilization of cyclin D1, which culminated in the acceleration of the cell-cycle kinetics and increased β-catenin, Snail, and Slug expression that promoted epithelial-to-mesenchymal transition. In addition, GSK3 suppression has been shown to stabilize the N-MYC protein (4). Although these observations have yet to be confirmed in neuroblastoma cells, we would nevertheless postulate a similar connection between RKIP and N-MYC.

Therefore, RKIP function transcends its known mitogen-activated protein kinase (MAPK)-inhibitory role, and it is becoming clear that this small molecule influences negatively and positively a multitude of fundamental cellular pathways.

Overall, the fact that didymin effects on neuroblastoma have been largely abolished by silencing RKIP and that work in a separate and independent model has shown a connection between RKIP, cyclin D1, vimentin, GSK3β, and other molecules that influence cellular growth, apoptosis, and motility suggest that didymin action may well be RKIP-related. Of course, more targeted experiments are needed in the neuroblastoma model system to further support these findings.

Importantly, this article reports on an extremely useful mechanism of action of the flavonoid didymin, namely, its ability to induce RKIP expression. Given the fact that RKIP is downregulated in an overwhelming number of aggressive and therapy-resistant cancer types (5, 6), many scientists are currently searching for compounds that can upregulate RKIP in various cancers, especially in early-staged disease. We know that a few drugs, such as rituximab, DETANONATE, NPI-0052, and trichostatin, can upregulate RKIP, and we can now add a naturally occurring compound to this list! Whether didymin will be effective against other cancer types remains to be tested. Nevertheless, the fact that didymin has shown some benefit in the treatment of non–small cell lung cancer and neuroblastoma is encouraging. The problem that needs to be addressed, in a well-planned scientific manner, is whether didymin treatment may be used for cancers that already express RKIP or should be limited to RKIP-depleted cancers. Such personalized approach to didymin therapy may be worth the effort.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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