Novel Flavonoid Didymin Inhibits Neuroblastomas—Response

Sharad Singhal

We sincerely appreciate and thank Dr. Fahd Al-Mulla for the constructive commentary on our recent publication about the role of the flavonoid didymin in targeting neuroblastomas. Our research has been focused on the chemoprevention of prominent cancers in United States and in this regard, our laboratory has actively pursued the assessment of the anticancer efficacy of novel molecules and the associated impact on signaling pathways of specific relevance for the initiation, survival, and progression of respective tumors (1–3).

Our initial studies revealed that didymin is an effective flavonoid to target neuroblastomas, which prompted the reported studies on the effects of didymin on critical signaling proteins that regulate cell proliferation, cell-cycle progression, and apoptosis in neuroblastomas. The mechanisms of action of didymin could involve a number of downstream mediators given that didymin is a flavonoid with potential antioxidant properties (4). The reactive oxygen species (ROS) stimulate the activation of critical signaling pathways including mitogen-activated protein kinase (MAPK) pathway (5). The modulation of ROS can lead to a plethora of effects on cellular proliferation and apoptosis (6). Indeed, as part of follow-up studies, we are seeking to address the role of ROS in mediating the effects of didymin in neuroblastomas. But, at the same time, it remains to be determined whether the apoptotic effects of didymin are independent of its antioxidant properties, as didymin could have direct effects due to physical binding to some of the cellular targets. Thus, many rational set of investigations could be pursued to characterize the relative role of proteins targeted by didymin in neuroblastomas.

The differential regulation of RKIP and N-Myc was a salient finding of our reported study, given the opposite roles played by the respective proteins in the incidence and progression of neuroblastomas (1, 7, 8). Silencing of RKIP leads to partial increase in the survival of neuroblastoma cells. Given the evidence pointing to the prominent role of RKIP in regulating the central axes of proliferative and apoptotic signaling through regulation of Raf, GSK3β, and cyclin D1, the studies by Dr. Al-Mulla are significant in directing the investigations of molecules such as didymin which enhance RKIP expression (9, 10).

In our studies, we did observe upregulation of N-Myc following the knockdown of RKIP in neuroblastomas. RKIP is a significant mediator of the anticancer effects of didymin, but the role of different effectors of the didymin response such as Akt, phosphoinositide 3-kinase (PI3K), GSK3β, and N-Myc in various RKIP-positive and -negative tumors remains to be established by further studies involving knockdown or overexpression of respective proteins. Also, future studies should address whether the differential regulation of N-Myc consequent to RKIP knockdown is mediated through GSK3β in neuroblastoma cells. Such studies would certainly benefit the rational development of didymin formulations as well as personalized combinations of anticancer drugs with didymin to achieve better clinical response in patients with different tumor genotypes and drug-sensitivity profiles.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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