Editorial

Type 3 deiodinase and consumptive hypothyroidism

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Maynard *et al*. [April 10, 2014 issue (1)] described consumptive hypothyroidism (CH) caused by increased expression and activity of deiodinase, DIO3 within the tumor of a patient with gastrointestinal stromal tumor (GIST). Most of previously described cases of CH have occurred in hemangiomas; however, it now has become evident that CH can occur in other types of tumors, including fibrous tumors, basal-cell carcinoma, colon cancer, GISTs. They also observed tyrosine kinase inhibitors induced DIO3 expression and could potentially decrease serum TH levels. Besides drug effects on DIO3 expression, activation of cell signaling pathways such as sonic hedgehog (SHH) and mitogen-activated protein kinase (MAPK) (2) can induce DIO3 expression (3,4), and lead to CH. Delta-like 1 homolog (DLK1) recently was reported by us to be increased in a tumor associated with CH (2) and may contribute to tumor growth. We did not find loss of imprinting as the mechanism for increased DIO3 expression, but observed increased SHH and MAPK signaling, both of which can induce expression of DIO3 (3,4). We also observed that DLK1, a gene that is regulated by the same common imprinted control region as DIO3, Intergenic Differentially Methylated Region (IGDMR), was up-regulated in the tumor. Its increased co-expression with DIO3 could contribute to the large size of tumors that typically cause CH.

Patients with CH may only represent the extreme end of a clinical spectrum of disorders associated with varying degrees of hypothyroidism due to dysregulated TH metabolism in cancer. As the authors point out, it is possible that some patients harboring cancers might initially present with subclinical hypothyroidism. Even in cases when DIO3 induction is limited, it still may be sufficient to cause local tissue hypothyroidism or intra-tumor hypothyroidism that could provide a relative growth advantage for the tumor. Of course, tissue and cell specific differences may impact on the effect of locally reduced thyroid signaling on the tumoral properties. Additionally, and of clinical interest, it may be warranted to screen for hypothyroidism in patients with tumors that commonly are associated with pathways that induce DIO3 expression such as SHH, MAPK signaling or HIFa. Clearly, there still is much to be learned about the effects of the hypothalamus-pituitary-thyroid axis on cancer growth and vice versa and the results of the opposed efforts of the local TH inactivation and the balancing HPT axis in the single patients. In any case, this interesting paper offers new insight into the role of D3 in human cancers (5) and the susceptibility of neoplastic patients to D3-mediated hypothyroidism.

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