The best way to defeat an enemy is to make him a friend.

—Abraham Lincoln

True therapeutic success in oncology relies on a sound understanding of the molecular arena of the cancer in question. Thyroid cancer has rapidly increased in global incidence in recent decades (1). Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are differentiated thyroid cancers (DTCs), which account for more than 90% of all thyroid malignancies. Most DTCs are indolent tumors and are usually curable. However, in surgically inoperable, radioiodine-refractory DTCs and in poorly differentiated thyroid cancers and anaplastic thyroid cancers (ATCs), the prognosis is poor with no effective treatment available. Although much progress has been made in understanding the molecular mechanisms of thyroid cancer in the past 5 to 10 years, as demonstrated by the elucidation of the role the MAPK and PI3K–AKT pathways play in differentiated thyroid cancer (2). Mutations in these two key signaling pathways, in genes such as RAS, BRAF, PI3KCA, and PTEN, account for 65% to 70% of DTCs (2). In this issue of the Journal, Liu and colleagues add to our current understanding of thyroid tumorigenesis by providing a compelling study of how alternative RAS signaling–related genes impact on thyroid tumorigenesis (3).

Compared with normal human thyroid tissue, the RAS GTPase-activating protein (RasGAP) gene, RASAL1, was commonly silenced in the thyroid cell lines surveyed, with consistently low mRNA and protein expression. Previous studies have shown that promoter hypermethylation in tumor suppressor genes (eg, PTEN, RASSF1A) is common in thyroid cancer (4–9), and again aberrant hypermethylation in the promoter region of RASAL1 was likewise associated with thyroid cancer cell lines and with primary thyroid cancers when compared with matched normal thyroid tissues here. Importantly, RASAL1 hypermethylation appears to be seen in predominantly in FTC and ATC compared with PTC and benign thyroid tumors. Sequence analysis of primary thyroid cancer samples for mutations in RASAL1 identified mutations in approximately 17% of ATCs, 5% of FTCs, and 3% of PTCs, but not in benign thyroid tumors. All of the mutations were located in the RAS GTPase-activating domain of RASAL1, with six of seven of the missense mutations located at highly conserved sites, and


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not surprisingly, functional characterization of RASAL1 mutants demonstrated their impaired ability to inhibit cell growth.

Strikingly, Liu and colleagues note that mutation and hypermethylation of RASAL1 are mutually exclusive (3). RASAL1 mutation-negative tumors had high levels of hypermethylation. Another striking finding was the mutual exclusivity of RASAL1 somatic alterations and classical mutations in the RAS pathway genes. The ability of RASAL1 to suppress both RAS-coupled MAPK and PI3K pathways is consistent with its function as a classical RasGAP, although as noted by Liu et al., it appears that RASAL1 alterations may preferentially result in activation of the PI3K pathway over the MAPK pathway, as seen by the overrepresentation of alterations seen in FTC and ATC over PTC (3). This aligns well with the fact that Ras itself is a classic dual activator of MAPK and PI3K–AKT pathways, but in thyroid cancer, it appears that RAS mutations seem to preferentially activate the PI3K–AKT pathway (10,11).

In the last 30 years, our understanding of Ras has evolved. We now know that the oncogenic potential of Ras is context dependent. Ras proteins cycle between “on” and “off” conformations that are conferred by the binding of GTP and GDP, respectively. Under physiological conditions, the transition between these two states is regulated by guanine nucleotide exchange factors, which promote the activation of Ras, and by GAPs which accelerate Ras-mediated GTP hydrolysis. Loss of GAP activity allows uncontrolled GTPase activity and can promote tumorigenesis, leading to tumor formation. In this issue of the Journal, Liu et al. (3) have provided the first direct evidence of yet another RasGAP—RASAL1—implicated in thyroid tumorigenesis. It is as yet not known whether germine mutations in RASAL1 result in cancer predisposition syndromes as seen in NF1-related disorders, another known RasGAP gene, which gives rise to neurofibromatosis type 1.

As noted by Liu et al. (3), RASAL1 has been implicated as a tumor suppressor gene for many years but without direct evidence to demonstrate its tumor suppressor gene function. Similar to our experience with Ras, reactivation of telomerase has been implicated in human tumorigenesis but the underlying mechanisms remain poorly understood till recently. Liu and colleagues and others have found that TERT promoter mutations are highly prevalent in especially advanced thyroid cancers. It is tantalizing that these studies suggest that acquisition of a TERT promoter mutation could extend the survival of BRAF or RAS-driven clones and enable accumulation of defects leading to disease progression (12,13). A landmark paper on somatic mutations in cancer was published recently, detailing the mutational signatures across a spectrum of cancers (14). In thyroid cancer, the key mutation signature was associated with overactivity of members of the APOBEC family of cytidine deaminases. It would be indeed interesting to see whether, similarly, cancers with this signature are associated with advanced disease as a consequence of accumulation of mutational defects. This is not addressed in the article by Liu et al. (3) but it would be interesting to explore whether TERT promoter mutations or mutations in the APOBEC family of genes and RASAL1 mutations coexist: Are thyroid cancers with such mutations more likely to harbor RASAL1 mutations as a result of accumulation of genetic insults? Both appear to be more predominant in aggressive or advanced disease. RASAL1 mutations resulting in impaired inactivation of the RAS signaling system may alone be sufficient for tumorigenesis, which is suggested by the cell line data in the study by Liu et al. (3). It remains to be explored whether RASAL1 is indeed less likely to coexist with other known classical thyroid cancer mutations in a wider series of thyroid cancer subtypes.

This study by Liu et al. (3) in the context of recent studies has certainly helped us further refine the molecular taxonomy of thyroid cancer (12–16). These discoveries, while exciting in themselves, add to our current armamentarium of understanding, and, more important, provide the oncology community new fertile ground for drug discovery. Given the lack of effective therapy in DTC, the question as to whether RasGAPs can be successfully targeted for therapy remains. It is perhaps fitting then that the National Cancer Institute has started a new initiative to vigorously tackle an old foe, the “undruggable” Ras (17). Indeed, “nothing is more imminent than the impossible” (Victor Hugo).

References

Notes
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