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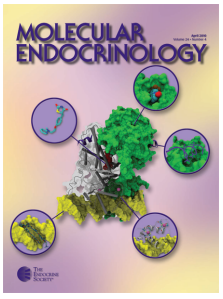

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Editorial

Targeted Therapy for Thyroid Cancer: Striking the Survival Signaling

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Cancer is a genomic disease. The genomic alterations that characterize each tumor are responsible for both the initiation and maintenance of the malignancy. Genomic medicine, which uses information from genomes to treat diseases, is a rapidly advancing field that applies specifically to guiding the treatment of cancer. In each tumor, specific genetic alterations can be the site for targeted therapeutic agents. Theoretically, targeted therapy is better than systemic therapies with antitumor agents because it is more focused and thus can be more powerful and less toxic. Based on this principle, a number of new drugs have been developed to hit specific targets, such as tyrosine kinase receptors, kinases, and oncogenes.

Although advanced cancer often has multiple genetic defects affecting diverse biochemical pathways, the survival of cancer cells becomes dependent on the continued activation of particular oncogenes (the phenomenon of oncogene addiction). Accordingly, targeting this single genetic mutation deeply affects cell viability. As a case in point, growth arrest and apoptosis are induced by RAF inhibitors in melanoma cells bearing *BRAF* mutations in culture and in murine xenograft models (1). These preclinical findings supported mutant BRAF as an attractive target for melanoma therapy and for those tumors that frequently harbor *BRAF* mutations such as papillary thyroid cancer (PTC). Many selective RAF inhibitors are currently in clinical trials in different types of cancer, including melanoma, PTC, colorectal, and non-small-cell lung cancer. Although clinical studies of selective RAF inhibitors have shown encouraging results with frequent early tumor responses, in a relevant fraction of patients this effect is of short duration with frequent relapse or no response. In some cases, development of resistance can be attributed to an elevated CRAF protein expression, gene amplification resulting in cyclin D1 overexpression, or point mutations of the downstream kinase isoform MAPK kinase 1 (MEK1) or other mutations (2–4).

These findings support the concept that most tumors harbor a constellation of genomic alterations, and these may determine the inconstant and sometimes unpredictable antitumoral effect of targeted therapy. These mutations can reside in the same cell or in different cells in the same tumor. Although sporadic, *BRAF* and *RAS* mutations can be present in the same melanoma in different cells (5). More recently, it has been reported that melanomas can contain both *BRAF* wild-type and *BRAF*-mutant tumor cells (6). In this regard, melanoma and thyroid cancer display some similarities. Although earlier studies claimed that *BRAF* and *RAS* mutations and *RET* rearrangements were mutually exclusive in PTC, subsequent studies have demonstrated the coexistence of multiple genetic alterations in the same tumor (7, 8). Simultaneous occurrence of *RET/PTC* and $BRAF^{V600E}$ and *RET/PTC* or $BRAF^{V600E}$ and phosphatase and tensin homolog (PTEN) rearrangements (*H4/PTEN* or *PTEN/H4)* was demonstrated in some PTC, although it was not revealed whether they occur in the same cell or in different cells (9–11). Finally, as in melanomas, PTCs are frequently composed of both *BRAF* wild-type and $BRAF^{V600E}$ tumor cells (Guerra A., M. R. Sapio, V. Marotta, E. Campanile, S. Rossi, I. Forno, L. Fugazzola, A. Budillon, T. Moccia, F. Fenzi, R. Rossi, and M. Vitale, submitted for publication). In this context, it seems unlikely that a single targeted therapy could be a definitive cancer treatment, whereas treatments with agents with a broader inhibitory profile, including different kinases and growth factor receptors involved in the

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Abbreviations: MEK1, MAPK kinase 1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase; PTC, papillary thyroid cancer; PTEN, phosphatase and tensin homolog.

pathological/physiological process, might be more effective.

Some drug targets are not specific aberrant factors in a specific cancer cell, but rather are a key point in a common physiological mechanism of both normal and cancer cells. Neoangiogenesis is a requirement of any solid tumor to grow beyond a diameter of a few millimeters (12). Humanized antibodies against the vascular endothelial growth factor receptor (bevacizumab) or multitargeted tyrosine kinase inhibitors that predominantly target the vascular endothelial growth factor receptor (sunitinib, pazopanib), alone or in combination with chemotherapy, improve progression-free survival for different tumors including breast cancer and renal cell carcinoma (13, 14).

Another attractive possibility is represented by therapies targeting physiological survival signaling pathways that are overactivated by oncogenes or by accompanying genetic alterations. Mutated RAS, RET/PTC, and almost all tyrosine kinase receptors can activate both the RAF-MEK-MAPK and the phosphatidylinositol-3 kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) signaling pathways, ensuring at the same time cell proliferation and survival (15, 16). Besides the above-mentioned oncogenes, genetic alterations are common along the PI3K/Akt pathway in thyroid tumors (17). Mutations or genomic copy gain of the catalytic subunits, the PI3K α-type (PIK3CA), are not uncommon in adenomas, follicular, and undifferentiated thyroid cancer, with a progressive increase in its prevalence from adenoma to more aggressive disease, which suggests a role of this genetic alteration in the progression of thyroid cancer (18). Deletion, mutations, and epigenetic inactivation through aberrant methylation of the PTEN gene also exist in thyroid tumors, all leading to activation of the PI3K-AKT-mTOR signaling pathway (19). Thus, irrespective of the genetic alterations responsible for tumor transformation, the PI3K-AKT-mTOR pathway is a common crossroad with a central role in regulating cell survival.

Quantitative assessment of phosphoprotein levels in different BRAF mutant cell lines has shown a significant association between PI3K-AKT status and resistance to inhibitors of the RAF-MEK-MAPK pathway, and it suggests a rationale for the investigation of a combination of anticancer agents and PI3K-Akt inhibitors. Ongoing studies in cells in culture and *in vivo* are investigating the anticancer effect of the novel allosteric Akt inhibitor, MK2206, in combination with several anticancer agents, including epidermal growth factor receptor inhibitors, topoisomerase inhibitors, antimetabolites, antimicrotubule agents, DNA cross-linkers, and more recently, MEK1/2 inhibitors (20).

In this issue of *JCEM*, Liu *et al.* (21) report the toxic effect of MK2206 in thyroid cancer cell lines, its genetic dependency, and its potential therapeutic application in combination with the mTOR inhibitor, temsirolimus. mTOR is a conserved serine/threonine kinase that regulates translation of pro-proliferative proteins necessary for cell growth and inhibition of apoptosis. It was discovered as the molecular target of rapamycin, an antifungal agent used clinically as an immunosuppressant. mTOR forms two distinct multiprotein complexes, the rapamycin-sensitive (mTORC1) and -insensitive (mTORC2) complexes. The latter can further phosphorylate Akt, thus creating a self-enhancement mechanism for Akt that neutralizes the rapamycin inhibitory effect. In preclinical studies, the mTOR inhibitor temsirolimus and other rapamycin-inhibiting analogs showed inconstant effects, probably due to their selective targeting of the TORC1 complex, which leaves the TORC2 complex free to activate Akt. In their study, Liu *et al.* (21) demonstrated the toxic action of MK2206 and the possibility to fulfill the inhibition of the Akt-mTOR signaling by using a combination of TORC1 and Akt inhibitors. Although MK2206 inhibited Akt phosphorylation in all cells, its cytotoxic effect was dependent on genetic alterations activating the PI3K/Akt pathway, supporting the concept that the cells had become addicted to PI3K/Akt overactivation.

An appealing feature of Akt/mTOR inhibitors is the possibility of treating advanced thyroid cancer also when resistance to single targeted therapy is conferred by multiple genetic alterations, or when the efficacy of agents highly selective for components of the RAF-MEK-MAPK signaling pathway is impaired by the overactivation of the PI3K/Akt pathway. This strategy is also worthy of investigation in advanced thyroid cancer.

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