Anaplastic (undifferentiated) thyroid carcinoma is one of the most aggressive malignancies known to humans. It carries an almost uniformly fatal prognosis and, despite accounting for only 1.6% of thyroid malignancies in the United States, is responsible for more than half of all deaths attributed to thyroid cancer (1–3). Worldwide, anaplastic carcinoma constitutes 1–7% of all thyroid cancer cases (4). This disease typically affects older adults, with some female predominance. Most patients present with a rapidly growing neck mass often associated with dysphagia, dyspnea, and vocal cord paralysis caused by widespread local invasion. Almost half of the patients have distant metastasis at presentation, and in most of the remaining cases complete surgical resection is not possible because of advanced local disease. A combination of local radiation and aggressive systemic chemotherapy is the currently recommended treatment modality; unfortunately, it has only modest response rates resulting in a median survival of 3–9 months in most series (5). In the face of this dismal prognosis, novel therapeutic approaches are essential. Their development, however, is dependent to a large extent on the better understanding of the pathogenesis and molecular basis for the initiation and progression of this cancer.

Anaplastic carcinoma arises from thyroid follicular cells and shows morphological features of a highly malignant, undifferentiated neoplasm. The tumor is characterized by sheets of markedly atypical cells with frequent multinucleation; large, bizarre nuclei; and multiple atypical mitotic figures; it reveals no follicular structures, colloid formation, or other features of thyroid differentiation. Although the pathogenesis is not entirely understood, several lines of evidence suggest that anaplastic carcinomas develop from pre-existing, well-differentiated thyroid carcinomas of papillary or follicular type (6). The clinical evidence supporting this progression is that many patients with anaplastic carcinoma have a long-standing history of thyroid cancer or history of a previous incompletely resected thyroid tumor. Pathological evidence is based on the presence of coexisting foci of well-differentiated thyroid cancer in up to 90% of anaplastic carcinomas. Finally, molecular evidence has recently emerged demonstrating that identical mutations or similar patterns of chromosomal gains and losses are detected in well-differentiated and anaplastic tumor components, implying a common origin (7–9).

Anaplastic carcinomas are characterized by complex chromosomal alterations, a high rate of aneuploidy, and profound chromosome instability as evidenced by numerous chromosomal imbalances resulting from gains and losses of entire chromosomes or discrete chromosomal loci (10, 11). Two general groups of specific genetic mutations have been identified in these tumors. One group represents genetic alterations that are found in both anaplastic and well-differentiated carcinomas, such as BRAF and RAS point mutations (7, 12). The fact that these mutations have been documented in well-differentiated and anaplastic cancers suggests that they are early events in thyroid tumorigenesis and are insufficient alone to lead to tumor dedifferentiation. The second group includes p53 and possibly CTNNB1 (β-catenin) mutations, which are frequently found in anaplastic carcinomas but not in well-differentiated cancers (13, 14), suggesting that these mutations may be directly involved in tumor dedifferentiation. The p53 tumor suppressor gene, which is inactivated in more than half of all anaplastic carcinomas, has been considered as a candidate for therapeutic intervention. Indeed, the reintroduction of wild-type p53 into anaplastic carcinoma cell lines reduces cell proliferation, restores some of the differentiation qualities, and increases tumor sensitivity to certain chemotherapeutic agents (15–17). The experimental attempts for adenovirus-mediated p53 gene therapy showed some promise in controlling anaplastic carcinoma cell growth (18), although this therapeutic modality has not been further tested in the clinical setting.

In this issue of the JCEM, the paper by Sorrentino et al. (19) identifies Aurora B as an important protein in the progression of anaplastic thyroid carcinomas and as an excellent candidate for target treatment. The Aurora kinases are key regulators of mitotic cell division (20, 21). In mammalian cells, this subfamily of serine/threonine kinases consists of three members: Aurora A, B, and C. They share a highly homologous kinase domain but differ in their N-terminal regions. The Aurora kinases exhibit unique tissue expression patterns and show distinct localization and expression profiles during the cell cycle. Aurora B regulates several crucial mitotic activities including chromosome alignment, segregation, and cytokinesis (cytoplasmic division after nuclear division) (22). To fulfill these functions, the protein undergoes localization changes as mitosis progresses. Specifically, Aurora B becomes associated with centromeres/kinetochores (the sites of chromosome attachment to microtubules) during prometaphase, redistributes to the spindle midzone during anaphase, and eventually localizes to the midbody between dividing cells. Deregulation of Aurora B kinase activity is associated with multiple defects in the mitotic machinery. Aurora B inactivation in vitro results in disruption of proper chromosome attachment to microtubules that affects the accuracy of chromosomal segregation into daughter cells. In mammalian cells, overexpression of the protein leads to chromosome instability and cell aneuploidy primarily through an increase in phosphorylation of histone H3 and subsequent disruption of chromosome segregation and chro-
mosome loss (23). Cell multinuclearity and polyploidy are additional consequences of Aurora B overexpression and are due to the disruption of cleavage furrow formation and cytoplasmic division in the absence of nuclear division abnormalities (24). These chromosome stability and ploidy defects are seen in aggressive malignancies. Indeed, Aurora kinases have been directly linked to carcinogenesis and cancer progression. Although most information in this regard has been accumulated for Aurora A, Aurora B overexpression has also been found in a variety of human cancer cells (25). Moreover, a correlation between the levels of Aurora B overexpression and invasiveness and clinical outcome has been documented in several tumor types (26, 27).

Sorrentino et al. provide in their study the first demonstration that anaplastic thyroid carcinoma cells exhibit an unusually high level of Aurora B protein expression (19). They initially identified this in tumor cell lines and then confirmed their finding in the surgical samples from human anaplastic carcinomas by demonstrating that these tumors uniformly showed markedly high Aurora B expression. This was not seen in normal thyroid tissue or less aggressive thyroid cancers, such as papillary carcinomas. These findings provide evidence that Aurora B plays an important role in tumor growth as well as the progression from well-differentiated to anaplastic thyroid carcinoma. Moreover, deregulated Aurora kinase activity is known to result in chromosomal instability, aneuploidy, and multinucleation and may therefore offer a biological mechanism for these characteristic features of anaplastic thyroid carcinoma.

Even more importantly, Sorrentino et al. tested the physiological significance of their findings by determining the effects of Aurora B inhibition on the growth of anaplastic thyroid carcinoma cells. They convincingly demonstrated that inhibition of Aurora B activity, either by RNA interference or by chemical inhibitors, resulted in dramatic reduction of cell growth, secondary to decreased H3 histones phosphorylation. Moreover, they demonstrated that inhibition of Aurora B kinase in cultured tumor cells led to slower tumor growth when injected into athymic mice. These cells, however, remained tumorigenic, consistent with the role of Aurora B in tumor progression rather than tumor initiation. These findings open the possibility for more direct clinical exploration, particularly because several ATP-competitive inhibitors of Aurora kinases have been synthesized already. The general interest in the development of inhibitors targeting the ATP-binding site at the kinase domain of protein kinases has surged after the clinical success of Gleevec (Imatinib) in treatment of chronic myelogenous leukemia (28). Two small molecule inhibitors of Aurora kinases, ZM447439 (29) and hesperadin (30), have been synthesized and are mostly directed against Aurora B. However, these compounds have not yet been defined as potential clinical candidates. Most recently, a potent and selective inhibitor of all three Aurora kinases, VX-680, has been introduced (31). It reportedly blocks cell cycle progression and induces apoptosis in several human cancer cell lines and suppresses tumor growth in vivo xenograft models of human cancer. Importantly, the effects were seen at well-tolerated doses that did not significantly affect nondividing cells. A number of unresolved issues remain. The mechanism of Aurora B up-regulation in anaplastic thyroid carcinoma cells is not clear. The possibilities include but are not limited to 1) increased phosphorylation by upstream effectors, 2) decreased degradation of the protein, or 3) gene amplification or activating mutation within the gene per se. In a broader sense, it remains unclear whether Aurora B overexpression is “abnormal” or whether it is merely a physiological response to high mitotic activity of the tumor cells. It will also be important to understand the mechanism by which protein overexpression leads to chromosome instability. A dominant negative mechanism has been proposed to explain the similar effects seen with Aurora B overexpression in human tumors and protein inhibition in the experimental models (20). In addition, it is important to determine whether p53 inactivation cooperates with Aurora B overexpression in the progression of thyroid anaplastic carcinoma. This has been suggested for Aurora A, because p53 binding has been found to directly inactivate Aurora A in certain cell types (32). Finally, the effects of the clinically relevant Aurora inhibitors need to be tested in thyroid tumors because their activity may significantly vary in different tumor types. Despite these uncertainties, the study by Sorrentino et al. identifies a novel and attractive cancer drug target and renews our hopes for a more successful treatment of this devastating thyroid disease.


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