Thyroid Cancer

Major finding: Combined use with pazopanib may improve paclitaxel activity in anaplastic thyroid cancer.

Mechanism: Inhibition of Aurora kinase A by pazopanib potentiates paclitaxel-induced mitotic catastrophe.

Impact: Pazopanib inhibits Aurora kinase A, a potentially useful therapeutic target in anaplastic thyroid cancer.

PAZOPANIB AND PACLITAXEL SYNERGIZE IN ANAPLASTIC THYROID CANCER

Anaplastic thyroid cancer (ATC) is among the most lethal human cancers, with a median survival of only 5 months. The kinase inhibitor pazopanib has shown single-agent activity in approximately 50% of patients with differentiated thyroid cancer (DTC), which led to its evaluation in ATC. However, although pazopanib monotherapy inhibited ATC cell growth *in vitro*, it failed to elicit any clinical responses in patients with ATC, prompting Isham and colleagues to investigate whether combination drug strategies could improve pazopanib efficacy in ATC. Combined use of pazopanib with the mitotic inhibitor paclitaxel, known to have single-agent efficacy in ATC but not in DTC, synergized to inhibit colony formation of all ATC cell lines tested. Adding pazopanib to paclitaxel significantly increased cell death in association with heightened mitotic catastrophe compared with paclitaxel treatment alone. Analysis of cell-cycle regulatory kinases revealed that pazopanib potently inhibited Aurora kinase A and B activity both in cell-free extracts and in ATC cells, but only Aurora kinase A was found to be specifically overexpressed in ATC patient samples compared with normal thyroid tissue, suggesting that it may be a therapeutic target in ATC and that its inhibition by pazopanib may underlie synergy between pazopanib and paclitaxel in ATC cells. Indeed, knockdown or small-molecule inhibition of Aurora kinase A synergized with paclitaxel to kill ATC cells, and Aurora kinase A knockdown blunted the synergy between pazopanib and paclitaxel. In a pilot study, the combination of pazopanib and paclitaxel also led to a durable response in an ATC patient, underscoring the clinical relevance of these observations, although a comparison of combination therapy with paclitaxel monotherapy is needed. Based on these findings, specific Aurora kinase A inhibitors may also be effective in ATC, particularly in combination with antimicrotubule agents. ■

Isham CR, Bossou AR, Negron V, Fisher KE, Kumar R, Marlow L, et al. Pazopanib enhances paclitaxel-induced mitotic catastrophe in anaplastic thyroid cancer. Sci Transl Med 2012;5:166ra3.

Stem Cells

Major finding: WNT and NF-κB cooperatively induce IEC dedifferentiation to promote tumor initiation.

Mechanism: NF-κB interacts with β-catenin to enhance transcription of stem cell–associated genes.

Impact: Inflammatory signals trigger bidirectional conversion of non–stem cells and tumor stem cells.

INTESTINAL EPITHELIAL CELL DEDIFFERENTIATION INITIATES TUMORIGENESIS

Mutational activation of the WNT pathway results in β-catenin stabilization and induction of downstream target genes, which stimulate the expansion of crypt stem cells that have been proposed to initiate intestinal tumorigenesis. Activation of canonical NF-κB signaling by chronic inflammation or oncogenes such as *KRAS* has also been implicated in tumor growth and progression, but the role of NF-κB in tumor stem cells is unknown. Schwitalla and colleagues used a genetic model of intestinal tumor initiation driven by constitutively active β-catenin expression in intestinal epithelial cells (IEC). These mice exhibited expansion of proliferative crypt stem cells and loss of differentiated enterocytes, as well as a significant increase in NF-κB activity in IECs mediated in part by TNF-α. Concomitant inhibition of NF-κB signaling in this model diminished crypt expansion and expression of WNT-induced stem cell markers, resulting in prolonged survival and suggesting that NF-κB activation regulates β-catenin–dependent transcription of stem cell genes. Consistent with this idea, RelA/p65 interacted with β-catenin in IECs and augmented the binding of mutant β-catenin to stem cell gene promoters. Furthermore, constitutive NF-κB activation in IECs enhanced the activity of mutant β-catenin and accelerated the accumulation of transformed stem cells both in crypts and in the villus epithelium. These aberrant villus crypt-like foci reexpressed stem cell markers including leucine-rich repeat containing G protein-coupled receptor 5 (Lgr5), suggesting that nonstem cells may regain cancer stem cell properties through cooperative NF-κB and β-catenin signaling. Indeed, although β-catenin alone was not sufficient to induce a tumor stem cell phenotype, combined activation of WNT and KRAS promoted NF-κB–dependent dedifferentiation of Lgr5-negative villus IECs and acquisition of tumor-initiating potential. These results demonstrate that inflammatory signaling modulates the bidirectional conversion of stem cells and differentiated IECs to stimulate intestinal tumor initiation. ■

Schwitalla S, Fingerle AA, Cammareri P, Nebelsiek T, Göktuna SI, Ziegler PK, et al. Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties. Cell 2013;152:25–38.