Blocking the Notch Pathway Inhibits the Epithelial-Mesenchymal Transition Status in Lung Cancer and Alters Chemoresistance

Notch pathway inhibitors combat chemoresistance and improve effectiveness of chemotherapy

Researchers at the University of Michigan have discovered that inhibitors of Notch, an important signaling molecule involved in cell differentiation, can be used at a low dose as productive chemotherapy sensitizing agents. This advance solves a prevalent problem with current chemotherapy strategies: Current approaches kill sensitive cancer cells, but cells with mesenchymal profile are resistant and survive the treatment. These cells eventually repopulate the tumor and cause cancer recurrence. Inhibiting Notch signaling transforms cells with a mesenchymal profile to a state in which they are susceptible to killing by chemotherapy drugs. The chemotherapeutic drugs industry is growing rapidly, with an estimated 3.3 million new patients requiring chemotherapy annually by 2015. This technology has the potential to enhance the effectiveness of chemotherapy treatments across multiple types of cancer.

Notch inhibition promotes epithelial-like cell status and inhibits EMT, facilitating cell killing by cytotoxic agents

Notch inhibitors have been used previously at high doses as cytotoxic drugs. In contrast, with this technology, low dose Notch inhibition can induce transformation of cells from mesenchymal profile to an epithelial profile that is sensitive to chemotherapy. Specifically, inhibiting Notch activity in lung cancer cells with a Gamma Secretase Inhibitor (GSI) promoted an epithelial-like phenotype and inhibited EMT. Moreover, GSI treatment rendered notch-positive cancer cells more sensitive to the chemotherapy agents cisplatin and docetaxel compared to untreated controls, and administration of Notch inhibitor with chemotherapy reduced tumor size in a mouse xenograft model compared to chemotherapy alone.

Applications and Advantages

Applications

• New therapeutic approach to sensitize tumors to chemotherapy

Advantages

• Prevents epithelial-mesenchymal transition
• Sensitizes mesenchymal-like cells to chemotherapy
• Low dose of Notch inhibitor required, reducing potential side effects
Inventors

Khaled Hassan