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Dr. Andrew Leiter's work has focused on identifying the origin of gastrointestinal endocrine cells that develop into carcinoid tumors. Previously, Dr. Leiter showed that intestinal enteroendocrine cells develop from progenitor cells of the developing gut that express the neurogenin3 gene. Dr. Leiter has created a mouse model that can specifically target expression of certain genes to neurogenin3-expressing cells, allowing him to study the effects of specific genes on the precursor cells of carcinoid.

In one recent study, Dr. Leiter's laboratory studied the effects of activation of the Wnt signaling pathway on the development of enteroendocrine cells. The Wnt pathway is activated in a variety of tumors including many tumors of the gastrointestinal tract. When expression of a mutant form of the β -catenin protein (capable of activating the Wnt pathway) was targeted to immature enteroendocrine cells in this mouse model, serotonin-producing intestinal tumors developed. These studies suggest that mutations that activate the Wnt pathway may play an important role in driving the development of serotonin-secreting intestinal carcinoid tumors.

In a similar study, the Leiter laboratory studied the effect of loss of the retinoblastoma (Rb) protein on enteroendocrine precursor cells. The Rb gene is a tumor suppressor gene that normally acts to regulate cell division. However, in a variety of tumors, Rb is inactivated by mutations, causing deregulation of cell growth. When inactivating mutations in Rb were targeted to neurogenin3-expressing enteroendocrine precursor cells, abnormal cell growth was observed. Interestingly, these effects were most pronounced in serotonin-producing enteroendocrine cells.

By allowing targeting of gene expression to candidate precursor cells of carcinoid tumors, Dr. Leiter's mouse model represents an important tool with which to study the effects of specific genes that may play a role in the development of carcinoid.

Recent Publications:

Wang Y, Giel-Moloney M, Rindi G, Leiter AB. Enteroendocrine precursors differentiate independently of Wnt and form serotonin expressing adenomas in response to active β -catenin. *Proc Natl Acad Sci USA* 2007 104(27): 11328-11333.

Kapoor A, Li HJ, Leiter AB. Intestinal development: the many faces of Wnt signaling. *Gastroenterology* 2007 133(2):710-712.

Schonhoff SE, Giel-Moloney M, Leiter AB. Neurogenin 3-expressing progenitor cells in the gastrointestinal tract differentiate into both endocrine and non-endocrine cell types. *Dev Biol.* 2004 270(2):443-54.