**Abstract**

Colon cancer is the fourth most lethal cancer in the U.S. As food passes through the colon, water and vitamins are absorbed and epithelial cells are sloughed off and replaced by a tightly regulated cell division process. Unregulated division can lead to the formation of polyps and tumors. β-catenin plays a role in regulating cell division and was modeled by the Messmer SMART Team (Students Modeling A Research Topic) using 3D printing technology. In non-dividing cells, a multi-protein complex of APC, GSK-3 and Axin phosphorylates β-catenin, signaling its degradation, thereby preventing cell division. When cell division is needed, a Wnt signal cascade causes the complex to release β-catenin, stabilizing the protein for nuclear translocation and binding to TCF, a transcriptional activator, thus triggering cell division. Competitive binding of the inhibitor proteins, ICAT and Chibby, to β-catenin negatively regulates this process. In colon cancer, mutations in APC or Axin impede binding of the complex to β-catenin, preventing degradation, leading to increased nuclear localization, binding to TCF and deregulated cell division. Additionally, survivin, an anti-apoptotic protein that enables tumor cell survival, is upregulated. Understanding β-catenin’s structure could help design drugs to promote binding of inhibitors to prevent the unregulated cell division of cancer. Supported by a grant from NIH-NCCR-SEPA.

**Colon Cancer**

Cancer is a disease caused by unregulated cell division affecting various parts of the human body, one of them being the colon.

- Colon cancer is the third most diagnosed cancer, and the second leading cause of cancer-related deaths in the United States.
- In 2009 in the US, over 106,000 people were diagnosed with colon cancer and approximately half are expected to die from it.
- The risk of developing colon cancer is 1 in 19, with a slightly higher risk in men than in women.

**Cell Division in the Colon**

The colon is responsible for the final stage of the digestive system. It absorbs nutrients and water from digested food and eliminates waste from the body. As food passes through the colon, dead cells slough off and must be replaced through cell division. β-catenin, a multifunctional glycoprotein, plays a pivotal role in this process through its involvement with the Wnt signaling pathway and the APC protein. About 85% of colon cancers are caused by mutations in APC.

**β-catenin and Cell Division**

- **Colon Lining**
- **Crypt**
- **Epithelium**
- **Polyp**
- **Regulated Cell Division**
- **Unregulated Cell Division**

**β-catenin**

β-catenin consists of an N-terminal tail followed by 12 armadillo repeats (ARM) and a final helix called helix C, which is located on the C-terminal end of the protein. The armadillo repeats and helix C bind transcription factors which are crucial positive and negative regulators of cell division. These regions of the protein are potential drug targets for cancer prevention and treatment.

**Role of Helix C in Binding to Chibby**

**Conclusion**

β-catenin plays an important role in Wnt signaling of cell division in processes from embryogenesis to cell replacement to tissue repair and wound healing to cancer through it’s interaction with proteins such as the transcriptional activator, TCF. Nuclear inhibitor proteins such as ICAT and Chibby interfere with the binding of β-catenin to TCF and thus negatively regulate gene activation and cell division. As β-catenin/TCF activation of gene expression has been implicated in multiple diseases from developmental disorders to colon cancer to Alzheimer’s, understanding the structural basis of Chibby binding to β-catenin and how this inhibits TCF binding and cell division, is critical in the development of medications and treatments for these diseases.

**Purpose:** To determine what part of β-catenin’s structure is important in binding to the nuclear transcription inhibitor, Chibby.

**Method:** Truncated mutant fragments of β-catenin were produced and assayed for strength of binding compared to intact protein. Fragments tested were 1) full length β-catenin; 2) β-catenin minus the N-terminal; 3) β-catenin minus N-terminal and all but 21 amino acids of the Helix C domain and 4) β-catenin minus the N-terminal and all of Helix C.

**Results:** Binding to Chibby is weakest when the protein is missing Helix C but is as strong as the intact protein when 21 amino acids of Helix C are present.