Newly discovered regulatory mechanism essential for embryo development and may contribute to cancer

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Researchers from Mount Sinai School of Medicine have identified a mechanism controlling the function of a protein that binds to DNA during embryonic development and may function to prevent abnormal tumor growth. When the protein, TCF3, is modified by a small molecule called a phosphate, it no longer binds DNA, changing the way the protein signals during development. This discovery identifies a new diagnostic marker (phosphorylated TCF3) that may be associated with cancer and could represent a potential drug target. The results are published in the current issue of *Developmental Cell*.

Led by Sergei Sokol, PhD, Professor of Developmental and Regenerative Biology at Mount Sinai School of Medicine, the research team analyzed frog embryos to get a better understanding of how cells "talk" to each other and differentiate into various cell types, e.g., neurons or muscle cells. One such way these cells communicate is through signaling proteins called Wnts, which function during embryonic development and malfunction in cancer, including colon carcinomas, melanomas, skin, lung and liver tumors. Dr. Sokol's team analyzed what happens when a cell responds to Wnt protein..

The researchers' results suggest that Wnt signal activates a special enzyme, called homeodomain-interacting protein kinase that adds a phosphate group to TCF3. This event changes the activity of TCF3 and activates gene expression during early development, allowing embryonic

tissues to develop tail structures. Although essential in the early embryo, the same process can cause tumor formation in the adult.

"Our study is the first to show an alternative mechanism of Wnt signaling, that operates in vivo to modulate the activity of TCF3," said Dr. Sokol. "We now know that this change in TCF3 activity leads to a profound alteration of target genes that are important in early development and are abnormally regulated in cancer."

These data potentially provide a diagnostic or therapeutic target in identifying and treating common types of cancer. If the presence of the phosphate molecule on TCF3 is identified, then the cancer may be caught earlier, providing more treatment options. Additionally, knowing that this modification of TCF3 may cause abnormal cell growth would allow researchers to develop drugs that can inhibit its action.

"While more research is needed, our study is a promising first step toward earlier diagnosis and better treatment for many common cancers," said Dr. Sokol. "We look forward to gaining further understanding of the role of TCF regulation for gene expression."

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