A Cytoplasmyc Player in Colon Cancer

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The MYC gene encodes a transcription factor that coordinates cell growth and division through a transcriptional program involving all three major eukaryotic RNA polymerases. This transcription factor is overexpressed in many cancers, and understanding how increased Myc levels promote tumorigenesis is an area of intense interest in cancer biology (Dang, 2012). In addition to its well-known role as a transcription factor, a transcriptionally inactive form of the Myc protein called Myc-nick has been characterized. Myc-nick lacks the DNA binding domain and nuclear localization signal of full-length Myc. Myc-nick is thus constrained to the cytoplasm, where it promotes acetylation of alpha-tubulin, leading to alterations in cell shape and changes in cell differentiation (Conacci-Sorrell *et al*., 2010). In the present study, postdoctoral fellow Dr. Maralice Conacci-Sorrell and colleagues in the laboratory of Dr. Robert Eisenman (Basic Sciences Division) analyzed the role of Myc-nick in cancer, finding that increased levels of Myc-nick promote resistance to chemotherapeutic drugs as well as changes in cell motility that might influence metastasis. "These findings suggest that Myc-nick plays an important role in Myc-induced tumorigenesis and that inhibiting Myc-nick formation and function may provide a means of attenuating cancer progression," said Dr. Conacci-Sorrell.

The researchers first analyzed Myc protein levels in tumors from mouse models of several cancers as well as human cancer cell lines and found substantial levels of Myc-nick in nearly all cases. They chose to focus on the role of Myc-nick in colon cancer cells, as overexpression of MYC due to aberrant upregulation of Wnt signaling is a major event in colorectal carcinogenesis.

Different areas of tumors are often exposed to different levels of oxygen and nutrients, and so the authors wondered if levels of Myc-nick might be affected by these environmental variables. They first observed that extended culturing of colon cancer cells led to increased Myc-nick levels, likely due to depletion of nutrients from the media. They also found that low-oxygen conditions (hypoxia) or depletion of glucose and glutamine also promoted production of Myc-nick, suggesting that hypoxia and/or nutrient depletion within the tumor microenvironment could trigger increased Myc-nick production.

The researchers next investigated the phenotypic impact of increased Myc-nick levels in colon cancer cells. They found that overexpression of Myc-nick led to increased cell survival during nutrient depletion. Increased Myc-nick was also linked to anchorage-independent cell growth, a major hallmark of many tumors.

Since increased levels of Myc-nick were found to be associated with resistance to stress-induced cell death, the authors asked if increased Myc-nick might also confer resistance of cancer cells to chemotherapeutic agents. They found that overexpression of Myc-nick substantially increased the survival of colon cancer cells when exposed to the widely used chemotherapeutic drugs cisplatin, oxaliplatin, etoposide, and imatinib. The researchers also found that Myc-nick overexpression increases the level of several markers of autophagy. Autophagy is associated with resistance to nutrient deprivation and chemotherapeutic drugs, thus suggesting a mechanism by which increased Myc-nick promotes the resistance of cancer cells to environmental stress.

Lastly, the researchers assessed the influence of increased Myc-nick on cellular morphology. They observed that Myc-nick-expressing cells formed filopodia, which are cellular protrusions involved in cell motility, environmental sensing, and cell-cell adhesion, and that, in the case of cancer cells, are often associated with potential for metastasis. Cells expressing Myc-nick showed increased levels of fascin, an actin-bundling protein often upregulated in cancer. Consistent with these observations, Myc-nick-expressing cells displayed increased motility. Furthermore, analysis of Myc expression in human colorectal cancer revealed that Myc-nick is often localized to the invasive edges of tumors.

While the transcriptional role of Myc in cancer has been extensively characterized, the potential involvement for its cytoplasmic derivative, Myc-nick, in cancer had not previously been studied. "Our characterization of Myc-nick contributes to our understanding of mechanisms by which Myc oncogenes promote cancer cell survival and tumor maintenance," said Dr. Conacci-Sorrell. "In addition to functioning as a transcriptional regulator of cell growth and proliferation, Myc promotes the survival and motility of colon cancer cells via a non-transcriptional mechanism through the activity of its cleavage product, Myc-nick."

Conacci-Sorrell M, Ngouenet C, Anderson S, Brabletz T, Eisenman RN. 2014. Stress-induced cleavage of Myc promotes cancer cell survival. *Genes Dev* 28(7):689-707.

See also:

Dang CV. 2012. MYC on the path to cancer. *Cell* 149(1):22-35.

Conacci-Sorrell M, Ngouenet C, Eisenman RN. 2010. Myc-nick: a cytoplasmic cleavage product of Myc that promotes alpha-tubulin acetylation and cell differentiation. *Cell* 142(3):480-93.

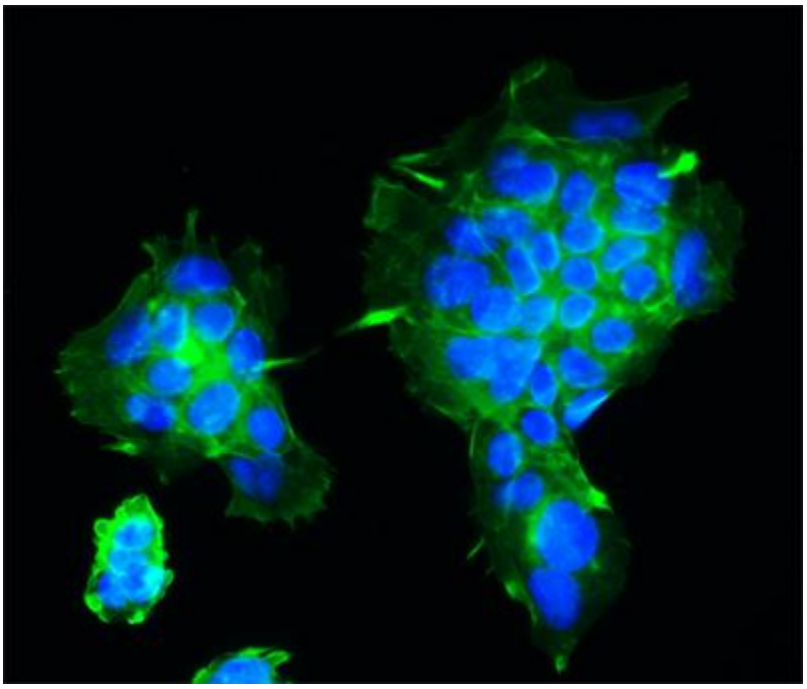

Image provided by Dr. Maralice Conacci-Sorrell.

Immunofluorescence of the actin cytoskeleton of motile colon cancer cells expressing Myc-nick. The cells were stained with phalloidin (green) to visualize actin and DAPI (blue) to visualize the nuclei.