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Dr. Matthew Meyerson's work has focused on the function and role of menin, the product of the multiple endocrine neoplasia 1 (MEN1) gene, in neuroendocrine tumors. Genetic deficiencies in MEN1 are responsible for many hereditary neuroendocrine tumors, including the majority of genetically inherited carcinoid tumors.

The work of Dr. Meyerson and his colleagues has shown that menin promotes methylation of histone H3 lysine 4 in neuroendocrine tumors. Histones are large “spool-like” structural proteins around which DNA is wound. The ability of genes on a given portion of DNA to be expressed can depend on whether that portion of DNA is wound or unwound around a histone protein. For example, if a portion of DNA is wound around a histone “spool”, that portion of DNA may not be freely accessible for gene expression. The winding and unwinding of DNA around histones can be regulated by methylation—the attachment by an enzyme of a methyl group (a carbon-containing chemical group)—of histones.

By inducing histone methylation, menin promotes expression of a group of genes that act to regulate and restrict cell growth, such as p27Kip1 and p18INK4c. Therefore, menin normally acts to restrict tumor cell growth, functioning as a “tumor suppressor” gene. Tumor cells with genetic mutations in MEN1 lose menin function and show deficient levels of histone methylation. As a result, growth-inhibitory genes whose expression requires histone methylation are expressed at low levels, enabling tumor cells to grow in an unregulated fashion.

Dr. Meyerson is also focused on identifying other genes that cooperate or compete with menin to regulate histone methylation and, potentially, tumor growth. Recently, it was discovered that the Rbp2 protein promotes histone *de*-methylation—the opposite of menin function. Therefore, menin and Rbp2 compete to regulate the level of histone methylation. Since menin acts to suppress tumor formation by promoting histone methylation and increased expression of growth-inhibiting genes, Dr. Meyerson has proposed that Rbp2 acts oppositely to promote tumor formation by reversing histone methylation and reducing expression of growth-inhibiting genes.

To test this hypothesis, his laboratory is constructing a mouse model of pancreatic islet cell neuroendocrine tumors. The islet cells of these mice have been engineered to lack the menin (MEN1) gene and develop islet cell tumors. Inactivating mutations in Rbp2 are being introduced concurrently into MEN1-deficient islet cells, to test whether the potential tumor-promoting effect of Rbp2 is required for growth of MEN1-deficient neuroendocrine tumors. If this hypothesis is correct, Rbp2 could be an exciting new drug target for the treatment of neuroendocrine tumors.

Recent Publications:

MacConaill LE, Hughes CM, Rozenblatt-Rosen O, Nannepaga S, Meyerson M. Phosphorylation of the menin tumor suppressor protein on serine 543 and serine 583. *Mol Cancer Res.* 2006 Oct;4(10):793-801.

Yokoyama A, Somervaille TC, Smith KS, Rozenblatt-Rosen O, Meyerson M, Cleary ML. The menin tumor suppressor protein is an essential oncogenic cofactor for MLL-associated leukemogenesis. *Cell.* 2005 Oct 21;123(2):207-18.

Karnik SK, Hughes CM, Gu X, Rozenblatt-Rosen O, McLean GW, Xiong Y, Meyerson M, Kim SK. Menin regulates pancreatic islet growth by promoting histone methylation and expression of genes encoding p27Kip1 and p18INK4c. *Proc Natl Acad Sci U S A*. 2005 Oct 11;102(41):14659-64.