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Penn study on silencing of tumor suppressor gene suggests new target for lymphoma

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Mariusz A. Wasik, MD, professor of Pathology and Laboratory Medicine, and Qian Zhang, MD, PhD, research assistant professor, both from the Perelman School of Medicine at the University of Pennsylvania, and their colleagues, found that a cancer-causing fusion protein works by silencing the tumor suppressor gene IL-2R common gamma-chain (IL-2Rγ). The results, which appeared in a recent *Proceedings of the National Academy of Sciences*, suggest news targets for lymphoma and other types of cancer.

Fusion proteins are created by two genes -- originally coding for separate proteins -- joining together. Translation of the fusion gene into an active protein results in a molecule with properties derived from each of the originals. Fusion proteins are relatively commonly found in cancer cells.

The team looked at a fusion protein called NPM-ALK. Anaplastic lymphoma kinase (ALK), which physiologically is expressed only by neurons in fetal life, causes cancer when it is mistakenly expressed in non-neural tissues as a fusion protein with nucleophosphin (NPM) and other partners. NPM-ALK works by silencing the tumor suppressor gene IL-2Rγ. The ALK fusion genes are active in several cancer types including some carcinomas of the lung, thyroid, and kidney.

The protein IL-2Rγ is shared by receptors for several proteins called cytokines that play key roles in the maturation and growth of normal immune cells called CD4+ T cells. The Penn team found that IL-2Rγ expression is inhibited in T-cell lymphoma cells expressing NPM-ALK

as a result of epigenetic silencing. The IL-2Rγ gene promoter is silenced by a chemical change to the DNA itself, in this case, the adding of a methyl group to DNA's molecular backbone.

Role of Epigenetic Silencing

Epigenetic gene silencing represents an important mechanism of inhibiting tumor suppressor gene expression in cancer cells. The silencing affects gene promoter regions within DNA, in two ways: methylation of the DNA and modification of histones and other proteins. The methylation is mediated by enzymes called DNA methyltransferases (DNMTs). Histones are modified by histone deacetylases.

Silencing of the IL-2Rγ promoter via methylation is induced in malignant T cells by NPM-ALK by activating another protein called STAT3. STAT3 increases expression of one of the DNMTs and facilitates attachment of this and other DNMTs to the IL-2Rγ gene promoter. Strikingly, when IL-2Rγ is expressed, NPM-ALK disappears from the cancerous T cells, and they eventually die. These results demonstrate that NPM-ALK induces epigenetic silencing of the IL-2Rγ gene and that IL-2Rγ acts as a tumor suppressor by reciprocally inhibiting expression of NPM-ALK.

"Epigenetic silencing is not an independent event, and genetics – in the form of the aberrant fusion protein – drives an epigenetic change," says Wasik. "Is this phenomenon generalizable? Can we overcome the tumor suppressor gene silencing using inhibitors of DNA methylation, which are already approved to treat some forms of blood cancer, to inhibit the expression of NPM-ALK and possibly other cancer-causing proteins in patients?"

This approach could potentially complement inhibition of fusion protein activity as is routinely done for BCR-ABL in chronic myelogeneous

leukemia and experimentally for ALK in lung carcinoma, lymphoma and other malignancies expressing ALK.

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