Study identifies key molecules in multiple myeloma

October 26 2010

New research links three molecules to a critical tumor suppressor gene that is often turned off in multiple myeloma, a presently incurable cancer of the blood.

The findings might offer a new strategy for treating this disease and other blood cancers, according to researchers at The Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) who led the study.

The silenced molecules are called miR-192, miR-194 and miR-215. All of them are microRNAs, a large class of molecules that are master regulators of many important cell processes.

The study, published in the Oct. 19 issue of *Cancer Cell*, suggests that re-activating these three molecules triggers expression of the P53 tumor suppressor gene. This, in turn, slows the growth and leads to the death of myeloma cells and could provide a new strategy for treating the disease.

"These findings provide a rationale for the further exploration of these microRNAs as a treatment for multiple myeloma, which has few therapeutic options," says principal investigator Dr. Carlo Croce, professor and chair of Molecular Virology, Immunology and Medical Genetics, and director of the Human Cancer Genetics program at the OSUCCC – James.

Multiple myeloma is a disorder of white blood cells called plasma cells. More than 20,100 Americans are expected to develop the disease this year and some 10,600 are expected to die from it. Myeloma begins as a benign condition called monoclonal gammopathy of undetermined significance (MGUS). Individuals with MGUS can live for many years without treatment. Then, for unknown reasons, this benign condition can evolve into multiple myeloma.

Studies investigating the molecular causes of the disease have shown a relationship between P53 and another gene called MDM2. They have also shown that myeloma cells often have healthy (i.e., unmutated) P53 genes but very little P53 protein. P53 protein levels are restored, however, when MDM2 expression is blocked.

The study by Croce and his collaborators, which examines the role of microRNA in regulating the P53 pathway in myeloma cells, shows the following:

- Expression of miR-192, miR-194 and miR-215 in multiple myeloma cells slows their growth and causes their death by activating the P53 gene.
- Multiple myeloma cells from patients show high MDM2 expression compared with MGUS cells and normal plasma cells;
- Expression of the three microRNAs dramatically lowers MDM2 expression levels and significantly increases P53 levels;
- Treating myeloma cells with the three microRNAs plus an MDM2 inhibitor caused a two-fold rise in P53 expression and a three-fold drop in MDM2 expression;

- Treating a myeloma mouse model with the three microRNAs caused a 50 percent reduction in tumor size compared with controls; treating the mice with the microRNAs plus an MDM2 inhibitor brought a five-fold reduction in tumor size.

- Expression of the three microRNAs reduced the ability of myeloma cells to migrate and metastasize.

Overall, Croce says, "our results provide the basis for developing a microRNA-based therapy for multiple myeloma."

Provided by Ohio State University Medical Center

Citation: Study identifies key molecules in multiple myeloma (2010, October 26) retrieved 2 May 2024 from https://medicalxpress.com/news/2010-10-key-molecules-multiple-myeloma.html

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