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Researchers say silencing of retinoblastoma gene regulates differentiation of myeloid cells

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Researchers at the Moffitt Cancer Center have found a potential mechanism by which immune suppressive myeloid-derived suppressor cells can prevent immune response from developing in cancer. This mechanism includes silencing the tumor suppressor gene retinoblastoma 1 or Rb1. Their data explains a new regulatory mechanism by which myeloid-derived suppressor cells are expanded in cancer.

Their study appeared in a recent issue of Nature Immunology.

According to the authors, two kinds of myeloid-derived suppressor cells - monocytic M-MDSCs and granulocytic PMN-MDSCs - regulate immune responses in cancer and other conditions. In experiments with tumor-bearing mice, they discovered that M-MDSCs acquire some of the physical characteristics of PMN-MDSCs. Acquisition of the PMN-MDSCs characteristics, they found, was "mediated" by the silencing of Rb1 by modifications in a histone deacetylase 2 (HDAC-2), an enzyme decoded by the HDAC2 gene.

"Our findings demonstrate the function of a newly discovered regulatory mechanism of myeloid cells in cancer," said study lead author Dmitry I. Gabrilovich, M.D., senior member of Moffitt's Immunology Program.

According to study first author Je-In Youn, Ph.D., a post-doctoral fellow in the Gabrilovich laboratory, Rb1 is among members of the retinoblastoma family of transcription regulators that integrate multiple cellular signals to control cell proliferation and differentiation. In their

experiments, the researchers found that when Rb1 was deficient in tumor-bearing mice it indicated a direct role for Rb1 in regulating M-MDSC differentiation toward PMN-MDSCs.

Their data suggested that Rb1 silencing could be initiated by HDAC-2 which, said Youn, is known to be involved in modulating the repressive activity on promoters of certain genes involved in cell differentiation.

They proposed that, in tumors, a large portion of M-MDSCs acquire the ability to differentiate into PMN-MDSCs and that it "appears that, in cancer, M-MDSCs probably acquire the ability to differentiate into PMN-MDSCs" and "may represent an important pathways for the accumulation of these cells in contrast to normal monocytes."

"We demonstrated that HDAC-2 can directly interact with Rb1 promoter and participate in silencing Rb1 expression," said study co-author Vinit Kumar, Ph.D., also a post-doctoral fellow in the Gabrilovich laboratory. He added that "silencing Rb1 expression in monocytes and other myeloid progenitors may be critical to the accumulation of PMN-MDSCs."

"If the role of HDAC-2 in this process is confirmed, the finding may offer an opportunity for therapeutically targeting myeloid cells in cancer and possibly in other pathologic conditions," concluded the researchers.

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