

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.

Provided by H. Lee Moffitt Cancer Center & Research Institute

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