

Stopping cancer from recruiting immune system double agents

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Credit: Rush University Medical Center

Cancerous tumors trick myeloid cells, an important part of the immune system, into perceiving them as a damaged part of the body; the tumors actually put myeloid cells to work helping them grow and metastasize (spread). A research team co-led by scientists at Rush University Medical Center have discovered a potential therapy that can disrupt this recruitment and abnormal function of myeloid cells in laboratory mice. The findings of their latest study were published on Dec. 19 in *Nature Communications*.

Myeloid [cells](#) are a type of white blood cell that kills invaders like bacteria and cancer. "In the cancer context, myeloid cells promote [tumor](#) growth and suppress the activity of T cells," says Vineet Gupta, Ph.D., professor and vice chairperson for research and innovation in the Department of Internal Medicine at Rush Medical College.

Gupta and Judith Varner, Ph.D., of the Moores Cancer Center at the University of California at San Diego (UCSD) in California, were co-senior corresponding authors on the study. Samia Khan, Ph.D., a post-doctoral fellow in Gupta's lab; and

Michael Schmid, Ph.D., and Megan Kaneda, Ph.D., with UCSD, were co-first authors.

Cancer recruit harmful myeloid cells, while suppressing helpful ones

Gupta's research focuses in general on integrins, a type of protein that are cellular receptors and regulate a number of biological processes. In this study, investigators looked at the integrin CD11b, which is present on myeloid cells and normally helps myeloid cell migration and its ability to fight disease.

Here, the researchers found that CD11b promotes development of myeloid cells into one sub-type, the M1 macrophage, that functions appropriately to suppress tumor growth. However, the tumors often suppress CD11b activity that results in development of the myeloid cells into a different type of cell, the M2 macrophage. These cells actually ward off T cells, which are vital to fighting disease, and M2s also secrete growth factors and promote the development of new blood vessels that allow cancer to grow and metastasize.

In previous research, agents developed to activate T cells have been "extremely effective in controlling tumor growth," Gupta says, but that approach, known as immunotherapy, has not resulted in a universal treatment for cancer. The hunt goes on.

Study found that CD11b is critical in regulating myeloid cells

In this study, the team explored how modifying the activity of CD11b affects myeloid cell behavior in the presence of cancer and if that could be used as a novel strategy to treat cancers. Using a small molecule discovered in the Gupta laboratory, Leukadherin-1 (LA-1), which in the body activates CD11b, the researchers developed a therapy that can boost the function of CD11b to promote the disease-fighting M1 type of myeloid cells, helping

create a microenvironment at the tumor site where T cells can enter and attack the cancer.

The study used two types of genetically altered mice. One set of experiments was done with otherwise normal mice that lacked CD11b. Transplanted tumors grew much larger in those mice as compared to the tumors in wild-type (normal) mice, suggesting that CD11b restrains tumor growth.

Exploring further the reason for this difference, the team found that CD11b plays a critical role in regulating the polarization of [myeloid](#) cells into M1 or M2 macrophages. In the absence of CD11b, most of the myeloids cells in tumors were the M2 sub-type, that help the tumor grow and spread.

Boosting CD11b activity helped reduce tumor growth

In a different experiment, the team used LA-1 to boost CD11b activity beyond its normal levels in wild-type (normal) mice, and discovered that this increase caused a significant reduction in [tumor growth](#) in treated animals. Then, to be sure that their pharmacological intervention was directly due to the effects of LA-1 on CD11b, they created a mouse with a "[point mutation](#)" (a genetic mutation at a single residue in the CD11b protein sequence) and created a situation in which CD11b was active all the time (which is usually isn't) in the genetically modified animals.

"The boost in CD11b activity in the mouse with the point mutation mimics the one imparted on CD11b in normal mice with administration of LA-1," Gupta says. "The results were the same," Gupta says. In both cases, the tumors shrank dramatically, suggesting CD11b activation as an novel target for [cancer](#) immunotherapy.

In this study, LA-1 showed a great deal of promise, although, Gupta says it will be years before a treatment based on this molecule becomes available to patients. The results are very encouraging and will continue to motivate the team to move this novel approach towards developing treatments for patients.

More information: Michael C. Schmid et al. Integrin CD11b activation drives anti-tumor innate immunity, *Nature Communications* (2018). [DOI: 10.1038/s41467-018-07387-4](https://doi.org/10.1038/s41467-018-07387-4)

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