'Treason' by immune system cells aids growth of multiple myeloma

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Multiple myeloma cancer cells thwart many of the drugs used against them by causing nearby cells to turn traitor - to switch from defending the body against disease to shielding the myeloma cells from harm - Dana-Farber Cancer Institute scientists report in the October issue of *Cancer Cell*.

The researchers found that immune-system cells known as plasmacytoid dendritic cells (pDCs) essentially assume a new identity in the presence of myeloma - promoting the growth and survival of malignant myeloma cells, helping them fend off drugs, and depleting the overall strength of the immune system. The discovery not only helps explain a little-understood aspect of myeloma biology, but also suggests a new angle of attack on the disease. Researchers found that compounds that alight on specific sites on pDCs restore the cells' original disease-fighting character and remove a trigger of myeloma cell growth.

"Our study found an unusually large number of pDCs in the bone marrow of multiple myeloma patients," says Dharminder Chauhan, JD, PhD, of Dana-Farber, who co-led the study with Ajita Singh, PhD. "pDCs are known to be immune system 'effector' cells - the first responders of the body's attack on disease. But why are they present in such abundance in myeloma patients' marrow?"

The focus on immune system cells exemplifies a new approach to the study of multiple myeloma, a cancer of bone marrow tissue that, despite numerous treatment advances in recent years, remains incurable.

Diagnosed in 15,000 Americans a year, it accounts for just 2 percent of cancer-related deaths, but is the fourth fastest-growing cancer in terms of mortality and is one of the top 10 causes of death in African-Americans. The disease's ability to resist even the latest drugs has prompted scientists to look more closely at the basic biology of the disease, particularly the interactions between myeloma cells and their cellular neighbors.

In the current study, Chauhan and his colleagues zeroed in on those interactions in experiments involving laboratory-grown samples of myeloma cells and animals with the disease. They found that when pDCs latch onto myeloma cells, a mutual release of proteins affects both sets of cells. In myeloma cells, these proteins cause a spurt of growth. In the pDCs, the effect is something like that of a police officer bribed to join a gang of hoodlums. The cells abandon their role as immune system sentinels and become the protectors of myeloma cells.

"This is the first time that immune system cells have been found to be converted to another function," says Chauhan, who is also a principal associate in medicine at Harvard Medical School. Investigators don't yet know how the conversion occurs, but they suspect the proteins cause a different set of genes to be activated within the pDCs.

Encouragingly, it appears possible to awaken errant pDCs to their proper duty. Researchers found that when compounds known as CpG ODNs (cytosine phosphate guanine oligodeoxynucleotides) attach to key receptors on the surface of pDCs, the cells resume their normal immune system function and stop spurring myeloma cell growth. Some CpG ODNs are already in clinical trials for other forms of cancer, and Chauhan and his colleagues hope to begin trials of the compounds in myeloma patients soon.

"In addition to drugs that destroy cancer cells themselves, treatments for

multiple myeloma may also agents that target the immune system's role in the disease," Chauhan says. "Our findings show the promise of this approach."

Adds the study's senior author, Kenneth Anderson, MD, of Dana-Farber, "This is a potential approach to the treatment of myeloma that is refractory to all current therapies, while increasing immune function and thereby decreasing infections in myeloma patients."

Source: Dana-Farber Cancer Institute