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Genetic regulator opens new avenues to AIDS, immune system research

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Researchers at Oregon State University and the California Institute of Technology have discovered that a genetic regulator which is critical to many life functions also plays a key role in the formation of "T cells," a type of white blood cell that's important in immune function.

The discovery, to be announced Friday in the journal *Science*, suggests that some types of immune function might be influenced by manipulation of this genetic regulator. This could be a target for drug development, and could open the door to new immune system-based therapies for everything from diseases of T cells, such as HIV/AIDS, to autoimmune disorders and allergies.

Other aspects of the research could be of interest to scientists trying to re-program cells to perform different functions, which is the basis of stem cell research.

The genetic regulator, or transcription factor, is called Ctip2, and it's also known as Bcl11b. It's a protein that controls gene "expression," or what aspects of a cell's genetic code will be turned on and which will be left silent. Discovered at OSU in 2000, Ctip2 has in recent years been found to be a master regulator of gene expression, controlling tissue formation in organs as diverse as tooth enamel, brain cells, skin, and T cells.

"Ctip2 is so important to various life functions that laboratory mice lacking this gene die within a few hours after birth," said Mark Leid, a professor and assistant dean in the OSU College of Pharmacy. "Ctip2 is

not expressed in every cell, but plays essential roles in several different organs. The new finding about its relationship to early events in T cell formation may be of substantial interest to immunologists and clinicians alike."

T cells are important players in what's called the "adaptive" immune system, or the ability of an organism to mount an attack against a new invader, fight it off and then provide full or partial immunity to it in the future.

Ctip2 helps regulate the complicated process that ends up creating T cells. Depending on the stage of development when it's knocked out, this can result either in T cells not being formed, or different kinds of cells being formed - something that would be of significant interest to researchers who are trying to re-program cells to perform different functions.

Part of what's remarkable about Ctip2, researchers say, is the range of seemingly separate yet critical functions it performs. Ctip2 is essential in the creation of teeth, the formation of skin, and T cells. In all of these cells and tissues, Ctip2 is involved in differentiation of one cell type into another, more mature cell. OSU researchers have also found that the amount of Ctip2 expressed by certain cancer cells is correlated with the aggressiveness of tumors, which may be helpful for diagnostic purposes.

Every cell in the human body, and that of plants and other animals, contains the entire "genome," or genetic blueprint of life of the particular organism. Research on genetic regulators has been of increasing interest in recent years because these proteins hold the key to which genes are expressed, instructing one cell to become a brain cell while another is directed to become a blood cell.

"I've always been in awe of how transcription factors direct complicated

events, such as development, in which mammals progress from a single, fertilized cell into a complex, three-dimensional organism in a relatively short period of time," Leid said. "It's just a beautifully choreographed dance, and timing is everything."

Ctip2 seems to be a very top-level regulator of development and differentiation in many different cell types, Leid said. It should be possible to develop drugs that decrease, increase or otherwise modify Ctip2 activity, and such drugs may be useful in the treatment of certain malignancies, such as leukemia, and skin cancers, he said.

Provided by Oregon State University