Why the immune system fails to kill HIV

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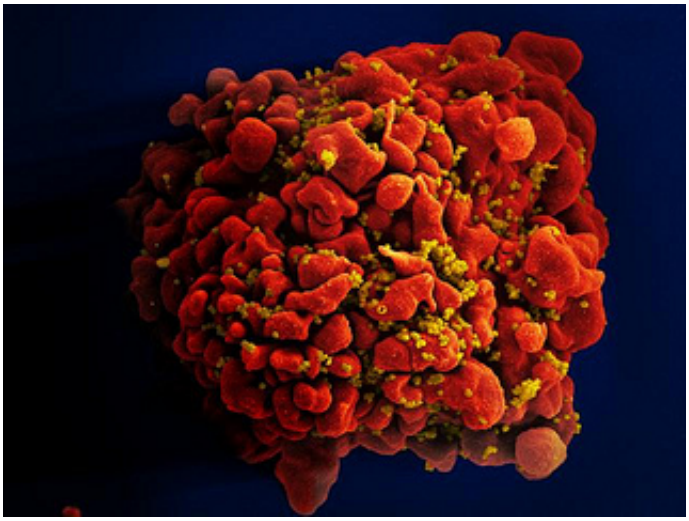

Scanning electron micrograph of an HIV-infected H9 T cell. Credit: NIAID

Our immune system contains CD8+ T cells which protect us from various diseases such as cancer and viruses. Some of them are specifically tasked with killing cells infected with the HIV virus – and researchers from Karolinska Institutet in Sweden, together with international colleagues, have for the first time identified a key explanation for why these cells are unsuccessful in their task. In simple terms, the immune system's ignition keys have not been turned all the way to the start position, which would enable the CD8+ T cells to kill the cells infected with HIV.

It has long been known that CD8+ T cells that are meant to target and kill the HIV virus lose important functions; they become exhausted and

cannot complete their task. In one study, published in the journal *PLOS Pathogens*, researchers have successfully shown at the molecular level what it is that weakens these important CD8+ T cells.

There are two transcription factors that are particularly important to CD8+ T cells. They are called T-bet and Eomes and work as ignition keys for the machinery of the immune system – they ensure that CD8+ T cells are correctly instructed to fight the specific disease. In simple terms, T-bet has the role of an instigator that induces CD8+ T cells to divide and mature. Eomes have a more regulatory role and are primarily active in building a memory against an infection that has completely healed, in order to be ready for a new episode of the infection.

Researchers have studied how T-bet and Eomes are expressed in a total of 64 HIV-infected people, the majority of whom were treated in the infection clinic at the Karolinska University Hospital and the sexual health clinic at the Stockholm South General Hospital. The study shows that the CD8+ T cells specifically targeting HIV-infected cells have a low expression of T-bet, but an increased expression of regulatory Eomes. This leads to CD8+ T cells that are maturing poorly and inhibit their ability to kill HIV-infected cells.

Unfortunately, this pattern of the transcription factors was present even when the participants' HIV was responding well to medication, in that the level of HIV virus sunk so low that it was not measurable in their blood.

"This probably explains why CD8+ T cells continue to function poorly despite long-term treatment with antiviral drugs. We have previously known this to be the case, though we have not known why", says Marcus Buggert, researcher at the Department of Laboratory Medicine at Karolinska Institutet.

The researchers hope to discover how the transcription factors' expression can be affected so that T-bet can be increased in patients with HIV. That would possibly give the immune system a chance of killing HIV-infected cells and thus making it easier to cure HIV infection.

"If we can get past this barrier and discover how to control the regulation of these transcription factors, this would open the door to creating a vaccine or cure for HIV. This could be one way of creating an effective immune response that is able to kill HIV-infected cells", says Annika Karlsson, senior research fellow in virology at the Department of Laboratory Medicine at Karolinska Institutet.

More information: "T-bet and Eomes are differentially linked to the exhausted phenotype of CD8+ T cells in HIV infection." Marcus Buggert, Johanna Tauriainen, Takuya Yamamoto, Juliet Frederiksen, Martin A. Ivarsson, Jakob Michaëlsson, Ole Lund, Bo Hejdeman, Marianne Jansson, Anders Sönnerborg, Richard A. Koup, Michael R. Betts, Annika C. Karlsson. *PLOS Pathogens*, online 17 July 2014, dx.plos.org/10.1371/journal.ppat.1004251

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