When Good Guys Go Bad
FoxO3a Mediating Apoptosis in HIV-positive T-Cells

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Abstract
Within every cell, DNA provides instructions needed to sustain life. DNA is used to make proteins which perform countless cellular functions. One example of a protein is FoxO3a, a transcription factor involved in regulating cell metabolism and apoptosis (cell death), among other processes. To perform these functions, FoxO3a binds to compacted chromatin and opens the DNA for access by other transcription factors and the transcriptional machinery. Because it can perform these functions, FoxO3a is known as a ‘pioneer’ transcription factor. The H3 helix of FoxO3a recognizes its cognate binding sequence within the DNA (GTAAACA). Once bound, the N and C termini wrap around the DNA, causing the DNA to unwind, while the two wings help to secure FoxO3a to the DNA.

Understanding the connection between FoxO3a and cell function enables researchers to explore potential therapies. For example, researchers are examining the potential role that FoxO3a may play in treating patients with HIV. FoxO3a has been suggested to regulate apoptotic genes in T cells, which are a vital part to the immune system. In healthy humans, T cells protect the body by killing abnormal or virus-infected cells. When a person contracts HIV, their T cells are attacked, and their immune defense is compromised. Inhibiting FoxO3a may prevent the up-regulation of the apoptotic pathway in T cells, thereby increasing the lifespan of the T cell slightly. Researchers hypothesize that inhibition of the apoptotic pathway may maintain the efficiency of the immune system for a short period of time and hopefully slow the progression of HIV.

Background
• AIDS has killed an estimated 25 million people since 1981. ¹
• 33 million people were infected with HIV/AIDS in 2007. ¹
• HIV is the virus that can lead to AIDS, and works by infecting T cells.
• T cells are part of the immune system which protects the body from infection, and infection of these cells triggers a cascade of events that ultimately leads to apoptosis (cell death). FOXO3a-induced apoptosis is good in most circumstances; however, not in the case of an HIV infection. As these T cells die, patients become more susceptible to infections. ²
• Down-regulation of FoxO3a has been shown to decrease apoptosis in memory T cells (the cells required for sustainable immune protection). ²
• These data suggest that down-regulating FOXO3a could allow T cells more time to fight HIV or other secondary infections. ²

Summary
• Down-regulation of FOXO3a decreases pro-apoptotic genes in T cells.
• These cells, often affected in HIV patients, have prolonged life spans resulting from FOXO3a’s inactivation or down-regulation.

Future Cures for HIV?
• Down-regulation of FOXO3a in HIV-positive individuals will allow for their T cells to survive and prevent the disease from developing into AIDS.
• T cells mature in the thymus and have receptors that can be directly targeted by specific proteins. Specific inhibitors of FoxO3a could be directly injected into the thymus, or targeted to the T-cells through these specific receptors.

Model of FoxO3a attached to DNA

Expressed genes

FasL
Bim-1

DNA
FoxO3a
Helix (FOXO3a binding site)

Apoptosis
Memory T Cell

HIV

When HIV infects FOXO3a within memory CD4+ T cells targets specific gene expressions, including FasL and Bim-1, both of which are involved in the apoptosis pathway. In HIV patients, down-regulation FOXO3a prolongs the life of memory T cells. A longer lifespan of memory T cells allows them to fight off intruding viruses. ³ & ⁴

FOXO3a
T CELLS

There is an inverse relationship between FOXO3a and T cells in HIV patients. As the FOXO3a is down regulated, longevity of memory T cells increases. ²

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