GENETICS

Schlafen 11 naturally blocks HIV

New research out of the University of California at San Diego has shown that the human protein schlafen 11 (encoded by *SLFN11*) inhibits HIV protein expression in a codon-dependent fashion. Expression of schlafen 11, which is part of a larger family of structurally unique proteins that are preferentially expressed in lymphoid tissues, is induced via the interferon regulatory factor 3 pathway. This pathway of the innate immune system is activated in response to pathogens, such as HIV and other viral particles.

The researchers leveraged the different schlafen 11 expression between two human embryonic kidney cell lines—HEK293 (which expresses *SLFN11*) and HEK293T (which does not express *SLFN11*)—to study how the gene and its corresponding protein affect viral progression. An additional cell line was produced whereby HEK293 cells were treated with short hairpin RNA against *SLFN11* to essentially knock out the gene (HEK293shRNA^{SLFN}). Infecting these cells with luciferase-tagged viruses resulted in comparable luciferase levels, regardless of whether HIV, murine stem cell virus (MSCV) or adeno-associated virus (AAV) was used. These results indicated that schlafen 11 does not affect the integration of the viral DNA into the host cell genome.

However, the resulting HIV titres of the cell lines after viral infection showed marked differences. The *SLFN11*-null cell lines had up to 15-fold higher HIV titres than the HEK293 cells. Furthermore, the levels of measured extracellular p24 protein (a component of the HIV capsid) and viral RNA closely mirrored the titre results. Combined, these findings suggest that schlafen 11 reduces the number of viral particles released from infected cells. Indeed, electron microscopy studies showed fewer virions in the cell cultures of *SLFN11*-positive cells than cells not expressing the gene.

The researchers then went on to investigate exactly how *SLFN11* and its gene product inhibit viral particle synthesis. They were able to demonstrate, using transfection techniques with various modified vectors, that protein synthesis is not shut down entirely by schlafen 11. Instead, the protein suppresses viral protein expression selectively by modulating translation-specific processes.

The next major step was to gain an understanding of how schlafen 11 selectively inhibited protein expression. “We used two viral vectors, one carrying the original HIV *Nef* gene (encoding negative regulatory factor) and another in which *Nef* was replaced with luciferase,” explained lead investigator Michael David to *Nature Reviews Urology*. “We observed that schlafen 11 inhibited the expression of *Nef*, but not luciferase. Thus, the inhibition had to be based on the intrinsic properties of the gene or transcript.” After excluding a number of possibilities, codon-bias emerged as one of the few options left. It seems that schlafen 11 exploits the viral codon preference for adenine-rich sequences to attenuate viral protein synthesis.

This ‘natural’ inhibition of HIV protein synthesis might go some way in explaining why some HIV-positive patients never experience high viral titres or symptoms of AIDS, even without medication. “Polymorphisms in *SLFN11* might contribute to the susceptibility of an individual to progress to AIDS,” David explained. “As such, variations in the *SLFN* family of genes might be useful in determining the risk of disease after HIV infection.” Indeed, one can envisage a future drug that elevates or activates *SLFN11* in HIV-infected individuals to help fight the virus. Additionally, screening at-risk individuals for the gene might help clinicians determine the likelihood of progression to AIDS and, accordingly, this knowledge could inform treatment. David and his team are currently working with several collaborators to determine whether polymorphisms in *SLFN11* correlate with clinical data.

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