Lethal reawakening

May 17 2016

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Retroviral DNAs integrate into host genomes, but their expression is normally repressed by cellular defense mechanisms. As an Ludwig-Maximilians-Universitaet (LMU) in Munich team now shows, when these measures fail, accumulation of viral proteins may trigger programmed cell death.

Mammalian DNAs contain large numbers of sequences that are derived

from retroviral genomes, which integrated into the germline of the host and were passed on to its descendants during the course of evolution. Normally these retroviral sequences are functionally disabled by epigenetic modification, thus ensuring that they cannot give rise to active viruses. However, if this silencing mechanism fails, expression of retroviral genes can disrupt the development of the host organism and may cause cancer. Researchers led by Gunnar Schotta at LMU's Biomedical Center have now looked at the consequences of such a breakdown of retrovirus silencing for the antibody-producing B cells of the immune system. Their findings are reported in the journal *Development*.

B lymphocytes form a central part of one of the two arms of the vertebrate immune system. An enzyme called Setdb1 is responsible for the specific repression of integrated retroviral gene sequences in B-cell genomes. It does so by adding an extra methyl (CH3-) group to one of the histone proteins associated with the viral DNAs in the B-cell's chromosomes. Schotta and his colleagues therefore asked what happens to B-cells in the absence of the protein. "When we generated mouse mutants that are unable to synthesize Setdb1, we found that the mutation disrupts B-cell development. The cells die at an early stage in the process, and no mature B-cells are produced," says Schotta.

Awash with retroviral proteins

In cells that cannot make Setdb1, it turns out, all the genes required for B-cell development function normally - but, in addition, the expression of integrated copies of a particular retroviral genome is strongly activated. "As we have shown, the sequences affected are coding sequences. In other words, they serve as blueprints for the synthesis of retroviral proteins. And these proteins are produced at very high levels in developing B cells," Schotta explains. "So we surmised that they are deleterious to the cells and account for the lack of mature B-cells in the

mutant mice."

The researchers went on to confirm this hypothesis. B cells are relatively small and, in comparison to many other cell types, their capacity for protein synthesis is quite limited. Further experiments revealed that the high-level expression of viral proteins in the mutant triggers the so-called unfolded protein response (UPR). This occurs when the rate of protein synthesis in a cell exceeds its capacity to fold them properly. Under these conditions, misfolded proteins accumulate in the endoplasmic reticulum (ER), an organelle that is involved in the synthesis, folding and dispatch of secretory proteins. The resulting ER stress induces the UPR, which initiates a process that reduces rates of synthesis and enhances rates of folding of proteins. If this fails to adequately relieve ER stress, the cell undergoes apoptosis (programmed cell death), as in the case of the mutant pro-B cells. "The production of a single specific retroviral protein is actually enough to activate the UPR," says Schotta, "and this is the first time anyone has shown how the activation of endogenous retroviral genes damages cells so badly that they are eliminated by apoptosis."

More information: Alessandra Pasquarella et al, Retrotransposon derepression leads to activation of the unfolded protein response and apoptosis in pro-B cells, *Development* (2016). DOI: 10.1242/dev.130203

Provided by Ludwig Maximilian University of Munich