RHEUMATOID ARTHRITIS

Lack of telomerase causes telomere shortening in RA

Telomere shortening, a chromosomal feature associated with cellular aging, is accelerated in immune cells from patients with rheumatoid arthritis (RA) compared with cells from healthy controls; however, the mechanisms and functional consequences of this finding were not well understood, until now. A paper published in *Proceedings of the National Academy of Sciences* shows that T cells in patients with RA are unable to upregulate expression of the enzyme telomerase, which makes these cells more susceptible to apoptosis.

“Telomeres are repetitive sequences at the ends of linear chromosomes that protect chromosomal ends from degradation and fusion, and thus are critical for chromosome integrity,” says Cornelia Weyand, the lead researcher on this paper. “Telomeres progressively shorten with each cell division, and thus have emerged as an excellent marker of the cell’s replicative history.”

Is the faster-than-normal rate of telomere shortening seen in patients with RA caused by increased rates of proliferation, or is it due to failures in appropriate telomere maintenance? To answer this question, the authors measured the activity of telomerase in naive T cells from patients with RA and from age-matched controls following T-cell receptor stimulation. “Telomerase is a reverse transcriptase that extends the 3’ ends of chromosomes,” says Weyand. “Here we show that RA T cells induce telomerase activity much less efficiently than healthy T cells do.” Interestingly, levels of telomerase were similarly reduced in T cells from newly diagnosed, untreated patients and from treated patients, regardless of disease duration and severity.

Next, the authors blocked the expression of human telomerase in primary human T cells to investigate the cellular effects of telomerase deficiency.

“Upon knockdown of telomerase activity, T cells become apoptosis-susceptible and die at higher rates than cells with intact telomerase activity,” Weyand explains. In addition, the clonal expansion of these cells was impaired in comparison with control cells. Subsequent overexpression of ectopic telomerase in RA T cells resulted in resistance to apoptosis and improved the rates of clonal expansion of these cells.

What are the clinical implications of this work? “By understanding how the T cell senses telomerase insufficiency or telomeric dysfunction and initiates the apoptotic machinery, we could disrupt excessive T cell death,” suggests Weyand. “This is an entirely new strategy for treating immune dysfunction in RA.”

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Original article Fujii, H. *et al.* Telomerase insufficiency in rheumatoid arthritis. *Proc. Natl Acad. Sci. USA* **106**, 4360–4365 (2009).