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WNT signaling and telomere capping can be mutually supportive: Potential therapeutic implications

Perturbation of telomere structure, including critical shortening, can cause telomere "uncapping", leading in turn to disruption of cell and tissue function. Lengthening by the enzyme telomerase is the primary mechanism by which the telomere shortening caused by genome replication and DNA damage is reversed. The consequences of telomere uncapping can be seen in human genetic diseases caused by partial loss of telomerase activity. An example is dyskeratosis congenita (DC), characterized by defects in tissues that depend most on telomerase, including those that naturally turnover rapidly (e.g. hematopoietic cells, GI epithelium) or divides following damage (e.g. lung and liver epithelium). Despite the need to maintain telomere length, even in normal humans telomerase levels are limited and thus telomeres shorten with age in most tissues, a strategy that has evolved evidently because it limits cancer progression. Recently we uncovered a novel positive feedback loop connecting telomere capping and the WNT signaling pathway in the intestinal stem cell niche. This pathway is used by cells to communicate with neighboring cells, particularly niche cells and the stem cells that they support. We leveraged this loop to rescue intestinal pathology via pharmacologic WNT stimulation in mice lacking telomerase (late generation Terc-/-) and in cultured human intestinal organoids derived from DC iPS cells. Remarkably, rescue involved improved telomere capping, demonstrating that capping can be influenced by extracellular factors and that it can involve length-independent mechanisms. However, WNT is also well established to upregulate expression of the catalytic and limiting component of telomerase, TERT, and thus WNT agonism can also enhance capping via telomere lengthening. Therefore WNT agonism might improve telomere capping by at least two mechanisms in diseases like DC. The evidence connecting telomeres and WNT signaling will be discussed, along with underlying mechanisms and recent efforts to use WNT and other pharmacologic approaches to rescue to the pulmonary epithelium of cultured DC human lung organoids. Finally, the possibility will be discussed that whereas enhancement of telomerase activity in younger individuals carries a cancer risk, such enhancement in individuals with DC, and perhaps in normally aged people, might have a net anti-cancer benefit.

Biography

Brad Johnson is a Professor of Pathology and Laboratory Medicine at the Perelman School of Medicine at the University of Pennsylvania, where he serves as Associate Director or the Penn Institute on Aging and Assistant Director of the Clinical Immunology Laboratory at the Hospital of the University of Pennsylvania. His research has focused for over twenty years on the basic mechanisms by which telomeres are maintained, and how telomere dysfunction impacts cell and tissue health.

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