Arch Bronconeumol. 2018;54(1):3–4

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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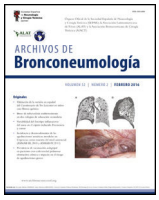

Editorial

Telomere Shortening in Idiopathic Pulmonary Fibrosis☆

Acortamiento de los telómeros en fibrosis pulmonar idiopática

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We are currently experiencing the rapid translation of a recent investigational advance into clinical practice: telomere testing and its implications in patients with pulmonary fibrosis. Idiopathic pulmonary fibrosis (IPF) is the most prevalent fibrosing interstitial disease (13–20/100 000 inhabitants) and the one with the worst prognosis.[1,2] The disease is defined as familial pulmonary fibrosis (FPF) when it occurs in 2 or more individuals from the same family,[1] and it is in this setting that the first studies have pointed to telomere alterations as a risk factor for pulmonary fibrosis.[3]

At the beginning of the 21st century, Selman et al. reported that the pathogenesis of pulmonary fibrosis was based on changes in tissue repair after alveolar damage; several profibrotic pathways and mediators prevent reepithelialization, perpetuating the damage and culminating in the invasion of the alveolar space by a proliferative matrix tissue that lacks respiratory functionality.[4,5] The regulation of some of these profibrotic mediators led to the first antifibrotic treatments capable of slowing disease progression.[2] However, we are as yet unable to stop this fatal degenerative progress, nor can the lung recover its reparative capacity to improve or cure the disease.[2,5] An understanding of why the tissue does not repair itself is essential if we are to prevent the perpetuation of the process. Recent studies in this area have pointed to accelerated aging and cellular reprogramming abnormalities as a source or cause of the reparative changes.[6] It is common knowledge that newborns regenerate, repair and restore damaged tissues to their original functional status, and that this ability reduces physiologically with age, to the point that a simple fracture in an elderly person is frequently associated with functional loss and even fatal complications. One of the mechanisms closely related with the physiological process of aging is progressive telomere shortening.[6] In diseases typically associated with accelerated aging and genetic instability due to premature telomere shortening, such as congenital dyskeratosis, pulmonary fibrosis develops spontaneously after the first decade of life.[7]

Telomeres are repeated sequences in the DNA and associated proteins (the shelterin complex) that are critical for the protection and stability of the internal sequences of the chromosomes: this function is called "capping".[6,7] Telomeres shorten in each cell division. Telomerase is a reverse transcriptase that carries its own RNA component and promotes correct chromosome end replication.[7] However, most human cells lack sufficient telomerase activity to maintain telomere size indefinitely, and the telomeres gradually shorten. When the telomeres shorten to a critical size, the cell cycle enters into permanent shutdown (senescence) or apoptosis.[7,8] Accelerated telomere shortening is associated with premature aging, abnormal tissue repair, and the resulting pathogenic consequences.[6,7] This dysfunction may be congenital due to genetic mutations, or acquired by epigenetic alterations, such as telomere methylation. In adult tissue, telomerase activity aimed at repairing tissue damage is expressed in germ cells and in stem cells.[8] In the last 10 years, the role of telomere size in the acquisition of pluripotency and somatic cell reprogramming has been underlined. This phenomenon would be of significance both in tissue embryogenesis, and later, in the reparative processes of cells and tissues.[6–10]

In IPF and FPF, mutations have been described in genes of the telomere protein complex, telomere subunits or regulatory proteins (TERT, TERC, DKC1, PARN, RTEL1, TINF1, OBFC1, NAF1) that contribute to telomere shortening and cell senescence by reducing telomere activity.[8–12] Exhaustion and decline of stem cells, both in the bronchial and alveolar epithelial stem cell niches, have been proposed as a contributing factor in altered regenerative capacity.[6–8] Telomere shortening is described in 25% of IPF patients and in over 50% of FPF patients, and contributes to increased epithelial apoptosis.[11] Patients with telomere shortening, particularly those with FPF, have a worse prognosis and more morbidity after transplantation.[9,10] It has recently been observed that the existence of telomere shortening is a factor for poor progress, irrespective of the radiological and histological pattern of the FPF.[9] However, the effect of telomere shortening on the development of the disease is still debated, and it has been indicated

☆ Please cite this article as: Molina-Molina M, Planas-Cerezales L, Perona R. Acortamiento de los telómeros en fibrosis pulmonar idiopática. Arch Bronconeumol. 2018;54:3–4.

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that telomere shortening is more of a catalyst than a direct cause of pulmonary fibrosis.[12] Le Saux et al. found that the induction of pulmonary fibrosis is greater in the presence of a TERT mutation, and that this effect could be inhibited in an animal model by inducing telomerase activity.[12] Gestelmir (GSE24-2), a dyskerin internal peptide containing 55 amino acids, induces telomerase activity, restores telomere length, and decreases aging in cells with telomere shortening in dyskeratosis.[13] Transfection of cells with GSE24.2 not only increases levels of hTERT RNA and hTR, but also modifies the metabolism of different anti-inflammatory and antifibrotic mediators.[13] Preliminary results show that gestelmir transfection of commercial fibrotic lung cell lines, modified by telomeric silencing, recovers telomerase activity and reduces oxidative stress.[13] In addition to these promising preclinical data, danazol, an androgenic analog, has been shown to inhibit telomere shortening in patients with different diseases associated with this alteration.[14] However, the data in pulmonary fibrosis are not conclusive, so it cannot be recommended for use until specifically designed studied have been conducted.

The study of telomere shortening in IPF, then, contributes not only predictive data on progress (biomarker), but also anticipates possible complications associated with transplantation, and represents a future therapeutic target for a subset of patients (precision medicine). For this reason, it provides useful non-invasive clinical information in many cases, primarily young IPF and FPG patients. However, this new knowledge is generating more questions than answers: Why do not all individuals with telomere shortening develop the disease? What determines the variability of the prognosis? What lung biology is associated with telomere shortening? What are the implications of having long telomeres? How does patient management vary? What about family members? Answering these and other questions with new research studies and international consensus will be of particular importance for the future clinical application of these advances in IPF and other fibrosing lung diseases.[15]

Funding

PI15/00710 and PI14/01595 ISCIII-FEDER Funds.

Conflict of Interests

Maria Molina-Molina has received grants from Boeringher Ing., Roche, Intermune, Glaxo SMK, Chiesi, Astra-Zeneca, Esteve, and BRN. The other authors have no conflict of interests.

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