EDITORIAL (SEE TENTOLOURIS ET AL., P. 2909)

Pathogenetic Loop Between Diabetes and Cell Senescence

Cell senescence has recently been postulated as an important cause/consequence of type 2 diabetes and its complications. Cellular senescence is defined as a limited ability of human cells to divide, and it becomes evident through phenotypic changes in morphology, gene expression, and function (1). It has long been known that genomic instability, a hallmark of premature aging disorders such as in the Werner syndrome, is associated with type 2 diabetes (2), and, recently, great attention has been paid to the potential impact of vascular cellular senescence on diabetes by means of the study on endothelial progenitor cells (EPCs). EPCs were discovered in 1997. They are derived from bone marrow and are mobilized to the peripheral circulation in response to different stimuli. Defined as circulating immature cells that contribute to vascular homeostasis and compensatory angiogenesis (3), EPCs are able to regenerate injured endothelium, accelerate re-endothelization, and limit the formation of atherosclerotic lesions. Their identification has prompted an explosion of interest regarding their role in the pathogenesis of micro- and macrovascular diseases. Different studies have demonstrated that EPCs are impaired in diabetic subjects and that high glucose levels appear to be the most important cause of enhanced EPCs senescence (4). Senescence leads to the impairment of proliferative activity and may have an important causative role in the development and progression of diabetes complications. The telomere hypothesis is a widely accepted explanation of the occurrence of senescence. In particular, telomeres are repetitive G-rich tandem DNA sequences and specialized proteins at the ends of eukaryotic chromosomes, and their length shortens as a function of cellular division. Short telomere length has been hypothesized to trigger the onset of senescence (5). Telomeres contribute to the maintenance of genome stability and integrity. They are necessary for successful DNA replication and extended proliferative life span both in cultured cells and in the whole organism (6). Telomere dysfunction has also been considered an important factor in the pathogenesis of atherosclerosis, hypertension, diabetes (7,8), and vascular aging (9). There is an ongoing debate whether oxidative DNA damage is one of the main causes leading to telomeric DNA damage and accelerated telomere shortening at cell division, as well as to senescent phenotypes in multiple cell types, such as endothelial and monocyte-macrophage cells, in type 2 diabetes (10,11). In support of this hypothesis, it has been found that nitric oxide (NO) can prevent endothelial senescence. In particular, the ingestion of NO-boosting substances (i.e., L-arginine, L-citrulline, and antioxidants) has been demonstrated to delay endothelial senescence under high glucose conditions (12). In this issue of *Diabetes Care*, Tentolouris et al. (13) report that in patients with microalbuminuria, telomere length was shorter than in those without microalbuminuria. The novelty of this study is the demonstration, for the first time, that type 2 diabetic patients with microalbuminuria have shorter telomere length than diabetic individuals without this complication, with a large difference of 590 bp between microalbuminuria-positive and microalbuminuria-negative subjects, implying a profound gap between biological and chronological age of the two groups. Previous publications have hypothesized that increased renal oxidative DNA damage in type 2 diabetes is associated with telomere damage and attrition. In particular, it has been suggested that DNA oxidation favors early expression of a renal phenotype of progressive glomerular cell senescence and proteinuria associated with accelerated endothelial and vascular cell senescence and atherogenesis (10). This hypothesis is supported by evidences that a biomarker of oxidative DNA damage, the 8-hydroxydeoxyguanosine, is more excreted in albuminuric than in normoalbuminuric diabetic patients (14) and that plasma 8-hydroxydeoxyguanosine is related to enhanced diabetic nephropathy (15). The findings of Tentolouris et al. also lead the authors to hypothesize that arterial stiffness, found in patients with microalbuminuria, may be due to the more pronounced "aging" of these patients.

Interesting findings are also emerging about the possible pathogenetic role of telomere shortening in inducing diabetes. It has recently been published that telomere shortening is present even at the stage of impaired glucose tolerance and may represent a nontraditional risk factor of diabetes (16). Progressive pancreatic β-cell senescence and failure have been highlighted as early features of type 2 diabetes (17). β-Cell telomere shortening has been demonstrated to predict the risk of β-cell growth arrest and senescence in human adult islet cell cultures (18).

The study of Tentolouris et al. does not explain the inner mechanisms responsible for the short telomere length in microalbuminuric patients, and further studies may be useful to clarify the causes of this relationship. However, it surely arouses scientific interest to verify, as stated by Tenolouris et al., "the links between WBC telomere length and diseases of aging". In fact, as mentioned above, cell senescence could be both a cause and a consequence of diabetes and its complications.

To date, solutions or therapies that may reverse this process can only be hypothesized. Even if cell-based models need to be translated into valid therapeutic strategies, potential therapeutic areas in this field are emerging. For instance, chemopreventive compounds that can decrease cell aldehyde load may counter some of the consequences of carbonyl stress (19), while a "causal" antioxidant therapy also deserves attention (20).

In conclusion, breaking the loop between diabetes and cell senescence by new defense methods against DNA oxidative damage seems to be an interesting path to explore for prevention of diabetes complications.

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