Autophagy: a two-edged sword in diabetes mellitus

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A fragility fracture is a serious complication in patients with diabetes mellitus as a result of hyperglycaemia, insulin resistance and the production of AGEs (advanced glycation end-products). In their paper published in the Biochemical Journal, Bartolomé et al. identified a role for autophagy in the differentiation, function and survival of osteoblastic cells in a high-glucose environment, and they also demonstrated that osteoblastic cell survival was limited by chemical and genetic inhibition of autophagy. These novel findings show the possibility of investigating a therapeutic strategy of maintaining autophagy in osteoblasts to lead to the prevention of diabetes-related osteopaenia. Autophagy is one of the common functions for maintaining cellular health, and the regulation of autophagy that is perturbed by diabetes mellitus may induce improvement of cellular functions not only for diabetes-related osteopaenia, but also for other systemic complications. However, systemic activation of autophagy may not always induce beneficial effects for non-targeted healthy cells, and autophagy should be controlled at a proper level at each disease stage in each target organ.

READERS’ CHOICE

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A fragility fracture is a serious complication in patients with diabetes mellitus. It induces impairment of activities of daily living, quality of life and survival in the affected population. The risk of fragility fractures increases not only in diabetes mellitus (Type 1 and Type 2), but also in rheumatoid arthritis, inflammatory bowel disease, coeliac disease, cystic fibrosis, hyperthyroidism and kidney disease [1]. In diabetes mellitus, hyperglycaemia, insulin resistance and the production of AGEs (advanced glycation end-products) induce a decrease in bone mineral density and reduce bone quality [2,3]. The mechanism of fragility fracture in patients with diabetes mellitus is not completely understood.

In volume 455 (part 3) of the Biochemical Journal, Bartolomé et al. [4] describe the protective role of autophagy for the differentiation, function and survival of osteoblastic cells in a high-glucose environment. Osteoblastic cell survival is impaired by high glucose and worsened by chemical and genetic inhibition of autophagy. These novel findings show the possibility of investigating the therapeutic strategy of maintaining autophagy in osteoblasts to lead to the prevention of diabetes-related osteopaenia. The role of autophagy in the interaction between osteoblasts and osteoclasts in diabetes-related osteopaenia is still unclear; however, the intervention to autophagy may provide beneficial strategies not only for diabetes mellitus, but also for other systemic diseases and complications.

To prevent fragility fractures, intervention should focus on each systemic disease-specific factor and common pathway, such as autophagy in bone cells. In diabetic mellitus, high-glucose exposure induced the production of ROS (reactive oxygen species) as well as protein oxidation, and there was a decrease in survival of osteoblastic cells [4]. One study describes how the AGEs that are formed after prolonged hyperglycaemia inhibit osteoblastic differentiation and increase apoptosis even without a high-glucose environment [5]. Advanced chronic kidney disease increases the accumulation of uraemic toxins, such as indoxyl sulfate and p-cresyl sulfate, which induce increases in free radical production and ROS from osteoblastic cells [6,7]. These reports suggest that various disease-related factors react with osteoblasts directly and induce cellular dysfunction, which leads to a reduction in bone quality. The treatment of systemic disease induces improvement of osteoblastic cellular function. In a uraemic environment, a reduction in serum indoxyl sulfate in rats with oral charcoal adsorbent shows improvement of kidney-damage-induced bone disorders with improvement of bone storage modulus and bone histomorphometry, such as an increase in the number of osteoblasts [8].

Autophagy is an important factor in maintaining cellular function and viability, and is related to cellular/organ damage owing to malnutrition, hypoxia, infection and various systemic diseases. Impairment of autophagy by knockdown of Atg7, an autophagy-related protein, in MC3T3-E1 cells induced cell dysfunction and inhibited osteoblast differentiation in a high-glucose environment [4]. Ablation of FIP200 [200 kDa FAK (focal adhesion kinase) family-interacting protein] also impairs autophagy in osteoblasts, which leads to terminal differentiation as well as nodule formation in vitro and leads to osteopaenia in vivo [9].

The regulation of autophagy that is perturbed by diabetes mellitus in all cell types may induce dramatic benefits not only for diabetes-related osteopaenia, but also for other systemic complications (Figure 1). Diabetes mellitus is characterized by insulin resistance and failure of pancreatic β-cells to produce insulin. The aggregation of ubiquitinated protein is increased in pancreatic β-cells during oxidative-stress-associated hyperglycaemia and is regulated by autophagy [10]. Pancreatic β-cell-specific Atg7-knockout mice show impairment of autophagy, and induced hyperglycaemia, glucose intolerance and hypoinsulinaemia [11]. The pathophysiology of some diabetes-related complications is also related to autophagy [12–14]. In kidneys, podocytes exhibit an unusually high level of autophagy as compared with inner medullary collecting duct cells [15]. Podocyte-specific deletion of Atg5 induced accumulation of oxidized and ubiquitinated proteins, and ER (endoplasmic

Abbreviations used: AGE, advanced glycation end-product; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species.

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reticulum) stress, which leads to late-onset glomerulosclerosis in aging mice [15]. Also, mTOR (mammalian target of rapamycin), a major suppressant of autophagy, in podocytes is activated in human diabetic nephropathy, and tightly balanced mTOR activity requires podocyte homoeostasis in diabetic nephropathy [16]. These reports suggest that a high level of autophagy is needed to maintain podocyte function, and the inadequate balance of autophagy is related to diabetic nephropathy. In cardiovascular disorders, macrophage foam cell formation is a hallmark of progressive atherosclerosis in patients with diabetes mellitus, obesity and so forth. Deficiency of Wip1 phosphatase, a negative regulator of Atm-dependent signalling, inhibits the progression of atherosclerosis in apolipoprotein E-knockout mice. This inhibitory effect is due to resistance of macrophage foam cell formation through up-regulation of autophagy [17]. In addition, macrophage-specific Atg5-knockout mice show increased atherosclerotic plaque formation, with an increase in both apoptosis and oxidative stress, and decreased efferocytosis [18]. These reports suggest that the control of autophagy in macrophages is crucial for determining macrophage pro-inflammatory and anti-inflammatory phenotypes, and for regulating the progression of atherosclerosis. Thus the impairment of autophagy in all cells is thought to play an important role in the onset and progress of diabetes mellitus and its complications, and the regulation of autophagy is a therapeutic target. Bartolomé et al. [4] reported that it is possible to maintain autophagy with treatments that lead to the improvement of osteoblastic cellular function under high-glucose situations. Furthermore, the activation of autophagy in dysfunctional osteoblasts may improve diabetes-related osteopaenia. Systemic intervention for autophagy will also have potential for the treatment of not only bone disorders, but also other complications, such as retinopathy, neuropathy, nephropathy and cardiovascular disease in patients with diabetes mellitus.

However, systemic activation of autophagy may not always induce beneficial effects for non-targeted healthy cells, and activation or inactivation of autophagy may need to be selected according to the disease situation. In fact, genetic deletion of mTOR in mouse podocytes induced glomerulosclerosis; however, mTOR activation is found in the glomerulus in diabetic nephropathy [16]. Furthermore, genetically reducing the mTOR copy number in podocytes prevented glomerulosclerosis and significantly ameliorated the progression of glomerular disease in diabetic nephropathy [16]. These results suggest that autophagy should be controlled at a proper level at each disease stage in each target organ. The mechanism and regulation of autophagy may be different in detail in each cell type [19], and the target for organ-specific regulation of autophagy will become a realistic intervention. We need to understand much more specifically the characteristics of the autophagy induced by disease-specific disorders in each cell and organ on the basis of further studies.

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