**SIRTing out the link between autophagy and ageing**

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Population-based studies of chronic kidney disease (CKD) paint a dismal picture. A recently conducted overview of 26 different studies of diverse populations concluded that the median prevalence of CKD was 7.2% in persons aged 30 years and older; in those aged 64 and older, the prevalence ranged from 23.4 to 35.8% [1]. In conglomerate, these data indicate not only the high prevalence of CKD in the general population but also emphasize the sharp increase in CKD among the ageing population—truly a major health care problem.

Ageing affects most organs and organ systems, including the kidney [2]. Various theories of ageing have crystallized into one view, the mitochondrial theory, that postulates accumulated abnormalities in the respiratory chain which result in overproduction of reactive oxygen species (ROS). The mitochondrial ROS theory of ageing has produced, however, controversial findings [rev in 3,4]. More recently, two seemingly independent theories of ageing have emerged: (i) the decline in sirtuin expression and/or activity and (ii) the reduction in autophagy. Support is growing for sirtuin-1 (SIRT1) and autophagy playing a critical role in this process.

Identification of the silent information regulator 2 (Sir2) in yeast [5] and a recent demonstration of its role in delaying ageing in *Saccharomyces cerevisiae* [6] have ignited interest in the role of members of this family in ageing-related processes. Seven mammalian homologues of this National Institutes of Health (NAD)-dependent deacetylase have been identified with SIRT1 and 2 expressed in the cytosol and nucleus, SIRT3–5 being mitochondrial proteins and SIRT6 and 7 expressed in the nucleus [7]. It has been demonstrated that SIRT1, the best studied of all, exerts pleiotropic actions in regulating diverse cell functions and responses to stressors, as depicted in Figure 1. It has been shown that activation of SIRT1 with resveratrol extends life span in mice fed high-caloric diet [8]. Similar effect can be achieved by activation of autophagy using mammalian target of rapamycin (mTOR) inhibitor rapamycin [9].

Autophagy is a physiological process executing the degradation of aberrant proteins and organelles, thus generating nutrients and maintaining survival, which is especially relevant to calorie restriction-induced autophagy. When overactive, this process accounts for type 2 caspase-independent cell death. In ageing, however, autophagy is repressed due to the deficiency in at least one of the key lysosomal membrane proteins, lysosome-associated protein 2A (LAMP-2A), and its restoration leads to a rejuvenated phenotype, as has been shown in hepatocytes [10]. Amino acids inhibit autophagy and their lack in the perfusate induces it [11]. Amino acids stimulate TOR and rapamycin inhibits it and induces autophagy [12].

An apparent link exists between the two latter hypotheses of ageing, SIRT1 and autophagy. Overexpression of SIRT1 has been shown to induce autophagy under normal conditions and during calorie restriction [13]. SIRT1/−/− neonate mouse show increased levels of p62, an in vivo marker of impaired autophagy [11]. These mice resemble Atg5−/− mice in that they display accumulation of abnormal mitochondria and exhibit early mortality [14]. Since induction of SIRT1 likely mimics caloric restriction to enhance autophagy, thus promoting degradation of damaged proteins and organelles [4], it appears that all three theories are interwoven through a process of mitochondrial degradation termed mitophagy. BNIP3L (NIX) is required for selective sequestration of mitochondria—mitophagy [15]. However, various diseases are associated with reduced levels and/or activity of SIRT1. For instance, Sun *et al.* [16] demonstrated that SIRT1 is downregulated in insulin-resistant tissues and that knockdown of SIRT1 alone induces insulin resistance (via repression of PTP1B).
How do these new findings pertain to the kidney? Does this organ age in accord with the above theories? In the April issue of the Journal of Clinical Investigation, three papers address this problem and attempt to unravel molecular mechanisms of kidney ageing.

The paper by Hartleben et al. [17] identifies glomerular podocytes as sites of ‘an unusually high level of constitutive autophagy’. Inhibition of autophagy in mice lacking one of the autophagosomal genes, Atg5, is accompanied by the accumulation of oxidatively modified proteins, reduction in protein ubiquitination, ER stress and proteinuria, as well as increased susceptibility to models of glomerular diseases in ageing mice. Interestingly, proteinuric diseases in mice and men were found to be associated with enhanced autophagy, perhaps, as a means to counteract the developing podocytopathy. The authors conclude that autophagy plays a protective role against podocyte ageing and injury. Unfortunately, no information on the expression of SIRT1 under these conditions has been provided. These data could potentially shed light on the early observation of podocytopathy as a leading abnormality accumulating with age in Milan normotensive rats [18].

The study by Kume et al. [19] pursues the mitochondrial ROS hypothesis of ageing. As a means to reduce mitochondrialopathy and stimulate SIRT1, investigators fed mice from 1 to 2 years of age with a calorie-restricted diet. This increased SIRT1 expression in the aged kidney and attenuated mitochondrial and renal injury. The authors demonstrate that these beneficial effects were due to deacetylation of forkhead box O3 (FoxO3) and activation of autophagic disposal of damaged mitochondria—mitophagy. It remains unclear, however, whether the observed benefit of a calorie-restricted diet taken for one-half of animals’ life was due to a reduction in mitochondrial ROS, activation of SIRT1 (or other sirtuins) with FoxO3-induced resistance to stress, and/or mitophagy— and which of these elements played a dominant role or whether they all are interconnected.

The study by He et al. [20] used a different approach to activate SIRT1, which they found to be abundantly expressed in mouse medullary interstitial cells where it increases cell resistance to oxidative stress. Deficiency of SIRT1 (SIRT1+/− mice) was associated with increased apoptosis and fibrosis after unilateral ureteral obstruction (U OU), whereas its activation in wild-type mice reduced apoptotic and fibrotic sequelae of UOO. In addition, SIRT1 deficiency curtailed COX2 induction in oxidatively stressed medullary interstitial cells, whereas exogenous PGE2 reduced apoptosis in stressed SIRT1-deficient cells. These data not only support the idea that SIRT1 serves as a protective function but also identify one of its targets as COX2. It remains to be established whether this effect of SIRT1 is due to its deacetylation of COX2 or is mediated via FoxO or other established targets of SIRT1.

Taken together, these studies give credence to the view that SIRT1 and its target proteins play an important renoprotective role, that it is accomplished by stimulation of autophagy/mitophagy, FoxO3 and COX2, among other potential mechanisms, and that deficiency of this mechanism(s) may be responsible for age-related decline in renal function and susceptibility to renal diseases. All the data appear to indicate that enhancing expression/activity of SIRT1 should have a therapeutic effect. While it is quite possible, there are several caveats related to potentially undesirable consequences of overactivation of SIRT1 and even cases describing potential benefits of inhibiting SIRT1 that need to be kept in mind.

Two inhibitors of SIRT1, sirtinol and splitomycin, have been found to induce senescence in tumour cells. This is associated with decreased expression of p53 and p-Rb, and G1 cell cycle arrest [21]. These data raise the question whether activation of SIRT1 can inadvertently promote
growth of silent tumours. There is also a possibility that the overactive SIRT1 system may lead to such upregulation of autophagic process that it would result in caspase-independent type 2 cell death. In addition, inhibition of SIRT1 with nicotinamide has been shown to protect neurons by reducing IGF-I/IRS-2/Ras/ERK1/2 signalling [22].

Finally, the findings reported herein may be pertinent not only to aged animals but also to young animals with chronic (kidney) diseases, which are prone to develop the stress-induced premature senescence [23–25]. It has been argued that some chronic diseases have the ability to vastly accelerate development of cell senescence, thus explaining the term ‘premature senescence’. It is not excluded that components of the axis SIRT1-autophagy-mitochondriopathy play a critical role in maintenance and progression of CKDs not only in aged but also in young individuals, thus mimicking senescence; however, the proof of this concept is still in the making.

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References


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