Commentary

Linking Klotho, Nrf2, MAP kinases and aging

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Oxidative damage of DNA, proteins, lipids and other molecules is one of the oldest mechanisms proposed to explain the phenomenon of aging [1, 2]. Reactive oxygen species (ROS) are generated in the mitchondria as by-products of normal aerobic respiration and in the cytosol by oxidases such as NADPH oxidase. It has been proposed that a decline in mitochondrial function leads to aging because of higher ROS production and increased damage to macromolecules [1]. This is debatable, however, because age-dependent mitochondrial DNA mutations can promote aging without causing increased ROS production [2]. High ROS levels can also regulate signaling via the stress activated-kinases, p38 and JNK. These pathways are often activated in aged tissues and contribute to the inflammation, apoptosis and senescence that is associated with old age. For example, JNK is activated in the liver of old rats and p38 is activated in the liver and brain of old rats as well as in the liver of old mice [3, 4].

In the September issue of Aging, C-C Hseih et al. report that the p38 kinase is activated in Klotho -/- mice and suppressed by Klotho overexpression [5]. This is dependent on the oxidation and dissociation of Ask-1 bound thioredoxin to generate the active Ask1-signalosome which, as previously shown, is an activator of p38 [6]. Klotho overexpressing mice live longer and are characterized by their resistance to oxidative stress [7]. Previous studies by C-C Hseih et al. have shown that the ASK1-signalosome-p38 pathway is suppressed in the long-lived and stress-resistant Ames and Snell dwarf mice [6, 8]. The current study demonstrates that a similar suppression of p38 signaling occurs in Klotho overexpressing cells and provides further evidence that oxidative stress, p38 activity and lifespan are closely linked.

Interestingly, this study also reveals that the stress-protective transcription factor Nrf2 localizes to the nucleus in Klotho overexpressing cells. Nrf2 is activated by oxidative stress and enhances transcription of genes containing an antioxidant response element (ARE). It is also believed to play an important role in some of the protective effects caused by caloric restriction and by GH/IGF-I deficiencies [9, 10]. Also, thioredoxin which is an inhibitor of Ask1, is a target of Nrf2 [11]. This implies that Nrf2 can regulate the expression of thioredoxin in Klotho mice thereby inhibiting the Ask1-signalosome-p38 pathway. Thus it is possible that the beneficial effects of Klotho are mediated, at least partially, by inactivation of p38 signaling.

The premature aging phenotype of Klotho -/- mice has been attributed to the absence of Klotho mediated suppression of the Insulin/IGF-I pathway [7, 12]. Klotho can activate the transcription factor FOXO, causing up-regulation of the mitochondrial MnSOD [7]. Because many of these cellular phenotypes are also promoted by reduced IGF-I signaling, the new study by C-C Hseih et al. not only confirms the major overlap between the pro-aging effects of Klotho -/- and IGF-I but also adds new players that can help identify common downstream anti-aging mechanisms.

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