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Title: SIRT6-induced activation of autophagy inhibits CSE-induced bronchial epithelial cell senescence

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Body: Introduction: Senescence is implicated in the pathogenesis of COPD, and cigarette smoke (CS) induces cellular senescence. SIRT6, a class III histone deacetylase (HDAC), has been demonstrated to antagonize cellular senescence, through the attenuation of IGF-Akt singaling. Autophagy is also regulated by IGF-Akt signaling through the mammalian target of rapamycin (mTOR). Autophagy plays a regulatory role in cellular senescence by eliminating damaged proteins, but a role for SIRT6 in autophagy activation has not been shown. Hence, we investigated the regulatory role for SIRT6 in autophagy activation in terms of CS-induced cellular senescence. Methods: Using human bronchial epithelial cells (HBEC), senescence associated beta-galactosidase staining and western blotting of p21 were performed to evaluate senescence. SIRT6 expression vector and siRNA were transfected into HBEC using the Neon® Transfection System. To characterize autophagy, western blotting for LC3 and p62 were performed. Autophagy was inhibited by knock down of LC3 and ATG5 by siRNA transfection. Results: CS extract (CSE)-induced HBEC senescence was inhibited by SIRT6 overexpression, while SIRT6 knock down and mutant SIRT6 (H133Y) without HDAC activity for H3K9 increased HBEC senescence. SIRT6 overexpression increased autophagy activation via attenuation of IGF-Akt-mTOR siginaling. Conversely, SIRT6 knock down and mutant SIRT6 (H133Y) inhibited autophagy activation. Autophagy inhibition attenuated the anti-senescent effect of SIRT6 overexpression. Conclusion: Deacetylation mediated by SIRT6 is involved in CSE-induced HBEC senescence via autophagy regulation, which can be attributed to attenuation of IGF-Akt-mTOR siginaling.