Editorial

Potential impact of oxidative stress induced growth inhibitor 1 (OSGIN1) on airway epithelial cell autophagy in chronic obstructive pulmonary disease (COPD)

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Provenance: This is an invited Editorial commissioned by Section Editor Dr. Xu-Guang Guo (Division of Clinical Microbiology, Department of Clinical Laboratory Medicine, the Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Wang G, Zhou H, Strulovici-Bare Y, *et al.* Role of OSGIN1 in mediating smoking-induced autophagy in the human airway epithelium. Autophagy 2017;13:1205-20.

Submitted Sep 26, 2017. Accepted for publication Oct 26, 2017.
doi: 10.21037/jtd.2017.10.153
View this article at: http://dx.doi.org/10.21037/jtd.2017.10.153

In a recent study published in the journal *Autophagy*, Wang and colleagues identified *OSGIN1*, which encodes OSGIN1, as a novel smoke-inducible gene in the airway epithelium (1). The authors reported significant up-regulation of *OSGIN1* mRNA in airway epithelial cells isolated from healthy smokers, compared to those from healthy non-smokers. Moreover, they demonstrated dose and time-dependent expression of *OSGIN1* in primary human basal airway epithelial cells exposed to cigarette-smoke extract (CSE) *in vitro*. These findings raise the intriguing possibility that OSGIN1 may play a role in smoking-related lung diseases, such as chronic obstructive pulmonary disease (COPD).

OSGIN1, also known as OKL38 and bone marrow stromal cell-derived growth inhibitor (BDGI), was first discovered in 2001 (2). It is a transcriptional target of the tumour suppressor p53 and directly interacts with p53 to regulate mitochondrial function (3). Accumulating evidence also indicates that *OSGIN1* is an oxidative stress response gene, and a transcriptional target of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a transcription factor that regulates anti-oxidant and cytoprotective cellular responses (4-6). Wang and colleagues showed that CSE-induced *OSGIN1* mRNA expression in primary human basal airway epithelial cells is associated with a concomitant increase in Nrf2-dependent genes, such as *NQO1* and *HMOX1*. Thus, it is possible that smoke-induced *OSGIN1* expression occurs in an Nrf2-dependent manner, although this remains to be investigated.

Macroautophagy, simply referred to as autophagy, is a fundamental homeostatic process that regulates cellular function in response to environmental cues. During the process of autophagy, double-membraned vesicles known as autophagosomes sequester compromised cellular components such as damaged organelles and aggregated proteins. Autophagosomes can then fuse with lysosomes, forming an autolysosome in which the engulfed components are degraded and recycled for re-use by the cell (7). Thus, by regenerating metabolites, autophagy preserves cellular homeostasis and promotes cell survival. Although it is clearly established that reactive oxygen species (ROS) are important mediators of autophagy, the mechanisms by which ROS regulate autophagic processes remain ill defined (8). Significantly, Wang and colleagues provide new evidence which suggests that OSGIN1 induces cellular oxidant stress and autophagy in airway epithelial cells. Using RNAseq data from primary human basal airway epithelial cells, they demonstrated strong positive genome-wide correlation between *OSGIN1* and many classical autophagy-related genes. Moreover, when *OSGIN1* was overexpressed in basal airway epithelial cells, a

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significant increase in the expression of two key autophagy-related genes, *MAP1LC3B* and *SQSTM1*, was observed. In addition, they demonstrated a dose and time-dependent effect of OSGIN1 on the formation of MAP1LC3B-positive puncta, thus providing morphological evidence of increased autophagosomes formation. Their data suggests that overexpression of *OSGIN1* also increases maturation of autophagosomes (fusion with lysosomes, or "flux", which ultimately results in degradation of the autophagosomes and their contents) in airway epithelial cells, suggesting true up-regulation of complete autophagy, rather than an increase in autophagosomes numbers due to defects in flux (9).

Almost 10 years ago now, Augustine Choi's group demonstrated that CSE induces autophagy in human airway epithelial cells *in vitro* (10,11). While these initial studies spurred intense interest into the role of autophagy in COPD pathogenesis, there is still no consistent understanding of the impact of smoke exposure on epithelial cell autophagy, nor how this drives the disease process in COPD. In some studies, it is reported that cigarette smoke accelerates the autophagic response, and that this in turn induces epithelial cell death. On the other hand, a number of studies report that smoke impairs epithelial cell autophagy (and mitophagy), and thereby results in the accumulation of defective autophagy complexes and cellular senescence (12). However, it is unlikely that epithelial cell autophagy proceeds in an unchecked manner under conditions of sustained oxidant stress (such as occurs in COPD). Notably, some investigators have shown that, while smoke exposure does induce autophagic signaling in airway epithelial cells, this is a transient response, and that prolonged exposure ultimately inhibits or impairs epithelial cell autophagy (13,14). One possible explanation for this is the concomitant activation of Nrf2 signaling, which is activated as an adaptive response to cellular oxidant stress.

Indeed, Zhu and colleagues showed that over-expression of Nrf2 inhibits CSE-induced autophagy in airway epithelial cells and, intriguingly, that SQSTM1/p62 is a down-stream effector of this response (15). Although SQSTM1/p62 was first identified as an autophagy adaptor protein, it also has a number of autophagy-independent functions. Significantly, it has been shown to activate the Nrf2-antioxidant response by sequestering Keap-1 through its KIR domain. It is also a transcriptional target of Nrf2, thus indicating the presence of a regulatory positive-feedback loop between Nrf2 and SQSTM1/p62. Of note, under nutrient rich conditions, SQSTM1/p62 also activates mTORC1, a major signaling molecule that acts to suppress autophagy (16). Thus in smoke-exposed epithelial cells, increased levels of ROS would be expected to increase Nrf2 signaling and SQSTM1/p62 expression, which in turn may activate mTORC1, and thereby suppress autophagy. This is consistent with the observation that over-expression of SQSTM1/p62 inhibits CSE-induced autophagy in airway epithelial cells (15). In the study by Wang and colleagues, stimulation of basal airway epithelial cells with CSE for 24 hours induced parallel increases in the expression of Nrf-2 dependent genes (*NQO1* and *HMOX1*), as well as OSGIN1 and SQSTM1/p62, at both the gene and protein level. Intriguingly, however, knockdown of *OSGIN1* using siRNA also led to increased expression of *MAP1LC3B* and *SQSTM1/p62* in cells exposed to CSE, suggesting a potentially complex dual role for OSGIN1 in the regulation of autophagy, inducing autophagy when overexpressed and negatively regulating CSE-induced SQSTM1/p62 expression.

Of note, Wang and colleagues examined OSGIN1 gene expression in small airway epithelial cells isolated from smokers with COPD. Surprisingly, levels of *OSGIN1* mRNA were similar to those detected in cells from 'healthy' smokers. It is important to note, however, that the COPD population from which cells were derived included people with varying levels of disease severity (GOLD stage I–IV), treatment naïve patients, and patients who were using β2-agonists, anti-cholinergic or inhaled corticosteroids. Thus, the heterogeneity in the population studied may have prevented any differences being observed, and certainly it will be of interest to determine whether OSGIN1 is differentially expressed in distinct endotypes and/or clinical phenotypes of COPD (17). Indeed, when cells from different patient groups (i.e., healthy non-smokers, healthy smokers, and smokers with COPD) were considered as one group, the authors could delineate sub-groups on the basis of low *vs.* high *OSGIN1* expression in small airway epithelial cells.

In COPD, there appears to be a decrease in Nrf2 expression and activity (18). Thus, given OSGIN1 is an Nrf2-dependent gene, it is conceivable that OSGIN1 expression and/or activity may also be decreased in certain patient sub-groups. Indeed, since OSGIN1 appears to negatively regulate SQSTM1/p62, it may be possible to speculate that in patients with low or insufficient levels of OSGIN1, cellular levels of SQSTM1/p62 are increased, leading to sustained activation of mTORC1 and autophagy suppression. However, reduced Nrf2 activity is not a universal finding in COPD, and is reported to be increased in some patients (19). Thus, alternatively, in patients with high levels of OSGIN1, suppression of SQSTM1/p62

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activity may enhance or accelerate the autophagic response. Further interrogation of the expression and function of Nrf2, OSGIN1 and SQSTM1/p62 in the airway epithelium of COPD subjects may help to clarify the role of autophagy in COPD pathogenesis.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Sukkar MB, Harris J. Potential impact of oxidative stress induced growth inhibitor 1 (OSGIN1) on airway epithelial cell autophagy in chronic obstructive pulmonary disease (COPD). J Thorac Dis 2017;9(12):4825-4827. doi: 10.21037/jtd.2017.10.153

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