Editorial

Cigarette smoke-induced autophagy: a deadly association?

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Cigarette smoke, and the mutagen agents it contains, is a universal conveyor of DNA alterations in the pulmonary airway cells, ultimately leading to cancer. In addition, the thousands xenobiotics and pro-oxidant agents contained in smoke participate in the pathophysiology of chronic obstructive pulmonary diseases (COPD) and emphysema by inducing cell death, chronic inflammation, and deregulated extracellular matrix degradation and remodeling. Adaptive cellular responses activated upon micro environmental stress, such as cigarette-smoke, are critical to prevent tissue damage and transformation. Acting at the cellular level, multiple (and usually evolutionary conserved) molecular circuitries are activated in response to stressful agents (1) with the aim to eliminate and reduce the intensity of the stressor (for example the activation of antioxidants circuitries, which will reduce the amount of reactive oxygen species); to promote cellular adaptation and metabolic reprogramming (which enables the cell to survive in the stressful microenvironment, for example in activating hypoxia-inducible genes to fuel glycolysis in case of hypoxia); to regulate the fate of the cell in activating both anti and pro apoptotic pathways, and whose net effect of these balancing processes will depend on the duration, the nature, and the intensity of the stress; and to engage communication networks with the cellular microenvironment through the release and secretion of inflammatory mediators (alarmins, chemokines, cytokines) that signal to the immune system that something wrong is going on. In parallel, secreted mediators of tissue remodeling act to promote tissue healing. A major issue in this kind of process is the resolution of the adaptive responses, which depends on the duration and the intensity of the stressor, because prolonged responses may become deleterious in promoting cell death, excessive inflammation and tissue remodeling. In addition, individual/genetic factors likely participate in these responses and their resolution (2).

Over the past few years, a growing body of experimentations provided evidence that autophagy is activated in response to cigarette-smoke-induced stress and in the pulmonary airways adaptation, and has been identified as a critical modulator of tissue damage (3). However, the molecular mechanisms driving autophagy in upon exposure to cigarette smoke are mostly unknown. Taking into account the multitude of biological functions of autophagy, it is reasonable to consider that this process is involved in the pathophysiology of smoke-induced pulmonary diseases. Recent experimental data provided evidence that autophagy increases mucociliary clearance and fosters COPD-associated cilia dysfunction (4), but in some stress context, promotes cells survival (5), reduces senescence of human bronchial epithelial cells (5), and suppress carcinogenesis (6). Macroautophagy (autophagy) is a homeostatic process that takes place in all eukaryotic cells, and involves the sequestration of cytoplasmic components in double-membraned autophagosomes, which subsequently fuse with lysosomes, where their cargoes are delivered for degradation and recycling (7). Autophagy is implicated

in numerous pathophysiological processes such as cancer, metabolic and neurodegenerative disorders, cardiovascular and pulmonary diseases, and in aging. Autophagy is a tightly regulated process, involving intracellular (for example energy scarcity) and extracellular (for example Toll-like receptors ligands) inducers.

The role of autophagy in cell viability is complex (8,9). In the mammalian system, cell death is often preceded or accompanied by autophagic vacuolization, a finding that initially led to the widespread belief that "autophagic cell death" would be mediated by autophagy. With the availability of genetic tools to block the autophagic machinery, it has become clear that autophagy constitutes an attempt of dying cells to adapt to lethal stress rather than a mechanism to execute a cell death program. However, many stress pathways sequentially elicit autophagy and apoptosis within the same cell. Generally autophagy blocks the induction of apoptosis, and apoptosis-associated caspase activation shuts off the autophagic process. However, in some context, autophagy has been shown to degrade the cytoplasm excessively, leading to "autophagic cell death". Therefore, the disruption of the relationship between autophagy and apoptosis has important pathophysiological consequences. For example, autophagy participates in the pathogenesis of COPD in promoting apoptosis and emphysema, by a mechanism involving LC3B, a critical regulator of autophagy, that interacts with the apoptosis-regulating proteins, Cav-1 and Fas (10,11).

Beyond the regulation of cell death programs, autophagy has functions in cancer (12). It can prevent tumorigenesis through the elimination of oncogenic protein substrates, unfolded proteins and damaged organelles. Alternatively, it can allow established cancers to grow through autophagy-mediated intracellular recycling that provides substrates for metabolism and that maintains the functional pool of mitochondria. Therefore, defining the context-specific role for autophagy in cancer and the mechanisms involved will be important to guide autophagy-based therapeutic interventions.

Finally, autophagy is a fundamental eukaryotic pathway with multiple effects on immunity (13), which can be particularly relevant in the pathophysiology of COPD, which involves aberrant airway inflammatory responses to cigarette smoke. Autophagy is induced by pattern recognition receptors and, through autophagic adaptors, it provides a mechanism for the elimination of intracellular microorganisms. Autophagy controls inflammation through regulatory interactions with innate immune signaling pathways, by removing endogenous inflammasome agonists and through effects on the secretion of immune mediators. Moreover, autophagy contributes to antigen presentation and to T cell homeostasis, and it affects T cell repertoires and polarization.

Oxidative stress is another process implicated in the detrimental effects of cigarette smoke, through multiple mechanisms involving inflammation and cell death, but also antiapoptotic and/or proliferative signaling pathways. Oxidative stress is a major driving force for autophagy, and in turn, autophagy is an effective antioxidant process, thus protecting against the deleterious consequences of oxidative stress (14). Autophagy favors the intracellular clearance of protein aggregates and altered/depolarized mitochondria, which are prone to produce reactive oxygen species. In addition, this effect has anti-inflammatory consequences in reducing the potency of damaged mitochondria to activate inflammasomes. A study recently published in the journal *Autophagy* provided insights into the interrelation between oxidative stress and autophagy in the airway epithelium (15). Based on a transcriptomic analysis of genes expressed in the human airway epithelium, a gene called "oxidative stress induced growth inhibitor" (*OSGIN1*), known to link oxidative stress and cell death, was markedly upregulated in smokers compared to nonsmokers. *OSGIN1* promotes apoptosis, likely through the translocation of *OSGIN1* to mitochondria, with subsequent cytochrome C release and executive caspases activation. Here, the authors provide evidence that *OSGIN1* (through its overexpression) induces autophagic flux in human airway epithelial cells (the precise regulatory mechanism involved has not been identified), which has been interpreted as a likely causal link between oxidative stress and autophagy induction. Importantly, the authors provided evidence (albeit indirect) that the relationship between oxidative stress-induced *OSGIN1* and autophagy probably occurs *in vivo* (in the airways of individuals exposed to cigarette smoke). Complicating further the picture are the findings that this relationship is context dependent. Although *OSGIN1* can enhance autophagic flux, suppression of *OSGIN1* expression does not influence the autophagic flux under normal conditions. However, upon cigarette smoke induced-stress, both upregulation and downregulation of *OSGIN1* can affect autophagic response evoked by smoking, which suggests that expression of *OSGIN1* needs to be tightly controlled in the airway epithelium.

In conclusion, this study supports the view that autophagy is obviously involved in the stress-response

to cigarette smoke in the airway epithelium, and is at the crossroads between oxidative stress and cell death. Modulating autophagy activity by using specific compounds appears to be an appealing therapeutic approach to prevent smoke-induced pulmonary damage.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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