Editorial: Neutrophil elastase and the lung: is it degradation, repair, emphysema, or fibrosis? What tilts it left or right?

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Until not so long ago, proteases were considered to be mere scissors, with the ECM as their main target, either for degradative or remodeling purposes. However, it is becoming obvious that protease actions are not limited to ECM degradation.

Indeed, cells themselves have been shown to be targets of proteases, and PARs have proven to be an important family of cell membrane receptors through which proteolytic enzymes may exert some of their activities [1].

In the mid-1960s, the seminal work of the Laurell and Eriksson group [2] indirectly identified proteases as likely culprits in the pathogenesis of the genetic form of emphysema (e.g., "ZZ emphysema") and suggested that antiproteases, such as A1Pi (and others), could be of therapeutic use in that pathology. Rodent models of protease instillation indeed subsequently confirmed that when compared with lung homeostasis (Fig. 1A), proteases can induce emphysematous lesions (Fig. 1B) [3]. These important breakthroughs led to the theory of "protease-antiprotease imbalance," now widely applied to other diseases, including other chronic lung diseases (see below).

One of the most important proteases involved in that process was identified as NE, a protease later identified as an antimicrobial mediator at homeostasis [4] and whose function was redefined more recently at the molecular level [5].

Irrespective, in the late 1980s/early 1990s, pathologists started recognizing that the emphysematous lung was by no means homogenous and that within the same lung, areas of remodeling/fibrosis could coexist with air space-enlarged areas, one of the cardinal features of emphysema [6, 7]. This suggested that the definition of this condition, put forward by the National Heart, Lung, and Blood Institute in 1984 as "a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis," may have been misleading.

The paper, by Gregory et al. [8], published in this issue of the Journal of Leukocyte Biology, adds credence to the possibility that NE, traditionally known as an "emphysema/chronic obstructive pulmonary disease inducer" (causing alveolar-wall damage in the peripheral lung and increasing mucus production in the airways), may, under certain conditions, also yield a fibrotic phenotype and may potentially participate in the generation of full-blown IPF. There is certainly no shortage of neutrophils, the main (or only) source of NE in IPF, and previous studies have shown that SLPI, an important mucosal inhibitor of NE, was protective in a hamster model of bleomycin-induced fibrosis [9]. With the use of a similar bleomycin model, Chua et al. [10] showed that NE−/− mice were protected when compared with WT mice, and they found reduced tissue levels of TGF-β, an important repair/fibrogenic cytokine.

Gregory et al. [8] convincingly show in the present manuscript that NE can, at nanomolar concentrations, induce fibroblast proliferation, promote wound closure of a fibroblast cell layer in vitro, and induce myofibroblast differentiation (Fig. 1C). In vivo, with the use of a different model than the one mentioned above (i.e., asbestos-mediated instead of bleomycin-mediated fibrosis), these authors also demonstrate lesser fibrotic lesions in NE−/− mice when compared with WT mice.

Mechanistically, the authors demonstrate that NE acts partly through cleaving IRS-1, activating the PI3K/AKT pathway, events leading to fibroblast proliferation (Fig. 1D). By contrast, the mechanisms underlying NE-induced myofibroblast differentiation were not fully deciphered in the present study and were shown to be mothers against decapentaplegic homolog 3 dependent (SMAD-3) but TGF-β independent.

Although the current study does not rule out the involvement of cell-surface
Figure 1. NE in the lung: From degradative to repair mechanisms gone wrong. (A) Protease inhibitors constitute a barrier against inadvertent spillage of proteases (such as NE) in the lung lumen or the interstitium, following ‘low grade’ micro-organisms or toxic stimuli. (B) In the presence of chronic stimuli such as cigarette smoke, the protease inhibitor shield may be inactivated by oxidants and overwhelming neutrophil inflammation occurs. Unrestrained elastase activity disrupts the alveolar-capillary barrier (epithelial cells, endothelial cells, interstitium molecules) and emphysematous lesions occur. (C) Unknown stimuli, present either locally or systematically, can yield lung idiopathic fibrosis. The local protease inhibitor shield is inactivated and proteases (such as NE) can induce (at low concentrations) in fibroblasts a proliferative and differentiation program into myofibroblasts. This results in intense matrix deposition and fibrosis. (D) NE, either directly or through the interaction with an unknown receptor (R), gets access to the cytosol through endosomal internalization. It can then degrade IRS-1, a regulator of the PI3K/AKT pathway, which when over-expressed induce the repair/differentiation/fibrotic program.

receptors (such as PARs; see above) as the first "port of entry" for NE, the latter was detected in the endosome. This is not the first time that NE is shown to be able to gain access to intracellular compartments, as Houghton et al. previously showed that NE could cleave the same IRS-1 in carcinoma cell lines [11]. Notably, in a different study, Le Gars et al. [12] also showed in vitro and in vivo that NE was able to access the cytosol of epithelial cells and could promote the degradation of calpastatin (yet another intra-cellular substrate), yielding calpain activation and ultimately, cystic fibrosis transmembrane conductance regulator degradation, a membrane Cl− channel that when mutated, causes the deadly cystic fibrosis disease.

Supplementary to the additionally required mechanistic studies to explain how and when NE can access cell cytosols and whether some kind of specificity does exist (so far, hepatocytes, epithelial cells, and fibroblasts have proven to be "hosts"), some tantalizing questions remain as to why fibrosis and emphysema (arguably most of the times for the latter) can be both (together or independently in different individuals) pathologies, where NE excess production is causative of the disease.

Could this all be simply a question of dosage? As numerous studies have already shown, epithelial cells and endothelial cells (and now fibroblasts) are quite sensitive to proteases, yielding cell apoptosis or necrosis and hence, disruption of the alveolar-capillary unit, followed by emphysema. It is probable that high doses of NE, generated chronically by "strong" stimuli, such as cigarette smoke, have mainly degradative effects leading to emphysema. By contrast, maybe through the targeting of a high-affinity receptor found at high concentrations on fibroblasts, lower noncytotoxic doses of NE may be, a contrario, profibrogenic. As NE bioactivity (and that of other proteolytic enzymes) is ultimately regulated by the concentration of its specific inhibitors (e.g., A1Pi, elafin, SLPI), these may actually represent some of the emphysema/fibrosis regulators and biasing factors that may, through their local effective concentrations (which can be compromised by excess oxidant concentration, for example), ultimately decide the fate of the injured tissue.

As suggested above and by other studies, emphysema and fibrosis are probably two sides of the same coin and represent exaggerated features of the normal degradation and repair that constantly occur to maintain homeostasis. A good example of the fine balance existing between the 2 pathologies was provided in a study by Bonniaud et al. [13], who showed that STAT-3 KO mice (in which TGF-β signaling is disrupted) had higher levels of MMP-9 and MMP-12, both important metalloproteinases in the lung. Importantly and unlike WT controls, STAT-3 KO mice spontaneously developed emphysema, presumably because of a deficient "day-to-day," normal repair to low-grade inflammatory insults. By contrast, when mice were
exposed to bleomycin, the impaired "fibrogenic potential" of STAT-3 KO mice was instead an asset, and these mice were protected against fibrosis when compared with controls.

Altogether, the mechanistic findings by Gregory et al. [8], showing that NE should be considered as a potential prorepair/fibrogenic mediator, have important implications. These results not only add NE as an important factor to the already long list of prorepair/fibrogenic agents but also show again that neutrophils are not only involved in the first line of defenses (which can sometimes go wrong and yield excessive inflammation) but also may play a role in the termination of proinflammatory responses through the engagement of (sometimes maladaptive) repair mechanisms.

REFERENCES

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EDITORIAL
Brown and Erickson NK cell reaping of Tfh cells

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EDITORIAL
Brown and Erickson NK cell reaping of Tfh cells: reckless slaughter or sensible pruning?

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Introduction

In patients suffering chronic hepatitis C virus or HIV infection, certain combinations of NK cell KIR genes and HLA class I genes have been linked with less morbidity and delayed progression to severe disease. These associations suggest that NK cells bearing 1 KIR or another may facilitate more effective virus clearance in patients that also carry a critical class I molecule. On the other hand, a protective genetic effect(s) observed during chronic infection may be a result of NK cell regulation of adaptive immune cells that are themselves vital in host defense. Whether a result of direct or indirect antiviral activity, the importance of NK cells is underscored in human NK cell deficiency, which results in severe susceptibility to herpesviruses and other infectious maladies and in the majority of cases, leads to premature death [1]. Analysis of mCMV-infected mice in many reports has confirmed the vital role of NK cells in host protection against herpesviruses as a result of expression of key receptors, such as Ly49H, which specifically bind and induce killing of infected target cells. Similar specific recognition mechanisms of other viruses highlight a central function of NK cells in viral immunity. Nonetheless, recent studies have shown that NK cells can negatively regulate virus-specific CD8+ and CD4+ T cells during persistent infection [2, 3], prompting viral immunologists to rethink the self-protective role of NK cells. Indeed, fratricide committed by NK cells was shown to aggravate considerably LCMV infection in a given host by

Abbreviations: GC = germinal center, FNAR = IFN-ω/βR, KIR = killer IgR, LCMV = lymphocytic choriomeningitis virus, m = murine, MHC-I = MHC class I, NCR1 = natural cytotoxicity triggering receptor, PD-1 = programmed cell death protein 1, Tfh = follicular T

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