In the 1980s, researchers found that healthy cells release small, membrane-wrapped packages that are now known as exosomes. They originate deep inside cells, where they are loaded with cargo including specific proteins and RNA before being released to travel beyond the cell.

Initially, researchers thought of exosomes as a means of intercellular communication. "At the time, people thought exosomes were only released to relay neurotransmitters or hormones," says pulmonologist Yang Jin of Boston University, Massachusetts. "Their importance has only been recognized in the last ten years or so."

Now, scientists know that nearly all cells shed exosomes. And Jin and others have found that these vesicles might be key to the symptoms of chronic obstructive pulmonary disease (COPD).

People with COPD — one of the leading causes of death worldwide — experience wheezing, fatigue and chronic coughing. It is especially prevalent in smokers, and research has found that both smokers and people with COPD have an increased number of exosomes circulating in their blood. The contents of these vesicles also differ markedly from those seen in non-smokers without the disease. "We don't know the true triggers of COPD," Jin says. "Looking at the cargo of vesicles in different groups of patients could potentially hold answers about how this disease develops."

In addition to working out the role of exosomes in the development of disease, several researchers are eyeing their therapeutic potential. Early studies suggest that vesicles derived from stem cells can aid tissue repair, and some scientists are considering the possibility of engineering vesicles to carry drugs to diseased tissues. But these efforts have been held back by a dearth of standardized methods to isolate and study vesicles. Advances in techniques over the past few years — and greater scientific consensus in creating standards for research into extracellular vesicles — are pushing the field forward.

Some of the clearest evidence linking exosomes to the symptoms of COPD emerged in 2019. While trying to understand how a particular protein exited immune cells, Edwin Blalock, a pulmonologist at the University of Alabama at Birmingham, found it inside exosomes, along with an unexpected travelling companion: the enzyme neutrophil elastase[1].

Elastase is a prominent player in COPD. The enzyme wears down the stretchy fibres of elastin and collagen that keep the lungs flexible. In healthy individuals, cells counter elastase's effects with an anti-protease called α1-antitrypsin (α1AT), and COPD was long considered the result of an imbalance between these two proteins. This view is bolstered by the fact that people with a genetic deficiency in α1AT are at much greater risk of developing COPD — even if they have never smoked — than are non-smokers without the mutation. The idea that higher levels of neutrophil elastase are linked to COPD "has been a cornerstone of the study of COPD for over six decades", says Blalock. "But the levels of elastase typically seen were never high enough to counter α1AT activity. That was the conundrum."

Blalock and his colleagues found that when elastase was packed on the surface of exosomes, it was protected from neutralization by α1AT. These exosomes also bore a marker called Mac-1 that helped them to bind to the extracellular matrix, where elastase then digests matrix fibres. The loss of elastin and collagen from the extracellular matrix causes lung tissue to become less flexible and alveolar spaces to widen, which in turn reduces the efficiency with which the lungs transfer oxygen and carbon dioxide into and out of the body.

When exosomes from people with COPD were injected into mice, the animals developed signs of COPD, including emphysema[1]. "This is the first instance of being able to have exosomes transfer a disease phenotype from a human to a mouse," Blalock says. "It's surprising, especially the rapidity with which the mice developed COPD after they first encountered these exosomes, and I think it points to their potency as effectors of damage."

Spurring symptoms

Neutrophils are not the only source of

form of the protein inside exosomes modulated inflammatory proteins in the lung and helped to maintain homeostasis after exposure to cigarette smoke. But the CCN1 fragments not encapsulated in vesicles caused a spike in the production of two proteins that digest the extracellular matrix, causing cells and tissues to die. The reason, Jin suggests, is that smoking and other stressors alter how proteins such as CCN1 are tagged for processing, resulting in the production of abnormal fragments that are not wrapped in an exosome.

Jin and others are also looking at microRNAs in exosomes; these are more stable and easier to detect than proteins. Several microRNAs are enriched in extracellular vesicles from lung epithelial cells exposed to cigarette smoke, according to one study[3]. Researchers found that one of these, miR-210, reduced autophagy, a process that is essential to clearing away damaged cells. The microRNA also increased the formation of collagen and cells associated with fibrosis, which stiffens lungs. All these functions could contribute to the development of COPD, says Takahiro Ochiya who studies exosomes at Tokyo Medical University, lead author of the study.

Because exosomes carry multiple molecules, it has long been hoped that their contents could be used as diagnostic or prognostic biomarkers. Not all those who smoke develop COPD, and not all those who have COPD are smokers. The