

# New mechanism links smoking to lung damage

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In the August 7, 2007, issue of PLoS One, researchers show how a poorly understood and previously unsuspected mechanism may be the key to understanding how life-style associated forms of oxidative stress, such as exposure to cigarette smoke, damage cells in the lungs.

Toxins in cigarette smoke, they show, open unpaired hemichannels--small portholes in the cell surface--that can, with very little provocation, turn into major breaches in the cell's integrity, leading to rapid cell death.

This discovery by researchers from the University of Chicago, the University of California at San Diego and the University of California at Los Angeles, suggests new ways to prevent smoking-related cellular damage and possibly to put the brakes on other diseases tied to oxidative stress, including atherosclerosis, neurodegenerative diseases and even senescence.

"Opening hemichannels allows stressful, often toxic, stimuli to flow directly into cells, overwhelming the delicate and carefully maintained balance within and triggering the signals that induce cell death," said study author Ratneshwar Lal, PhD, professor of medicine at the University of Chicago.

"We were surprised to find out how little it took to cause such damage, only a small change in membrane electrical properties," he added, "and by how much damage it could cause."

Hemichannels form a small gated pathway from the interior of a cell, through the cell membrane to the cell surface. They usually connect with an identical hemichannel from an adjoining cell to form a gap junction. By directly connecting two cells, gap junctions enable them to exchange the chemical signals they use to coordinate their activities and maintain metabolic and ionic homeostasis among connected cells in a tissue.

About fifteen years ago, scientists realized that some hemichannels had no partners; they led directly from the cell's interior to the fluid extracellular space. In 2000, Lal and colleagues showed that cells used these channels to increase their volume, opening as necessary to take in water and calcium ions that allowed cells to reorganize their cytoskeleton and mechanical properties commonly related to cell growth and differentiation.

In this study, they looked at the effects of oxidative stress on unpaired (or non-junctional) hemichannels found in the membrane of cells from the lungs and the heart--the primary targets of cigarette smoke.

When they exposed these cells to low levels of an extract made from cigarette smoke, the non-junctional hemichannels opened. This allowed toxic molecules found in the smoke to flow directly into the cell, and vital metabolites such as ATP and NAD, to leak out, leading, ultimately, to cell injury and death.

Drugs that prevented hemichannels from opening protected the cells from similar exposures. Treating the cells with silencing RNA for the hemichannel protein also protected cells by preventing the creation of these channels.

"It required very little stress to open these channels," Lal said.

"Substances found in smoke and other pollutants can alter the electrical potential of the cell's membrane. A small shift in the membrane's

electrical potential, which we know occurs in many oxidative stress situations, appears to open these channels and allow unregulated flow. This can weaken and kill cells."

Cells have multiple membrane channels that carefully control the flow of specific small molecules in and out of the cell, including calcium, sodium and potassium ions, each of which passes through a specific type of channel.

Hemichannels, however, with ports nearly twice the size of an ion channel, are not as specific, permitting more rapid, less regulated flow of molecules up to the size of 1000 Daltons--wide enough to allow exchange of many signaling and messenger molecules, such as ATP and small metabolites that are essential for normal cell sustenance.

"We suspect that this mechanism could play a major role in the onset of diseases such as emphysema, which is associated with smoking," said Lal." Previous studies have found a role for hemichannel malfunction in stroke.

"Improperly opened hemichannels may play a role in many other diseases tied to environmental stimuli," Lal said, "or even to normal aging, where oxidative stress is thought to contribute to the gradual accumulation of multiple small damaging hits. Finding and testing drugs or other mechanisms that can selectively block these unpaired channels offers a novel approach to disease prevention."

Source: University of Chicago Medical Center

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