Scientists advance safety of nanotechnology

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Scientists have identified for the first time a mechanism by which nanoparticles cause lung damage and have demonstrated that it can be combated by blocking the process involved, taking a step toward addressing the growing concerns over the safety of nanotechnology.

Nanotechnology, the science of the extremely tiny (one nanometre is one-billionth of a metre), is an important emerging industry with a projected annual market of around one trillion US dollars by 2015. It involves the control of atoms and molecules to create new materials with a variety of useful functions, including many that could be exceptionally beneficial in medicine. However, concerns are growing that it may have toxic effects, particularly damage to the lungs. Although nanoparticles have been linked to lung damage, it has not been clear how they cause it.

In a study published online today (Thursday 11 June) in the newly launched Journal of Molecular Cell Biology [1] Chinese researchers discovered that a class of nanoparticles being widely developed in medicine - ployamidoamine dendrimers (PAMAMs) - cause lung damage by triggering a type of programmed cell death known as autophagic cell death. They also showed that using an autophagy inhibitor prevented the cell death and counteracted nanoparticle-induced lung damage in mice.

"This provides us with a promising lead for developing strategies to prevent lung damage caused by nanoparticles. Nanomedicine holds extraordinary promise, particularly for diseases such as cancer and viral infections, but safety concerns have recently attracted great attention and

with the technology evolving rapidly, we need to start finding ways now to protect workers and consumers from any toxic effects that might come with it," said the study's leader, Dr. Chengyu Jiang, a molecular biologist at the Chinese Academy of Medical Sciences in Beijing, China.

The first nanomaterial was developed by German scientists in 1984. Nanomaterials are now used in a variety of products, including sporting goods, cosmetics and electronics. The fact that unusual physical, chemical, and biological properties can emerge in materials at the nanoscale makes them particularly appealing for medicine. Scientists hope nanoparticles will be able to improve the effectiveness of drugs and gene therapy by carrying them to the right place in the body and by targeting specific tissues, regulating the release of drugs and reducing damage to healthy tissues. They also envision the possibility of implantable nano devices that would detect disease, treat it and report to the doctor automatically from inside the body. The US Food and Drug Administration has approved some first generation nanodrugs. One example is Abraxane, a nanoformulation of the anti-cancer chemotherapy paclitaxel.

Lung damage is the chief human toxicity concern surrounding nanotechnology, with studies showing that most nanoparticles migrate to the lungs. However, there are also worries over the potential for damage to other organs.

In the study, the researchers first showed, through several independent experiments, that several types of PAMAMs killed human lung cells in the lab. They did not observe any evidence that the cells were dying by apoptosis, a common type of programmed cell death. However, they found that the particles triggered autophagic cell death through the Akt-TSC2-mTOR signalling pathway. Autophagy is a process that degrades damaged materials in a cell and plays a normal part in cell growth and renewal, but scientists have found that sometimes an overactivity of this

destruction process leads to cell death.

The researchers also found that treating the cells with an autophagy inhibitor known as 3MA significantly inhibited the process, increasing the number of cells that survived exposure to the nanoparticles.

"Those results, taken together, showed that autophagy plays a critical role in the nanoparticle-induced cell death," said Dr. Jiang.

The scientists then tested their findings in mice. They found that introducing the toxic nanoparticles significantly increased lung inflammation and death rates in the mice, but injecting the mice with the autophagy inhibitor 3MA before introducing the nanoparticles significantly ameliorated the lung damage and improved survival rates.

"These experiments indicate that autophagy is indeed involved in lung damage caused by these nanoparticles and that inhibition of this process might have therapeutic effects," Dr. Jiang said. "We will likely need to look for additional new inhibitors to block lung damage as this particular compound is not stable in humans, but this gives us a promising lead for the first time."

"Our study has identified the principle for developing such compounds. The idea is that, to increase the safety of nanomedicine, compounds could be developed that could either be incorporated into the nano product to protect against lung damage, or patients could be given pills to counteract the effects," Dr. Jiang said, adding that the findings could also provide important insight into how nanopaticles cause other toxic effects.

It is not clear whether other types of nanoparticles would cause lung damage via the same mechanism, but some may, Dr. Jiang said. The group's research also suggests that blocking autophagic cell death could

perhaps be useful in combating other causes of lung damage.

Source: Oxford University Press