Peroxisomes—the hybrid organelle

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Like the human body itself, cells have structures within them that perform special tasks. These cellular structures are called organelles, and discovering more about organelles is key to unlocking the reasons why certain cells misbehave, causing diseases such as Parkinson's, for example.

In a paper published in *Nature* on Feb. 1, 2017, a team of researchers from the Montreal Neurological Institute and Hospital of McGill University: Ayumu Sugiura, Sevan Mattie, Julien Prudent, and Heidi M. McBride, examined the origins of organelles called peroxisomes. They found that this very important organelle has two origins, which is unique in the field of cellular biology.

We spoke with Heidi McBride, the senior author of the study, to learn more about this discovery:

What are peroxisomes?

Peroxisomes are small, membrane bound organelles inside of every cell. They get their name because they neutralize cellular peroxide, which is very toxic, into water. This study looked at how peroxisomes may be born in mammalian cells - including humans. We made a surprising discovery: new peroxisomes are formed as a hybrid organelle. That means they come from two distinct sources, in this case the organelles endoplamic reticulum and mitochondria.

Is it unusual for an organelle to have a hybrid nature

like this?

Yes! It is really the first example of such a hybrid organelle within cell biology. Only the mitochondria and peroxisomes were known to be isolated, self-sufficient organelles able to grow and divide on their own. These two organelles have always been unique in that way. Mitochondria have their own DNA that is a remnant from their early origins as an alpha-proteobacteria, and mitochondria still retain much of their autonomy. Peroxisomes have been more complicated to figure out, but it was generally accepted that in addition to their autonomous growth and division, that they could sometimes be generated as a sub-domain of the endoplasmic reticulum. Our works leads to a complete re-evaluation of this model.

Do they do anything else besides break down peroxide?

In addition to enzymes that neutralize peroxide, they also have essential roles in breaking down complex fatty acids. Many human diseases are a result of mutations in this pathway, where there is an accumulation of very long chain and branched fatty acids, for example in X-linked adrenoleukodystrophy. But peroxisomes also have specific functions in different tissues, for example in the liver they house enzymes that make bile, which is transported into the gut to break down food. In the brain they are critical to make a specific protective lipid called plasmalogen, which makes up nearly 70 per cent of the myelin sheets that wrap around neurons. So these are very important organelles that are largely unstudied in the context of disease.

Myelin … that makes me think of MS, where the myelin sheath around neurons is damaged. Could

there be a link between peroxisome development and MS?

It is not clear how peroxisomal dysfunction may contribute to neurodegenerative disease, particularly in multiple sclerosis where the myelin is lost and axons become exposed. We are now looking at how peroxisomes behave in models of MS, and whether or not increasing their numbers may help combat the toxicity and work towards rebuilding the myelin sheets. This work provides a new framework to look at peroxisomal formation and growth, allowing us to move into more complex systems that are very relevant to disease.

Are there any diseases where peroxisomes are already known to play a role?

Yes. There are many rare diseases where peroxisomes cannot form, or cannot perform their function. For example, a condition called Zellweger syndrome results in patients either completely lacking peroxisomes, or with peroxisomes that remain "empty" and without function. These patients are extremely ill, as they cannot make myelin, nor bile, and they accumulate many toxic metabolites from peroxide to fatty acids. The lifespan of these patients is only a few months to about two years. There is currently no treatment for these patients, so learning how we may trigger new peroxisomal biogenesis could be important to develop new strategies for therapy.

What role do mitochondria play in the formation of peroxisomes?

Mitochondria are well known as the "energy powerhouse of the cell", using the oxygen that we breathe to convert glucose and fat into cellular

energy. However, mitochondria do a great deal more than this. Like peroxisomes, they perform many additional biochemical tasks. Some of these tasks are shared with peroxisomes, particularly the breakdown of fatty acids, but also in the generation of bile in liver and plasmalogen in the brain. Both organelles also play important roles in neutralizing toxic chemicals. However, mitochondria had not been implicated in the formation of new peroxisomes until our study. We found that in skin cells from Zellweger patients lacking peroxisomes, that some peroxisomal proteins are inserted into the mitochondria, while others targeted the endoplasmic reticulum. These proteins are then packaged into small membrane vesicles that are ejected from each organelle. When they fuse together, the proteins that had been separated within distinct organelles now come together and assemble into a larger protein complex that act like a gate allowing entry of a host of peroxisomal proteins and enzymes into the newly born peroxisome. We saw this occur also in normal, healthy cells where the number of peroxisomes was greatly reduced, suggesting that there is some kind of sensing mechanism that "knows" when to make peroxisomes from scratch, and when to just let them grow and divide from pre-existing peroxisomes. How this sensing system works in the brain or other organs is a major question for our future work.

What implications does this have for future research?

We hope that this work may shine new light on this essential and understudied organelle. Mitochondrial dysfunction has been increasingly linked to many disease states, including Parkinson's, MS, Alzheimers, cancer and many others. Given the close links between mitochondria and peroxisomes, we wonder how dysfunctional mitochondria may impact peroxisomal activity and biogenesis, and how this may contribute to the worsening of disease. There are many new questions raised, as we must now gain a better understanding of the mechanisms and signals that initiate the formation of newly born peroxisomes, and their contribution

to both rare and common disease. We believe this work will have a great impact on the field of peroxisomal biology, and in time, we will understand the impact on human disease progression.

More information: Ayumu Sugiura et al. Newly born peroxisomes are a hybrid of mitochondrial and ER-derived pre-peroxisomes, *Nature* (2017). DOI: 10.1038/nature21375

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