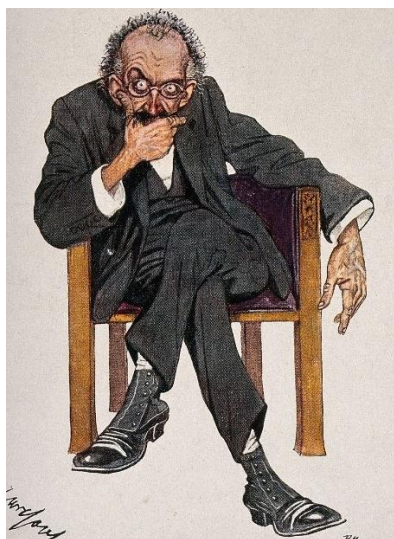


## on the makings of transparency

Vivienne Baillie Gerritsen

As I wonder how to begin this article, I am distractedly examining my fingers. They are not getting younger. A nail or two need a trim, and there is a hint of cracked skin on the tip of one thumb. It occurs to me that I would be unable to notice any of this – and take action – unless I had eyes which can see. Eyes are no doubt one of the most intricate organs shared by animals – save by those, of course, who are born naturally blind like the star-nosed mole or the eyeless shrimp. The transparency of the eye's lens is perhaps one of the most remarkable feats Nature has achieved. It certainly fills you with awe. The lens has to be literally akin to glass. If it is not, light will be helplessly scattered, and all we would be able to see is a distorted image of our surroundings. For almost two centuries now, anatomists have known that the lens is made up of fibrous cells whose organelles have been destroyed so that light can beam through without being dispersed or absorbed. It is only recently, however, that scientists discovered how cell organelles are actually broken down to clear the lens. In mice and probably humans too, the answer is a protein known as PLAAT3 which attacks the characteristic phospholipids that form an organelle's membrane.



The Psychiatrist

Carl Josef Pollak (1877-1937)

Central to the eye, both in structure and function, the human flat bubble-shaped lens is lodged behind the iris where it bathes in an aqueous humour on one side and a vitreous one on the other. Scholars have studied the anatomy of the eye for as long as we recall, which does not come as a surprise since it is one of the five senses we feel it would be very difficult to live without. Eyes are paramount to animals, be it just to spot prey or predators, not to mention mates. Vision comes in particularly handy when we need to move from one

place to another, buy food, read, write, tend to a wound or care for our children. It is also a wonderful channel through which we perceive beauty. But for all this, the lens – like the cornea and the vitreous humour – must allow the smooth passage of light to the retina.

Understanding how an eye accomplishes vision, how the sum of its physical properties allows us to perceive the shapes and colours of the outer world, was fundamental to the design of the first telescopes and microscopes in the 17<sup>th</sup> century. One essential parameter to consider was transparency. Humans knew how to make glass but how does Nature manage to create something you can see through? The first to offer the beginnings of an answer was the Austrian anatomist Carl Rabl who, in 1851, described systematic organelle degradation in the developing lens of several animals thus literally clearing the inside of a cell. The eye lens is made up of long and fibrous cells which are stacked one upon the other in concentric sheets. While certain zones of the eye lens are made up of cells that retain their organelles, the cells which form the core of the lens – the organelle-free zone (OFZ) through which light must pass without being scattered, distorted or absorbed – have been emptied of theirs.

What is meant by organelle degradation? Several organelles are found in a cell's cytosol, all working in unison to keep the cell alive and healthy: the nucleus, mitochondria, lysosomes, the endoplasmic reticulum, the Golgi apparatus, peroxisomes, endosomes...

Besides taking up space and light, each of these organelles has a membrane that, like the cell's membrane, is composed of a phospholipid bilayer. Early on in embryonic development, lens cells destined to become part of the OFZ gradually lose their organelles as the latter are literally torn apart, and the pieces discarded. Initially, scientists thought that this singular organelle breakdown was caused by some form of cell autophagy. However, it is now clear that members of a protein family known as the PLAAT family are responsible for it.

The phospholipase A (PLA) /acyltransferases (AT), or PLAAT, family of proteins are involved in a wide array of biological processes. They achieve this by acting both as (O- and N-) acyltransferases and phospholipases (A) to modify parts of membrane bilayer phospholipids – first by producing N-acylphosphatidylethanolamines (NAPEs) and then N-acylethanolamines (NAEs). NAEs are a class of bioactive lipid engaged in biological processes as varied as nociception, the modulation of inflammation, energy regulation, fat catabolism and antiapoptotic activity. PLAATs are modest-sized enzymes all of which carry a highly conserved NCEHFV sequence in their C-terminal region critical for activity, a catalytic triad composed of two histidine residues and an asparagine residue to help stabilize the reactions, and a C-terminal transmembrane spanning domain which localizes the enzymes to endomembranes.

The PLAAT family has five members: PLAAT1-5. In humans, or mice for that matter, PLAAT3 seems to be actively involved in lens fibre cells, specifically those destined to become part of the OFZ. Just before organelle degradation, PLAAT3 is rapidly directed, via its C-terminal transmembrane domain, to endomembranes that have already been partially damaged. Instead of repairing the damage as one would expect, PLAAT3 continues to tear down the membrane until the targeted organelle literally falls

apart, and the debris is swept away by the cell's cleaning facilities dutifully summoned to the site. Why would a cell not resort to autophagy to wipe out its organelles, you may wonder? Energy may be the answer, and perhaps even time. Or, in a way, common sense... Autophagy would require each organelle to be engulfed within... another organelle in order to be disposed of. This is not only energy-costing but, intuitively, such a choice does not seem to pave the way to transparency. One question emerges: why does PLAAT3 not degrade the cell's membrane? Probably because specific features – other than endomembrane damage – are required to direct PLAAT3 to a given organelle.

Is organelle degradation sufficient for optimum transparency? OFZ fibre cells must rely on all sorts of post-translational modifications to keep going – while nothing can be repaired or replaced! They have to count on glycolysis, for instance, since their mitochondria have been eradicated and cannot supply the cell with ATP. As a result, hordes of micro- and macromolecules are present in the cells' cytosols, which, taken together, are great scatterers and absorbers of light. Yes, but despite the usual high presence of proteins, interactions are so short and rapid that transparency is not undermined. Certainly, the eye lens and perhaps even more so the OFZ are designed in such a way that it forces admiration. The intricacy of an eye, the subtleness of the physics and biochemistry involved in sight, the communication needed between every component part, however small, makes you realise how infinitely complex and fragile eyesight is. Loss of sight – however it happens – is probably due to an impairment of either of the many pathways leading to, or sustaining, transparency, among which the doings, or undoings, of PLAAT3. Understanding the eye lens and how transparency is created could for example lead to therapies for the treatment of cataracts other than surgery, which is the only current possibility. And thank goodness for that.

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## Cross-references to UniProt

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