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Microbiology

A soil bacterium unmasks a human enzyme

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ABSTRACT

We now know the human genome and, with it, most of the proteins we make, but we don't know what a good number of these proteins do. Thanks to a social soil bacterium and studying how it responds to light, we have now identified the human protein needed to make a special class of abundant, yet enigmatic, lipids that are important in human biology and health.

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Life, as we know it, exists thanks to membranes. As active functional barriers between a living cell and its environment, and between compartments within the cell, membranes ensure selective entry and exit of substances, energy generation, and the sending, receiving, and processing of signals essential for cell viability. Although proteins and sugars are crucial constituents of cell membranes, their major basic structural components are lipids of high chemical and compositional diversity. Besides their structural role, lipids have other critical functions, such as in signaling. Identifying the various lipids and their functions, and understanding why and how they are generated with such diversity, how lipid homeostasis is maintained, and how its misregulation causes various diseases are significant challenges in biology and medicine.

Three types of lipids comprise biological membranes- phospholipids, glycolipids, and sterols. A large and diverse group found in all living organisms is glycerophospholipids, in which two ester bonds link two fatty acids to glycerol with a phosphate moiety. In a particular class of these lipids known as plasmalogens (because they were considered the source of "plasmal", the aldehyde produced in cell plasma exposed to acidic conditions), one ester is replaced by a vinyl ether bond. This bond confers special properties to plasmalogens, which have proposed membrane organization, signaling, and antioxidant roles.

Plasmalogens are found in few bacteria. Like cholesterol, another well-known lipid, they are

found in animals but not in plants. In humans, they are abundant in the brain and heart. Their levels rise in the early stages of life and during myelination in the development of nerve cells but begin to drop with the onset of middle age. Neurodegenerative disorders like Alzheimer's and rarer ones like Zellweger syndrome have been tied to decreases in plasmalogen levels, which are also abnormal in various cancers. Although sought for over five decades, the critical enzyme that generates the vinyl ether bond, and hence plasmalogens, in humans and other animals remained unknown. We have now unmasked that elusive enzyme.

Our discovery of the human enzyme owes, surprisingly, to a non-pathogenic soil bacterium called *Myxococcus xanthus*, which makes plasmalogens. We have been studying for many years how the aerobic (oxygen-requiring) *Myxococcus* responds to light to ultimately produce carotenoids, the pigments responsible for the yellow, orange and red colors in carrots, tomatoes and many flowers, birds and fish, and which are sources of vitamin A, necessary for vision. Carotenoids help neutralize a very reactive form of oxygen produced under light called singlet oxygen, which can damage cellular components and cause cell death. Thus, when exposed to light, *Myxococcus* protects itself by producing carotenoids to act as a sunscreen.

We had already established that *Myxococcus* needs many factors to produce carotenoids in response to light, one of which is a protein we named CarF. Proteins similar to CarF but of unknown functions existed in animals and plants, as deduced from their genomes. Even humans had one called TMEM189. Some features in CarF and TMEM189 proteins suggested that they may be involved in lipid synthesis. We, therefore, decided to test this possibility. To address this, we examined what lipids known to be present in *Myxococcus* were absent in cells lacking CarF, and found that plasmalogens were missing. In addition, plasmalogens reappeared in CarF-deficient *Myxococcus* transformed to produce CarF again, human TMEM189, or any analogous proteins from roundworm, fruitfly, fish or mouse (this was not observed with the plant proteins, consistent with plants lacking plasmalogens). Feeding *Myxococcus* with a known precursor yielded plasmalogen only if CarF was present. And human cell lines devoid of TMEM189 lacked plasmalogens. Hence, we concluded that both CarF and human TMEM189 are responsible for the production of plasmalogens. Besides identifying TMEM189 as the human enzyme for plasmalogen synthesis, we established that plasmalogens are crucial for transmitting the light signal in *Myxococcus*, providing a clear example of the proposed signaling role of plasmalogens.

It is remarkable how a bacterium has helped unmask a human enzyme and that, despite the enormous evolutionary distance, humans and a bacterium share a protein with the same function. With the identity of the long-elusive human enzyme for plasmalogen synthesis in hand, we can now directly assess the enigmatic roles of these lipids in human health and disease.