Commentary

Commentary on Fatty Acid Wars
The Diffusionists Versus the Translocatists

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Cluster of Differentiation 36 (CD36) is an integral membrane protein and a member of the class B scavenger receptor family that binds many ligands—oxidized low-density lipoprotein, native lipoproteins, and oxidized phospholipids. In addition, CD36 has been shown to enhance the uptake of long-chain fatty acids, and CD36 null mice show a defect in fatty acid uptake as well as intestinal processing of dietary fat. CD36 has been implicated in fatty acid transport in heart, skeletal muscle, adipocytes, human pancreatic β-cells, and fibroblasts; muscle-specific CD36 overexpression enhances fatty acid oxidation in contracting muscle, reduces plasma triglycerides and fatty acids, while increasing plasma glucose and insulin, thereby producing a diabetic phenotype. Based on these findings, CD36 has been postulated to be a fatty acid transporter; yet, many questions remain about the function of this promiscuous lipoprotein receptor. At the molecular level, what is the activity of CD36, what are the consequences of that activity, and what are the attendant mechanisms?

The existence of fatty acid translocators in cells has been somewhat controversial. Although there is a clear need for transporters for cargo such as glucose, which is highly soluble in water because of its numerous hydroxyl groups but for the same reasons is insoluble in hydrocarbon-like environments such as the central region lipid bilayer membranes, a similar argument for fatty acids is difficult to make. Approximately 50% of membrane fatty acids are protonated at physiological pH and have low energy barrier for crossing the phospholipid bilayer. Given this, what physical property of the fatty acid would not be soluble in the bilayer interior? Likely none; in vitro studies have shown that free fatty acids rapidly diffuse across artificial membranes. Fatty acid movement from the extracellular space to the cytoplasm comprises desorption from albumin into the aqueous phase, t1/2 of ≈30 ms for palmitic acid, and association with the outer membrane leaflet and translocation across the plasma membrane which are both fast. The last step, desorption from the inner leaflet, is chain length dependent, with a half-time of ≈3 ms for palmitic acid. There is some debate on rate constant, with some reporting that translocation is rate limiting for fatty acid entry into cells so that a fatty acid translocator such as CD36 might be required.

Other fatty acid translocators have been reported. One, fatty acid transport protein, was discovered by an expression cloning strategy that identified cells with increased internalization of a fluorescent fatty acid. It was later shown that this protein is actually a fatty acyl coenzyme A synthase, which converts fatty acids to their coenzyme A analogs that are trapped within the cell by the coenzyme A moiety, which cannot pass through membrane bilayer interior. Other analogous examples of metabolic trapping include overexpression of enzymes catalyzing the first 2 steps in the acylation of glycerol-3-phosphate accelerates fatty acid uptake. Thus, diversion of fatty acids products that cannot spontaneously escape from the cell reduces the cytoplasmic fatty acid concentration and increases the fatty acid gradient across the cell membrane so that diffusive fatty acid translocation is controlled by mass action and not kinetics.

A similar debate about fatty acid transfer into cells via CD36 has ensued. Most agree that CD36 stimulates cellular fatty acid uptake. The question has been, “What is the mechanism?” A major advancement in our understanding of this was provided by a recent study by Xu et al that compared fatty acid uptake by control and CD36-transfected HEK cells and separated the membrane transport steps from intracellular metabolism. The control cells are ideal for this study because fatty acid metabolism is slow on the time scale of fatty acid transfer from the extracellular space to the cytoplasm and these cells do not express the confounding transport effects of caveolin-1, CD36, and fatty acid transport protein.

Chemical kinetics showed that the rates of oleic acid binding and transport across the plasma membrane in control and CD36 expressing were the same. The investigators further showed that CD36 increases intracellular glycerolipid synthesis, mostly as triglycerides that are visible as lipid droplets. The diversion of fatty acids to esterification creates a concentration gradient between the plasma membrane (high) and cytoplasmic (low) fatty acid concentrations. So how can more fatty acids accumulate in the cell without a change in the rate of entry? The answer lies in the rest of the kinetic picture. In the absence of esterification, some fatty acids return to the plasma membrane so that the main effect of esterification is not on fatty acid transport into the cytoplasm but rather on diversion of fatty acids from return to the plasma membrane to glycerolipid formation. In a more physiological context, when a cell is in contact with plasma, enhancement esterification diverts fatty acids from the competing process, exit from the cell.

Thus, activities that create concentration gradients of fatty acids between the cytoplasm (low) and the extracellular space (high) will enhance the diffusive flow of fatty acids into the cell. This could occur by intracellular metabolic trapping via...
fatty acid activation,18 conversion to glycerolipids,19,20,23 oxidation,24,25 and likely other esterification pathways or by concentrating fatty acids at the outer leaflet of the cell membrane, for example, CD36. The present study encourages a redirection to search for new mechanisms by which CD36 enhances metabolism and to further test the generality of the fatty acid gradient model to determine whether other activities that create a gradient also enhance cellular fatty acid uptake.

Disclosures

None.

References


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