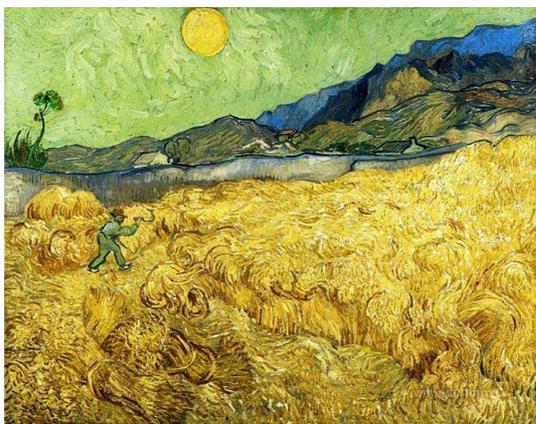


a tighter mesh

Vivienne Baillie Gerritsen

A fabric whose weave is slack is less resistant to strain than one whose knit is close. These physical principles of toughness are followed by Nature all the way down the molecular scale. At the cellular level, protrusions known as microvilli grow at the apical end of the epithelial cells that line the intestinal tract. Each protrusion is like a finger dipping into the gut lumen. There can be up to one thousand protrusions on the end of each cell, which together form a fuzzy lining that looks like the bristles of a very long brush, hence its name: the brush border. These protruding digits are not free to wiggle as they wish however. Each protrusion is linked firmly to neighbouring protrusions thus making the whole system tougher in a realm – digestion – where tissues can undergo severe mechanical insults. But you need something to tighten the mesh. This is performed by proteins that belong to a family known as the cadherins, namely cadherin-related family members 2 and 5.



Wheat field with a reaper (1889)

Vincent van Gogh

Light microscopy was developed and became popular during the course of the 17th century. Microvilli, however, are too small to be observed individually under a light microscope although the brush border, as a whole, is by all means visible. The Italian biologist and physician Marcello Malpighi (1628-1694) is known to be the father of histology, and there is a great chance he noticed the fuzzy border on the edge of the cells that line the intestinal tract – but he would not have been able to distinguish the individual microvilli. For this he would have needed a scanning electron

microscope which only came into being more than 200 years later. This high resolution microscope was designed in the 1930s by the German physicist Ernst Ruska (1906-1988). But it was only commercialized in the 1960s, which is about the time the ultrastructure of microvilli was first described (1965).

What do microvilli look like? Imagine an “elongated cube”, or cuboid, with hundreds of finger-like protrusions undulating at one of its ends. Now imagine a network of cuboids – or epithelial cells – joined to one another, thus forming a tissue. You would observe a whole area of microvilli waving in unison much in the way a field of wheat undulates in the wind. If you zoom in a little further, you will make out thread-like structures that link one microvillus to another in the manner of the spokes of a wheel. Each microvillus is delineated by the plasma membrane and its structural core is an elongated bundle of 20 to 30 cross-linked actin filaments which form the microvillar skeleton. The whole point of protrusions such as microvilli is to increase the area of a cell’s membrane without increasing the cell’s volume; as a consequence any function carried out by the membrane – absorption, secretion, cellular adhesion, navigation, mechanotransduction or host defense for instance – is increased manifold.

One remarkable observation: microvilli are not only similar in length but also in diameter. So

there must be something that guides and shapes their development. This may be carried out in part by cadherin-related family members 2 and 5, also referred to as CDHR2 and CDHR5. CDHR2 and CDHR5 are bound to one another in the extracellular microvillar area and are linked, at either end, to two neighbouring microvilli; they form the thread-like links observed under the microscope. The two cadherins are calcium-dependent adhesion proteins and probably responsible for driving the assembly of microvilli and forming the brush border. Indeed, adhesion proteins are known to play essential roles in many biological processes, one of which is the organisation of cells during tissue morphogenesis. CDHR2 and CDHR5 interact to form microvillar clusters – like bunches of flowers – that expand as morphogenesis rolls on and more and more microvilli are incorporated. As an epithelial cell approaches its final differentiated state, its apical surface usually has one huge cluster made up of about one thousand microvilli. CDHR2 and CDHR5 are also known to link microvilli at their tip – a localisation which has its purpose: if microvilli were bound in their middle, or further down, the tip of a microvillus would be free to link to the base of another for example, and clustering would become utterly disorganized.

So CDHR2 and CDHR5 form the link between two microvilli thus driving brush border assembly. But how exactly? CDHR2 and CDHR5 are transmembrane proteins that interact with one another in the extracellular space between two microvilli. One CDHR2 from one microvillus interacts with one CDHR5 from a neighbouring microvillus, thus forming the characteristic

thread-like link between them. Each cadherin cytoplasmic end is further associated with cytoplasmic cytoskeletal proteins – which probably form an important anchoring point for CDHR2 and CDHR5 – and that in turn are ultimately linked to the central actin core. In this way, one microvillus is held tightly to its immediate neighbour. As epithelial cell differentiation continues, the microvilli become more and more densely packed and the brush border is gradually organised. CDHR2 and CDHR5 act then not only as cell to cell adhesion proteins but also as subcellular structural proteins able to drive brush border assembly while regulating the individual dimensions of microvilli.

Microvilli are proving to be very similar to their inner ear counterparts – stereocilia – whose structure and function are currently far better known, and can thus be used as a model to understand microvilli. The dense packing of brush border microvilli has proved to be essential; if anything is mal-assembled, it can give rise to intestinal pathologies. Delving into microvillus intimacy – i.e. getting to know in detail all the proteins involved in microvillar genesis and function – will help to understand what goes on in the small intestine and the colon. We already know that CDHR2 and CDHR5 have a critical role in shaping the epithelial surface of the gut system. How exactly they do this should shed more light on our understanding of gut diseases that are associated with inherited or infectious causes, besides providing a basis with which scientists can develop targeted treatments with regards to specific intestinal pathologies.

Cross-references to UniProt

Cadherin-related family member 2, *Homo sapiens* (Human) : Q9BYE9
Cadherin-related family member 5, *Homo sapiens* (Human) : Q9HBB8

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