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Slime with a design

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We have all stuck our fingers down a drain and felt that viscous slime that lines its walls. Revolting though it may seem to our tactile senses, such biofilms – as they are known – are a world in themselves. The slime is secreted by various microscopic organisms and – despite a poor understanding of its function – it is used in a number of industries, including the food industry, for its viscous properties. And today, scientists are discovering the potential of this gelatinous matter in the field of therapeutics. What is this slime made of? Mainly, the polysaccharide alginate. And GDP-mannose dehydrogenase is the enzyme which has a major role in its biosynthesis.

Alginate was first discovered and described in the 1880s by the Scottish chemist E.C.C. Stanford when he extracted a 'viscid mass' from brown algae. Since its chemical properties resembled neither gelatin nor starch, it was given a new name: algin. Based on its properties, Stanford suggested a variety of uses for algin, such as a stiffener for fabrics, the insulation of electrical appliances, or the fining of wines and spirits. In fact, the alginic acid industry started in Japan as early as the 1920s.

Brown algae

Source: NOAA, USA

Alginate is a copolymer of beta-D-mannuronic acid and alpha-L-guluronic acid, of which there is a varying amount depending on the organism which has produced it: algae or bacteria. In an attempt to diversify the number of combinations, bacterial alginates are also O-acetylated on some of the mannuronate blocks. One of alginate's most interesting aspects is that it can suck up vast quantities of water and the resulting viscosity and gel-forming capacities it then bears are what industries seek.

GDP-mannose dehydrogenase (GMD) is involved in one of the most important steps of alginate biosynthesis. It boosts the synthesis of GDP-mannuronate which, once polymerised, supplies the initial polymeric product of alginate. It is thought that GMD functions as a homodimer. Each monomer is made up of two globular domains linked by an alpha helix. In order to synthesize GDP-mannuronate, GMD has to lodge both the substrate and the cofactor NAD(H), which it does thanks to 'domain-swapping'.

Domain-swapping happens when the C-terminal domain of one monomer clubs up with the N-terminal domain of the other. The two active sites are therefore hybrid. This is a fascinating example of protein cooperation. However it does imply that the enzyme must be supple since the formation of GDP-mannuronate is a two-step oxidation which involves the initial release of NAD+, and the binding of a second NAD(H), while holding onto the intermediate substrate. GMD literally hugs its substrate and cofactor; both ligands are deeply buried within the two clefts with only 10% of their surface peeking over GMD's shoulder.

Why be immersed in a gooey coating? Perhaps for the sake of protection and cell adhesion. Alginate, for example, is used to coat cysts in

some microbes, enabling the cells to survive long periods of drought…but it also has the power of warding off the host's immune system. Biofilms may also be a means of cell communication. Colonies of microbes can secrete alginate and form what has been termed a 'slime city', where diverse colonies live off each other, and the waste of one becomes the nutrient of the other, while the biofilm acts as a motorway for the different substrates. For patients suffering from cystic fibrosis, the effects of alginate can be lethal since mucoid strains of *Pseudomonas aeruginosa* use alginate to adhere to the surface of the patients' lungs. The formation of a biofilm then protects *P.aeruginosa* from the host's immune response… as well as antibiotic therapy.

Since GDP-mannose dehydrogenase is such a key enzyme in alginate synthesis, the knowledge of its 3D structure and function will help to find a way to inhibit alginate production – in the event of *P.aeruginosa* infection – by inhibiting GMD one way or another. What is more, since there is no alginate-biosynthesis in humans, the specific inhibition of GMD should have few side effects.

Despite the drawbacks of *P.aeruginosa* alginate, microbial goo is already used extensively to form capsules around cells which secrete specific substances such as insulin-producing cells for patients with diabetes, for example. In their 'naked' state, the same cells would be digested. Soon, alginate-encapsulated islets of Langerhans could function as a bio-artificial endocrine pancreas. Alginate is also good at stimulating immune cells to secrete cytokines, such as tumour necrosis factor for example, and could therefore be effective in cancer therapy.

Besides the development of novel therapies, alginate has been used for years in the textile and paper industry, for example, to improve dye and ink adhesion, respectively. Alginate is also added to all kinds of food and drink; its viscous properties are used in salad dressings, cake mixtures and ice-creams. It is also added to beer to keep the foam afloat, or to fruit drinks to hold the pulp in suspension. Alginates are also used to treat water, where their aggregation properties enhance flocculation.

The list of alginate use is long and will get longer. Currently, commercial alginate is extracted from brown seaweeds though there is a growing interest for microbial alginate, which is of higher quality but remains more costly. Scientists are even looking into its production by extreme microbes that live in hydrothermal vents. It is thought that such extreme conditions must produce extreme GMDs, which in turn must produce extreme alginates… In the meantime, as you lick your ice-cream, give a thought to GDP-mannose dehydrogenase which participated in its making.

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