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unnatural stuff

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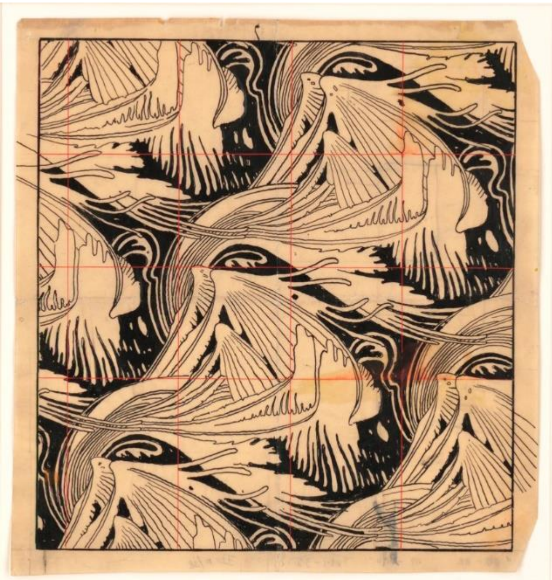
Ever had to deal with tiny polystyrene balls clinging to your carpet? Or admired the neat narrow grooves stamped onto a vinyl record? Perhaps you have just acquired a sleek viscose shirt. Polystyrene, PVC, vinyl, acrylic, rayon, viscose, nylon, PET, polyester – these are words we never think twice about as they slip into a conversation. Epoxy resin and polyurethane are another two, although perhaps less well known. Others are hidden behind more descriptive names such as the popular cling film we wrap around food, which is made out of polyethylene. And there are many more. Their common denominator? Each of these materials are manmade polymers. In other words, they are artificial; Nature does not provide them. However, she can come up with some of the building blocks. Itaconic acid is one, and was first discovered in the fungus *Aspergillus itaconicus* which was named after it. Today, widely used in the synthesis of polymers to make lubricants, thickeners, rubber or resins for example, itaconic acid is provided in quantity by *Aspergillus terreus* – with the help of an enzyme known as CAD, or *cis*-aconitic acid decarboxylase.



Tessellation

by Koloman Moser (1868-1918)

Polymers have a fascinating history. While polymers such as plastics have become less and less popular for the part they now play in polluting the planet, the reason they were developed in the first place was, ironically, to preserve materials of natural origin that were rare or becoming scarce. Two wonderful examples: ivory and silk. As the story goes, towards the end of the 19th Century, a prize of $10,000 was offered to the person who could think up a substitute for ivory. In 1869, after several fruitless trials to produce something stable, the American engineer John Wesley Hyatt finally treated cellulose – which he extracted from cotton fibre – with camphor. The end product – known as celluloid today – had the colour of ivory and could be moulded into all sorts of shapes. It was subsequently used for making items such as billiard balls, false teeth and piano keys. Nylon, made from petroleum, appeared quite some time later, and successfully replaced another scarcity: silk. In the 1930s, the very first nylon was used to make toothbrush bristles. Nylon 'silk' stockings – still frequently called 'nylons' – appeared in 1940 and 64 million pairs were sold within a year.

To cut a long and engaging story short, over the past 150 years, many different polymers have emerged with tailored physical and chemical properties – such as plasticity, strength, elasticity, adhesiveness, resistance to water, resistance to heat and so on. We rub shoulders with manmade polymers on a daily basis. They are used to make our grocery bags and our clothes. They are used in wire insulation, squeeze bottles, toys, outdoor furniture, household and medical appliances, blankets, tents, footwear, luggage, helmets, paints, fingernail polish, eyeglass frames, CDs and… chewing gum. Many of the building blocks are snatched from Nature, and sometimes quite accidentally. Itaconic acid – or methylidenebutanedioic acid ($C_5H_6O_4$) – was discovered in the 1830s while manipulating citric acid. A century later, a filamentous fungus was found to produce the exact same acid, using sugar as a carbon source, and was subsequently called *Aspergillus itaconicus*. Its fellow fungus, *Aspergillus terreus*, also synthesizes itaconic acid – and at a far higher rate. This turned out to be of industrial interest since polymers of the acid are used in materials such as lubricants, thickeners, coatings, cosmetics and synthetic resins.

How does *A.terreus* synthesize itaconic acid? There is a cycle known as the Krebs cycle, the citric acid cycle or the tricarboxylic cycle – a cycle many of us had to study at school because it is a vital pathway used by cells to make energy from a carbon source such as glucose. The Krebs cycle – named after Hans Adolf Krebs who worked it out – takes place in the mitochondrion. Itaconic acid, however, is synthesized in the cell cytosol. Yet both are linked. One of the components produced during the Krebs cycle is citric acid, which is modified to produce cis-itaconic acid. Cis-itaconic acid is then ferried out of the mitochondrion into the cytosol where it is decarboxylated by the enzyme CAD to produce itaconic acid. Itaconic acid is then released into the extracellular environment – from where it can be plucked to manufacture polymers. This occurs with relative ease thanks to the acid's reactive methylene group which is able to self-polymerize.

Does *A.terreus* synthesize aconitic acid so that our nail polish can be finer? No. So why is it synthesized in the first place? Though it had been used as a precursor for industrial polymer synthesis for years, no one knew what its role was in cells until fairly recently. Note: itaconic acid is not only synthesized in *Aspergillus*. In 2013, the acid was found to have antimicrobial activity in mammals and seemed to be involved in the innate immune response. This could imply that the acid is part of *Aspergillus*'s immune response too. Indeed, itaconic acid is able to stall what is known as the glyoxylate shunt, which interacts with the Krebs cycle and is essential for bacteria to survive while they infect. If the shunt is hindered, the bacteria die. This prompts the question: why does itaconic acid not kill us too? So far, the answer has not been found but there seems to be no toxic effect on cells as they synthesize the acid possibly because it is immediately secreted and used.

Like itaconic acid, CAD is not particular to filamentous fungi either and the 3D structure of the human enzyme has been elucidated. Although many differences are found between the *Aspergillus* and the human enzymes, their overall structure is similar. The enzymes work as dimers, where each monomer consists of one small domain and a larger domain, and an active site which is thought to be located in between. Of notable interest are polymorphisms found close to the active site, 20% of which seem to belong only to genomes of African and African American ancestry. These polymorphisms will no doubt have been selected because they proved to be an advantage to these populations. Possibly because they protected them from certain infectious bacteria – such as mycobacteria which have been co-evolving with humans on the African continent for the past 2.6 million years at least.

Poly-itaconic acid production does not depend on fossil fuels, thus making it a choice bio-based polymer, as it can replace the petroleum-based acrylic acids we currently use. To meet ever-growing demands – including demands no one has thought of yet – scientists are continuously looking for ways to produce more itaconic acid faster. The annual production of itaconic acid is currently about 40,000 tons and the most practical way of synthesizing it remains via fermentation by *A.terreus*. So, it could be a question of making the fungus faster and more furious – perhaps by tampering with CAD, or components of the Krebs cycle. Certainly, there is no doubt that the science of polymers, and their use on a daily basis, has improved human life in many ways, and continues to do so. The downside is the pollution it has created and continues to do. As always, it comes down to responsibility and common sense – two notions that are so easy to sweep aside.

Cross-references to UniProt

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