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> ONE MONTH, ONE PROTEIN <

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no license to kill

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Organisms need resources to thrive. If they do not have them, they will find ways to get them. For many humans today, a job and a supermarket down the road provide the very basics of what we need to survive but, not so long ago, our ancestors would travel great distances to find a safe place to sleep and track down food for their families. In so doing, they will have steered clear of territory already occupied or perhaps, on the contrary, decided to compete for its resources. There are various ways of doing this. You can annihilate your adversaries, scare them off, get them to provide for you or render them harmless. Over the millennia, humans have practised each of these ways with panache. Microorganisms, too, show similar imagination. Like street sweepers, they have learned to deal with whatever hinders their way by clearing the path before them. Take, for example, the fungus *Aspergillus fumigatus* which, in the presence of the bacterium *Streptomyces rapamycinicus* secretes a secondary metabolite that renders the bacterium temporarily unable to germinate. The metabolite is known as fumigermin and is synthesized by the enzyme fumigermin synthase.

'One year the milkweed'

by Arshile Gorky (1904-1948)

The term 'secondary metabolite' was coined by the German biochemist Albrecht Kossel (1853-1927). More commonly known as toxins or natural products, secondary metabolites (SMs) are defined as organic compounds which are not directly involved in an organism's normal growth, development or reproduction – although they do sustain all three. As an illustration, flowers produce scents and pigments to attract pollinators, reptiles spit poison to paralyse their prey and bacteria secrete various compounds to gauge their population density. Humans have been swift to discover the benefits of many SMs and have used them for centuries as medicines, pigments, flavouring but also as recreational drugs – like tobacco, alcohol and the psychedelic substances of magic mushrooms.

Albrecht Kossel lived in enthralling times when, thanks to technical progress, scientists were rapidly gaining knowledge on the chemical aspect of life. In this light, Kossel turned his attention to the cell nucleus which he spent a lifetime studying. A pioneer of cell biology and protein chemistry, he was the first to unveil the four different components of DNA – cytosine (C), guanine (G), adenine (A) and thymine (T) – as well as point out the amino-acid content of the nucleus in the form of histones. Although the chemical structure of nucleic acids and amino acids remained unknown in his lifetime, he is considered a pioneer of cell biology and protein chemistry and, by the 1920s had already an inkling of how proteins were built and what they could do: "*The number of Bausteine* [editor's note: building blocks] *which may take part in the formation of the proteins is about as large as the number of letters in the alphabet. When we consider that through the combination of letters an infinitely large number of thoughts can be expressed, we can understand how vast a number of properties of the organism may be recorded in the small space which is occupied by the protein molecule.*"

Fumigermin, a secondary metabolite (or polyketide) produced by the fungus *Aspergillus fumigatus* has a structural feature which belongs to many biologically active metabolites: the alpha-pyrone. Alpha-pyrones are six-membered cyclic unsaturated esters, and are found across all kingdoms of life where they act as intermediates or end products in metabolic pathways, but also as signal molecules to attract partners or ward off competitors and predators. Their biological activities are multiple and their application in medicine just as widespread, where their properties are used for their antimicrobial, antifungal and immunomodulator action for instance, but also to fight diseases as varied as Alzheimer's, cancer, tuberculosis and HIV.

The polyketide fumigermin is secreted by the fungus *Aspergillus fumigatus* when it encounters the soil-dwelling bacterium *S.rapamycinicus*, and it is their interaction which triggers the synthesis of fumigermin synthase in *A.fumigatus*. In fact, it seems that fumigermin is only synthesized by a single strain of *A.fumigatus* (ATCC 46645) when it comes across different strains of *S.rapamycinicus*; other strains of *A.fumigatus* synthesize similar metabolites with similar activities, but not fumigermin itself. Fumigermin synthase, like other polyketide synthases, characteristically sports six protein domains, each of which carries out a different enzymatic reaction to act – like a factory assembly line – as a ketosynthase, an acyltransferase, a dehydratase, a methyl transferase, a ketoreductase and, finally, an acyl-carrier in the making of the alpha-pyrone fumigermin.

Once synthesized, fumigermin is secreted by *A.fumigatus* and enters *S.rapamycinicus* where it tampers with the bacterium's capacity to germinate. How fumigermin enters the bacterium is not yet known – it may occur via passive diffusion for example, or perhaps there are specific transporters. Whichever way, the bacterium is unable to produce spores and is left in a dormant state, while the fungus takes advantage of the surrounding resources. However, scientists found out that *S.rapamycinicus* spore germination is reversible which would imply that the fungus does not set out to kill its competitor but simply keeps it at bay for a while – or at least as long as fumigermin is secreted – while it laps up the soil's riches. This is a surprising and intriguing discovery since most similar metabolites are lethal.

Here is an organism – *S.rapamycinicus* – whose presence induces another – *A.fumigatus* – to produce a metabolite that will temporarily stunt its vitality. It is a peculiar state of affairs but one which must have a meaning that scientists have not yet grasped. Could it be that the bacterium prefers to be flung into a dormant state rather than be liquidated altogether? Or has it not yet found a way to counteract fumigermin? Time will tell, no doubt. We are a far cry from the early days of cell chemistry and Albrecht Kossel's initial discoveries, but Nature continues to remind us how rich and colourful she is.

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Fumigermin synthase, *Aspergillus fumigatus* : Q4WKW9

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