TUM researchers cast light on the mechanics of a bacterial protein blocker

Anti-cancer agent from mother nature

When bush beans become inflicted with morbid brown spots, the culprits are Pseudomonas bacteria. Upon besetting a plant, these harmful microbes release a substance that confuses the plant's defence mechanisms – a substance that may actually prove to be a godsend for humans in the future. This is because the substance also curbs the growth of cancer cells. A team including scientists from the Technische Universität München (TUM) have succeeded in working out the structure of this bacterial matter and have uncovered the substance's hitherto unknown mode of action. (Published in Nature vol. 452, 755-758; 10. April 2008)

Attacking plants is no easy task for bacteria, as the waxy plant surfaces and cell walls present formidable, hard-to-surmount obstacles. And when a bacterium does manage to penetrate this barrier, a plant will often fire up an active line of resistance: It spawns a full arsenal of specialized proteins to activate biochemical defence mechanisms against the pathogen. For this bulwark to function properly, proteins suppressing the underlying mechanism must be removed from the cells. Cellular disposal units, the so-called proteasomes, assume this task. They break down specifically targeted proteins produced by the cell into their basic building blocks.

However, the biochemical defence lines of plants are not insurmountable: Bacteria known as *Pseudomonas syringae pathovar syringae* – Pss in short – secrete a small but very effective protein ring called Syringolin A. These seed confusion in the leaf cells of the involuntary Pss host, the bush bean, thus rendering the Pss bacterial attack successful.

The team of scientists that includes partners from TUM, the Max-Planck Institutes in Martinsried and Dortmund, as well as colleagues from Switzerland, Great Britain and USA, has resolved the question of what exactly this protein ring triggers within the leaves of the bush bean: Syringolin A blocks the proteasomal hydrolytic centres by forming a irreversible covalent chemical bond with the active site nucleophiles. This leads to a veritable protein pile-up in the bush bean leaves, wreaking havoc on the plant's defences.

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The scientists were also able to cast light on the structure and the proteasomal binding mechanism of Syringolin A – and in the process discovered an entire family of substances: They found a series of similar bonds in other microorganisms that function analogous to Syringolin A.

These discoveries are significant not only for the development of crop protection agents for use on plants like the bush bean. Syringolin A & Co may well be applicable to the future treatment of cancer, as well. Human tumour cells also produce many proteins and rely on properly functioning proteasomes. One synthetic proteasome suppressant has been available as a therapeutic agent for a number of years already. It could receive company from the natural substance Syringolin A, which has already shown a growth suppressing effect in experiments with cultivated cancer cells.

The biochemist Groll sees further potential in Syringolin A & Co: Assuming suitable derivatives can be found, it is conceivable that they could be used to fight bacterial human or plant pathogens. In any case, the cornerstone for the discovery and exploration of these novel substances has now been laid.

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