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Statins: 50 years old and with new surprises in store

IN BYGONE DAYS

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In 2023, it was 50 years since the first statin was isolated from fungi and its structure determined. This finding is a fascinating parallel story to the discovery of penicillin.

Penicillium citrinum Pen51. *Photo: jopelka/iStock*

When it became clear that cholesterol in plasma was an important risk factor for developing atheromatosis in arteries, several strategies were devised to reduce plasma cholesterol concentration. Numerous different medications have been developed for this purpose. Perhaps the most significant pharmacological advance was the discovery of drugs that inhibited the production of cholesterol in the liver, namely statins. In 2023, it was 50 years since the Japanese biochemist Akira Endo (b. 1933) and his colleagues isolated and determined the structure of the first statin (1, 2). The fascinating story behind his work is a remarkable example of nature's own contribution to important medications.

Inspired by Fleming

Biosynthesis of sterols plays an important role in many biological systems. Cholesterol was discovered in gallstones in 1789 and was the first sterol to be identified (3). Akira Endo hypothesised that since sterols are important biological substances, some cells must contain synthesis inhibitors that can prevent the growth of other cells that would threaten their proliferation (1, 2). He speculated that there could be an analogy to antibiotics (penicillin and streptomycin) that are produced by certain fungal species. The hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase) enzyme catalyses a rate-limiting step in the synthesis of sterols, including cholesterol (4).

Inspired by Alexander Fleming's (1881–1955) success with penicillin-producing fungi, and equipped with a newly developed method for large-scale assays of HMG-CoA reductase activity, Endo and his colleagues at the company Sankyo began searching various fungal species in 1971 for inhibitors of this enzyme (1, 2). Akira Endo was awarded the European Society of Cardiology 2021 Gold Medal for this pioneering work (5). Over a two-year period, he and his

colleagues tested approximately 6000 species of fungi. In 1972, they identified a potent and irreversible HMG-CoA reductase inhibitor – citrinin, which was already known and had been shown to be nephrotoxic.

Akira Endo (b. 1933). Photo: CC BY-SA 3.0

> ***«In the summer of 1973, they isolated three active inhibitors in cultures from the blue-green mould* Penicillium citrinum Pen51. *The mould was isolated from rice they had collected from a shop selling grain in Kyoto»***

They continued their work, and in the summer of 1973, they isolated three active inhibitors in cultures from the blue-green mould *Penicillium citrinum Pen51* (1, 2). The mould was isolated from rice they had collected from a shop selling grain in Kyoto. This blue-green mould resembles the fungi that contaminate fruits like oranges and melons. All three substances inhibited cholesterol synthesis both in vitro and in vivo. The researchers continued their

study using the most active inhibitor, which was given the name ML-236B, later known as compactin and mevastatin. This was the first statin. This reversible inhibitor of HMG-CoA reductase was structurally determined towards the end of 1973 (1), which is therefore considered the breakthrough year for the discovery of statins.

Nature knows best

From 1974, Endo and his colleagues at Sankyo conducted further studies on compactin. Some time later, researchers at Beecham Group (now GlaxoSmithKline (GSK)) found that compactin was also produced by another mould, *Penicillium brevicompactum* (2). However, compactin (mevastatin) was not used in humans due to the toxic effects observed with extremely high doses in rats. In 1979, researchers in Merck and Endo's research group independently identified a statin produced by the moulds *Aspergillus terreus* and *Monascus ruber*, respectively (2, 5). This substance was named lovastatin and is in clinical use. By applying the fascinating analogical reasoning from the discovery of penicillin, researchers had succeeded in isolating potent cholesterol-lowering HMG-CoA reductase inhibitors.

Aspergillus terreus *colony on rose Bengal agar. Photo: CCo*

Several species of fungi from nature had thus facilitated this important therapeutic innovation. Based on the two naturally occurring statins, compactin (mevastatin) and lovastatin, semi-synthetic and synthetic statins were developed for clinical use (2, 5). A new category of medications was therefore developed that achieved its intended mechanism of action and met expectations for clinical application.

However, the story of statins does not necessarily end there. Do the statin-producing fungi have a broader 'strategy' for self-protection beyond the almost monofactorial inhibition of sterol synthesis? Could there be additional mechanisms and effects that might turn out to be beneficial or potentially harmful? Such aspects have now been revealed as gateways to increasing insight into the overall effects of statins, as discussed below. Statins do more than just reduce cholesterol, they can also be used in cancer treatment.

Cholesterol-independent mechanisms

Although Akira Endo's intention was to use antifungal substances for lowering cholesterol, other mechanisms and effects of statins have also been identified that are likely to lead to a broader clinical application in the future. Firstly, there are several molecular reaction steps from HMG-CoA reductase to cholesterol, i.e. 'downstream' of this enzyme. All these steps and their intermediates are attenuated by statins. Therefore, statins induce a variety of effects parallel to but independent of the lowering of cholesterol (6, 7). These are known as pleiotropic effects.

> ***«Numerous cohort studies have demonstrated therapeutic benefits of statins for various types of cancer»***

The significance of the pleiotropic effects is not fully understood. They may support the clinical effect of cholesterol reduction and/or induce other effects or even clinically significant side effects. Reduced levels of coenzyme Q_{10} due to statin use can potentially have adverse effects on mitochondrial function (8). Pleiotropic effects include, inter alia, reduced cell growth and proliferation, changes in signalling molecules and reduced oxidative stress (7). Numerous cohort studies have demonstrated therapeutic benefits of statins for various types of cancer (9), particularly prostate cancer (10). It has been suggested that both cholesterol reduction and pleiotropic mechanisms play a role here (9, 11).

Epigenetic mechanisms

Akira Endo's speculations about fungal HMG-CoA reductase inhibition were originally based on the effects expected 'downstream' of the enzyme. However, entirely different mechanisms of action for statins have recently been proposed. When statins inhibit HMG-CoA reductase, changes also occur 'upstream' of this enzyme. Thus, statins will increase the substrate acetyl-CoA (12), which in turn

can enhance protein acetylation – one of the mechanisms for post-translational modification of proteins. Statins also inhibit enzymes that deacetylate histones (12, 13) and other proteins. This was a completely unforeseen and surprising mechanism. Allen et al. (12) suggest that increased histone acetylation through epigenetic mechanisms (i.e. altered DNA function) may contribute to the anti-cancer effects induced by statins and to other pleiotropic effects and side effects.

New diabetogenic mechanism proposed

There has been discussion about the significance of the diabetogenic effect of statins. Researchers in the field have been seeking to better understand the unclear mechanisms for this effect (14). Statin-mediated increase of the substrate acetyl-CoA will also elevate acetate levels (15). Acetate is one of the short-chain fatty acids that stimulates the FFA2 and FFA3 receptors, leading to inhibition of insulin secretion. This led us to propose that this mechanism contributes to the diabetogenic effect of statins (16), which would be a completely new mechanism in addition to those previously proposed (17).

The challenge is on

Some fungi produce HMG-CoA reductase inhibitors, the most notable of which are statins. This finding is a fascinating parallel story to the discovery of penicillin. However, research has shown that fungi employ an apparently broader 'mechanistic strategy' than inhibition of cholesterol synthesis. This has the potential to expand clinical application and offer insights into certain side effects. Perhaps further painstaking, patient searches among thousands of fungal species will yield new and important drug categories and reveal surprising mechanisms of action.

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