HMG-CoA

HMG-CoA is an intermediary in the biosynthesis of many structures that the body needs. These structures are isoprenoids and, among other compounds, cholesterol. José was the one who actually discovered HMG-CoA.

What makes HMG-CoA so special is the fact that it does not, like some other intermediaries in many metabolic pathways, revert back to its original components. Instead, it goes on to yield cholesterol and other steroids, both in the test tube and in laboratory animals. Since this was the first irreversible intermediary discovered in the steroid pathway, it became an extremely crucial step in controlling the reactions necessary for cholesterol analysis.

Previous hypocholesterolemic compounds that had been prepared and tested affected the early steps of this synthesis. However, they proved to be enormously toxic because they interfered with the synthesis of many other compounds in addition to cholesterol and steroids. Synthetic chemists had prepared phenolic derivatives of earlier steps along this pathway, but these compounds, while slowing cholesterol biosynthesis, also stopped fatty acids synthesis. They also interfered in many other metabolic pathways. Hence HMG-CoA proved to be a key place for the designing of practical clinical hypocholesterolemic agents.

When José started this work, it was known that tagged acetyl Co-A yielded labeled cholesterol, but the intermediary steps involved were not known. The first experiment carried out, using tagged[1] 14-C materials, showed that if two carbons on the acetyl group were labeled, then every carbon of the newly recovered biosynthesized cholesterol would also be labeled. Thus, no carbons other than those of the acetyl group were required as carbons of cholesterol.

He believed that the next intermediary from the two-carbon acetyl precursor would be a four-carbon compound. If he depicted the acetyl group as an arrow, then the second step would be one of three possibilities to give a four-carbon intermediary. The arrows could face each other whether head to head, tail to tail, or head to tail. The compounds corresponding to these would be diacetyl, where they would face each other. This compound was first isolated then synthesized by none other than Borodin, the famous Russian composer, who isolated it from butter. It is the compound used to lend different products a buttery taste. Borodin used it to flavor Russian

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[1] Organic compounds, tagged (or labeled) are materials in which some of the normally 12-C present in the carbon skeleton of the molecule have been replaced by a carbon that can be pinpointed and readily measured, 14-C and 11-C by their radioactivity, 13-C by mass spectrometry.

wine. When José made this compound radioactive and tested it in biological systems, no real production of labeled cholesterol occurred.

The next compound that José tested was the tail to tail (its name is succinic acid) and that failed, too. But the third compound, when labeled singly or in all its compounds, yielded the expected results. The acetoacetyl group proved to be the four-carbon intermediary he was seeking, for it yielded the labeled cholesterol in the appropriate positions.

Now José wanted to determine the next intermediary, one that would be a six-carbon group. He tried several of the possibilities, and finally one proved successful. This one was HMG-CoA.

The next intermediary was discovered in José's lab by a post-doctorate, Dr. Toveramina of the Merck Lab. Surprisingly it turned out to be a five-carbon compound (mevalonic acid). This compound also did not revert to HMG or to acetyl but, after being polymerized, went to geraniol, then to farnasyl prophospate (rose oil), and then to squalene (the oil of sharks). Squalene yielded, after several more intermediaries, lanosterol (lanolin found in the skin). Then after several further steps, they finally obtained labeled cholesterol. The steps in the metabolic pathway had been completed.

Later on, pharmaceutical houses also prepared modifications of some of the intermediaries close to the final compound. Some of these (i.e. lanosterol modification) would prove to be impractical and dermatologically undesirable. Therefore the attack of cholesterol biosynthesis became concentrated on modifying the structure of HMG-CoA by adding chemical groups all along its skeletal structure. Currently there are over fifteen useful clinical compounds that are pharmaceutically approved and are good practical inhibitors of cholesterol synthesis. These compounds are called "statins", each company naming its own modification. (Merck has Lova-statin, Squib Prava-statin, Davies Atorva-statin, etc., their more recognizable trade names being Mevacor, Provocal, Lipitrol, etc.)