Statins (3-hydroxy-3-methylglutaryl [HMG]-CoenzymeA [CoA] reductase inhibitors) are very effective in lowering serum low density lipoprotein (LDL) cholesterol levels, and many studies have shown that statins are also effective in reducing the incidence of cardiovascular events. A recent study has shown that cardiovascular events can be prevented by reducing serum cholesterol levels via statin therapy even in normocholesterolemic, apparently healthy subjects who have an elevated serum C-reactive protein level; however, statins have also been associated with several adverse effects, such as myopathy and hepatic dysfunction. Rhabdomyolysis is the most severe form of myopathy; according to the Food and Drug Administration, it manifests as distinctive clinical signs and a serum creatinine kinase concentration of more than 10,000 IU. The incidence rate of rhabdomyolysis ranges from 34 to 44 per million person-years in patients receiving statin monotherapy (excluding cerivastatin). It is reported that the case fatality rate of rhabdomyolysis is approximately 10%. Thus, it is vital to elucidate the mechanism underlying statin-induced rhabdomyolysis and prevent its occurrence.

High serum concentration of statins is related to the development of myopathy, and drug interactions and several genetic factors that bring about this condition have been proposed as the risk factors that render patients susceptible to statin-induced myopathy.

Several mechanisms have been proposed for statin-induced myopathy at the cellular level. One such mechanism is the statin-induced reduction in the levels of coenzyme Q10, which is an end product of the mevalonate pathway and a component of the mitochondrial electron transport system; this reduction possibly causes an abnormality in the mitochondrial respiratory system, resulting in mitochondrial dysfunction. However, some animal experiments and human studies have shown that the administration of statins reduces coenzyme Q10 levels in the serum but not in the muscle tissue. Moreover, recent trials in which the effectiveness of coenzyme Q10 administration in patients with statin-induced myopathy was examined have shown contradictory results; hence, the reduction in coenzyme Q10 levels is less likely to be the chief mechanism of statin-induced myopathy. Another proposed mechanism of statin-induced myopathy is the reduction in cholesterol levels, which may result in lower levels of cholesterol in myocyte cell membranes. An in vitro study showed that reducing cholesterol levels by inhibiting squalene synthetase, a downstream enzyme in the cholesterol synthesis cascade, did not result in myotoxicity, thus rendering this an unlikely mechanism. The reduced isoprenylation of several proteins may be linked to statin-mediated muscle toxicity, but few reports have confirmed this hypothesis.

Thus, the precise molecular mechanism underlying statin-induced myopathy has not yet been established. Yu et al. have proposed that cell apoptosis may play a role in statin-induced myopathy, which has also been suggested in previous studies, after discovering that an anti-apoptotic gene, Birc4, is repressed and a pro-apoptotic gene Cflar is induced by the treatment of differentiated C2C12 myotube cells with a relatively high concentration of simvastatin. Both the repression and the induction of the abovementioned genes were detected through microarray experiments and confirmed by measuring protein expression levels. These results suggest that the 2 newly identified genes, Birc4 and Cflar, may be related to statin-induced myopathy. However, the precise mechanism of how these genes are in fact related to cell apoptosis remains obscure and future studies should focus on elucidating this mechanism.

Another topic that might benefit from discussion is the difficulty frequently faced while carrying out
microarray experiments. The currently available microarrays encompass probes specific to most transcripts existing in human cells. A vast amount of data on the expression profiles of these transcripts can be obtained easily after RNA is extracted from cells or tissues. Although microarrays enable high-throughput screening of transcript expression profiles, the results cannot be interpreted in the same way. This is partly because only a small number of the genes have been well documented in terms of their function, and the investigator often needs to manually search through the literature. Recently, several endeavours aimed at resolving this issue have been undertaken, including the establishment of the Gene Ontology (GO) database\(^\text{24}\), which is also referred to in this study\(^\text{22}\). The GO includes the ontology itself and the associations between gene products and the ontological terms. Enormous effort has been invested in this project, and GO has been used in various applications\(^\text{25, 26}\). However, there are certain limitations concerning the GO annotations, which have been discussed in detail in a recent review\(^\text{27}\). The lack of a system enabling high-throughput analysis of microarray results may require investigators who screen for genes of interest using microarray technology to revert back to studying individual gene expressions using traditional molecular biology techniques as in this study, and future improvement in this area is necessary.

References

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