The Endogenous Regulator 24(S),25-Epoxycholesterol inhibits Cholesterol Synthesis at DHCR24 (Seladin-1)

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The oxysterol 24(S),25-epoxycholesterol (24,25EC) can affect cholesterol metabolism at multiple points. Previously, we proposed that 24,25EC has an especially significant role in fine-tuning cholesterol synthesis, since it parallels cholesterol production, and without it, acute cholesterol synthesis is exaggerated. 24,25EC is structurally similar to desmosterol, a substrate for the enzyme 3β-hydroxysterol ∆24-reductase (DHCR24, also called Seladin-1) which catalyzes a final step in cholesterol synthesis. In this study, we reveal a novel mode by which 24,25EC can regulate cholesterol synthesis, by interfering with DHCR24, resulting in the rapid accumulation of the substrate desmosterol, at the expense of cholesterol. This effect was independent of DHCR24 protein levels, and was observed in multiple mammalian cell-lines, including those of hepatic and neuronal origin. We also determined that the specificity of this effect was restricted to certain side-chain oxysterols, notably those oxygenated at C-25. Importantly, endogenous levels of 24,25EC, manipulated by genetic and pharmacological methods, were sufficient to reduce DHCR24 activity.

Together, our work introduces a novel role for 24,25EC in cholesterol homeostasis, through its rapid inhibition of cholesterol synthesis at DHCR24. Also, our work provides new insights into a little studied area, the post-transcriptional regulation of DHCR24, an important enzyme in human health and disease.