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Topical Mevalonic Acid Stimulates *De Novo* Cholesterol Synthesis and Epidermal Permeability Barrier Homeostasis in Aged Mice

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Extracellular lipids of the stratum corneum, which are composed of cholesterol, fatty acid and ceramides, are essential for the epidermal permeability barrier function. With damage to the barrier, a decreased capacity for epidermal lipid biosynthesis in aged epidermis results in an impaired repair response. Mevalonic acid is an intermediate after the rate-limiting step in cholesterol biosynthesis, and is catalyzed by HMG-CoA reductase. In the present study, we investigated the effect of topical mevalonic acid on the murine epidermal permeability barrier function, comparing it with that of cholesterol. Topical treatment of aged mice with acetone caused a number of dependent linear increases in TFWL, more rapidly than that in young mice. Administration of mevalonic acid on the dorsal surface of aged mice enhanced resistance against disruption of the permeability barrier by subsequent acetone treatment, whereas cholesterol revealed no effect. In acetone damaged aged mice, administration of mevalonic acid enhanced the recovery rate of the barrier function more than cholesterol. In young mice, neither mevalonic acid nor cholesterol had any effect on resistance against acetone damage nor the recovery rate from acetone damage. In the skin of mice topically administrated mevalonic acid, a stimulation of cholesterol synthesis and HMG-CoA reductase activity were observed, whereas no stimulation by cholesterol was observed. These data indicate that a topical application of mevalonic acid enhances barrier recovery in aged mice, which is accompanied by not only acceleration of cholesterol biosynthesis from mevalonic acid but also stimulation of the whole cholesterol biosynthesis via an increase of HMG-CoA reductase activity.