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### **Liver X receptor agonists – perspectives of application in prophylactics and treatment of skin photoaging**

Liver X receptors  $\alpha$  and  $\beta$  (LXR $\alpha$  and LXR $\beta$ ) are ligand-activated transcription factors which form heterodimers with the retinoid X receptor (RXR) and, upon ligand binding, regulate the expression of target genes. LXR are activated by oxygenated cholesterol derivatives (oxysterols) which are formed from cholesterol either enzymatically or non-enzymatically by reactive oxygen species. LXR regulate the expression of genes involved in cholesterol export from the cell, its reverse transport to the liver and biliary excretion. LXR $\alpha$  and  $\beta$  are abundantly expressed in human epidermis, whereas LXR $\beta$  predominates in rodent epidermis. Transcriptional activity of LXR and the expression of target genes decreases following skin exposure to ultraviolet (UV) irradiation. LXR $\beta$  knockout mice exhibit many features of preliminary skin aging. Natural and synthetic LXR agonists reduce wrinkle formation in the skin exposed to UV light by suppressing inflammatory cytokines and prostaglandin E2 production, normalizing proteolysis/antiproteolysis balance, and improving epidermal barrier formation. In particular, in experimental models LXR agonists stimulate keratinocyte differentiation, augment synthesis of proteins forming cornified envelope like involucrin, loricrin and flaggrin, and stimulate synthesis and secretion of transglutaminases which are essential for cross-linking of these protein in the stratum corneum. In addition, LXR agonists stimulate synthesis of skin ceramides, their incorporation into lamellar bodies and secretion to the extracellular space, as well as extracellular maturation of epidermal barrier lipids. Consequently, LXR agonists improved epidermal barrier integrity, accelerate maturation of epidermal barrier in fetus/neonate, improve restoration of epidermal barrier after mechanical or chemical injury, and protect against skin dehydration during aging. LXR agonists are potential new therapeutic agents for the prevention and treatment of age-associated skin abnormalities.