SUMMARY

Role of the endocannabinoid system in the regulation of biological processes of human skin derived cells

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In our experiments, we have investigated the role of the endocannabinoid system in the regulation of key biological processes of human epidermal keratinocytes and sebaceous gland-derived sebocytes. We have previously identified the expression of the endocannabinoid system is various elements of the hair follicles. In the first phase of our study, we have analyzed the functional expression of the system on sebaceous gland-derived sebocytes. Similar to the sebaceous glands, we have indestified the existence of CB2 receptor of immortalized SZ95 sebocytes whereas the expression of CB1 was not confirmed. Furthermore, our collaboration partners have shown that these cells produce endocannabinoids, i.e. AEA and 2-AG. We have also found that the endocannabinoids markedly and dose-dependently stimulated sebaceous lipid sysnthesis and induced a chiefly apoptosis-driven cell death. Besides, endocannabinoids significantly stimulated genes expression of various members of the PPAR nuclear receptor family (PPARδ and -γ) and of PPARγ target genes. It was also whown that these actions were selectively mediated by CB2-coupled signaling involving the MAPK pathway. Since cells with "silenced" CB2 exhibited significantly suppressed basal lipid production, our results collectively suggest that human sebocytes utilize a paracrine-autocrine, endogenously active, CB2-mediated endocannabinoid signaling system for positively regulating lipid production and cell survival.

Using human cultured keratinocytes (which express CB1, CB2, and TRPV1) and skin organ-culture models, we have provided the first evidence that AEA markedly suppresses keratinocyte proliferation and induces cell death, most probably due to a Ca^{2+}-influx, both *in vitro* and *in situ*. Moreover, we also present that these cellular actions are mediated by a novel, most probably constitutively active signaling mechanism which involves the activation of the metabotropic cannabinoid receptor CB_1 and a sequential engagement of the "ionotropic cannabinoid receptor" transient receptor potential vanilloid-1 (TRPV1). Hence, the data reported here may encourage one to explore whether the targeted manipulation of the above signaling pathway of the cutaneous ECS could become a useful adjunct treatment strategy for hyperproliferative human dermatoses such as e.g. psoriasis or keratinocyte-derived skin tumors.

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