Skin Cancer

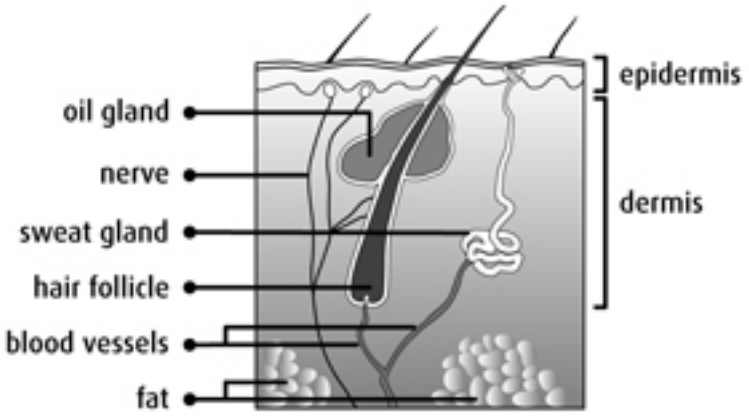
Excerpt from www.cancer.ca:

Skin cancer starts in the cells of the skin. The skin is the body's largest organ. It protects the organs inside your body from injury, infection, heat and ultraviolet light from the sun. The skin helps control your body temperature and gets rid of waste materials through the sweat glands. It also makes vitamin D and stores water and fat.

The skin has two main layers. The layer at the surface is called the *epidermis*. Below the epidermis is the *dermis*.The epidermis is made up of 3 types of cells:

- *Basal cells* are continually being made deep in the epidermis. Newly made round basal cells push the older cells toward the surface of the skin to become squamous cells.
- *Squamous cells* are old cells. As they move toward the skin's surface, they become thin and flat.
- *Melanocytes* are also found deep in the epidermis, in between the basal cells. Melanocytes are cells that make melanin, which gives colour to your skin.

The dermis contains nerves, blood vessels, sweat glands, oil glands and hair follicles.



The most common types of skin cancer are squamous cell cancer and basal cell cancer. Both are known as non-melanoma skin cancer and they can usually be treated successfully.

Melanoma

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Cannabinoid receptors as novel targets for the treatment of melanoma

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ABSTRACT

Melanoma causes the greatest number of skin cancer-related deaths worldwide. Despite intensive research, prevention and early detection are the only effective measures against melanoma, so new therapeutic strategies are necessary for the management of this devastating disease. Here, we evaluated the efficacy of cannabinoid receptor agonists, a new family of potential antitumoral compounds, at skin melanoma. Human melanomas and melanoma cell lines express CB_1 and CB_2 cannabinoid receptors. Activation of these receptors decreased growth, proliferation, angiogenesis and metastasis, and increased apoptosis, of melanomas in mice. Cannabinoid antimelanoma activity was independent of the immune status of the animal, could be achieved without overt psychoactive effects and was selective for melanoma cells *vs.* normal melanocytes. Cannabinoid antiproliferative action on melanoma cells was due, at least in part, to cell cycle arrestat the G1-S transition via inhibition of the prosurvival protein Akt and hypophosphorylation of the pRb retinoblastoma protein tumor suppressor. These findings may contribute to the design of new chemotherapeutic strategies for the management of melanoma.—Blázquez,C., Carracedo, A., Barrado, L., Real, P. J., Fernández-Luna, J. L., Velasco, G., Malumbres, M., and Guzmán, M. Cannabinoid receptors as novel targets for the treatment of melanoma.

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Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors

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Nonmelanoma skin cancer is one of the most common malignancies in humans. Different therapeutic strategies for the treatment of these tumors are currently being investigated. Given the growth-inhibiting effects of cannabinoids on gliomas and the wide tissue distribution of the two subtypes of cannabinoid receptors (CB_1 and CB_2), we studied the potential utility of these compounds in anti–skin tumor therapy. Here we show that the CB_1 and the CB_2 receptor are expressed in normal skin and skin tumors of mice and humans. In cell culture experiments pharmacological activation of cannabinoid receptors induced the apoptotic death of tumorigenic epidermal cells, whereas the viability of nontransformed epidermal cells remained unaffected. Local administration of the mixed CB_1/CB_2 agonist WIN-55,212-2 or the selective CB_2 agonist JWH-133 induced a considerable growth inhibition of malignant tumors generated by inoculation of epidermal tumor cells into nude mice. Cannabinoid-treated tumors showed an increased number of apoptotic cells. This was accompanied by impairment of tumor vascularization, as determined by altered blood vessel morphology and decreased expression of proangiogenic factors (VEGF, placental growth factor, and angiopoietin 2). Abrogation of EGF-R function was also observed in cannabinoid-treated tumors. These results support a new therapeutic approach for the treatment of skin tumors.

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Anticancer activity of anandamide in human cutaneous melanoma cells

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Abstract

Cannabinoids are implicated in the control of cell proliferation, but little is known about the role of the endocannabinoid system in human malignant melanoma. This study was aimed at characterizing the *in vitro* antitumor activity of anandamide (AEA) in A375 melanoma cells. The mRNA expression of genes that code for proteins involved in the metabolism and in the mechanism of AEA action was assessed by RT-PCR. Cell viability was tested using WST-1 assay and the apoptotic cell death was determined by measuring caspase 3/7 activities. A375 cells express high levels of fatty acid amide hydrolase (FAAH), cyclooxygenase (COX)-2, cannabinoid receptor 1 (CB_1), transient receptor potential cation channel subfamily V member 1 (TRPV1) and G-protein-coupled receptor 55 (GPR55) genes. AEA induced a concentration-dependent cytotoxicity with an IC_{50} of 5.8±0.7 μM and such an effect was associated to a caspase-dependent apoptotic pathway. AEA cytotoxicity was potentiated by FAAH inhibition (2-fold increase, $p<0.05$) and mitigated by COX-2 or lipoxygenase (LOX) inhibition (5- and 3-fold decrease, respectively; $p<0.01$). Blocking CB_1 receptors partially decreased AEA cytotoxicity, whereas selective antagonism on the TRPV1 barely affected the mechanism of AEA action. Finally, methyl-β-cyclodextrin, a membrane cholesterol depletory, completely reversed the cytotoxicity induced by the selective GPR55 agonist, O-1602, and AEA. Overall, these findings demonstrate that AEA induces cytotoxicity against human melanoma cells in the micromolar range of concentrations through a complex mechanism, which involves COX-2 and LOX-derived product synthesis and CB_1 activation. Lipid raft modulation, probably linked to GPR55 activation, might also have a role.

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