NOVEL ASPECTS OF CANNABINOID SIGNALING IN HEALTH AND DISEASE OF HUMAN SKIN

BACKGROUND

Although **atopic dermatitis** (AD) and **psoriasis** (PSO) are not directly life-threatening diseases, they are estimated to affect **~15-30%** (AD) and **~2%** (PSO) of the **children** as well as **~2-10%** (AD) and **~1-8.5%** (PSO) of the **adults**. They impair quality of life of millions worldwide, hence, they result in **significant financial and psychological burden to the society** (Bieber 2008; Griffiths et al. 2017). Since research efforts of the past decades failed to unravel the fine details of their pathogenesis, **we still lack universally effective tools to manage them**. Thus, there is an **emerging demand** from both patients and the medical community to better understand their pathogenesis, which would hold out the promise of identifying novel therapeutic targets.

Despite of the many existing differences between their clinical appearance and molecular background, **pathogenesis of AD and PSO share certain fundamental aspects**. i) Both **AD** and **PSO** are characterized by a **complex disorganization** of multifaceted **cutaneous barrier functions**, including regulation of proliferation and differentiation of epidermal keratinocytes (Greb et al. 2016; Kubo et al. 2012; Oláh et al. 2012; Schmuth et al. 2015). ii) They are **multifactorial, inflammation-accompanied** diseases, in which keratinocyte ↔ professional immune cell cross-talk is disturbed (Greb et al. 2016; Kubo et al. 2012; Kuo et al. 2013b; Oláh et al. 2012; Schmuth et al. 2015). Although many open questions await to be answered, in light of the above findings, **epidermal keratinocytes are definitely key players** in the process, since their appropriate differentiation is crucially important in the development of the physicochemical barrier (Oláh et al. 2012), and they can also regulate cutaneous immune responses via the production of various cytokines and chemokines (Karsak et al. 2007). Hence, revealing further details about the regulation of their proliferation/differentiation balance, and of the keratinocyte ↔ professional immune cell cross-talk is likely to help to understand the pathogenesis of AD and PSO, and holds out the promise to establish novel, targeted and causative therapeutic approaches.

Mitochondrial activity, as well as extracellular vesicle (EV)-mediated intercellular communication are recently emerging, yet so far less studied regulators of cutaneous (patho)physiology, whereas the endocannabinoid system (ECS), and, in a wider sense, the complex cutaneous cannabinoid signaling were already shown by us and others to be deeply involved in regulating biology of human skin (Oláh and Bíró 2017; Tóth et al. 2019). Indeed, we showed that the skin-ECS i) negatively regulated human hair growth, as well as proliferation and survival of epidermal keratinocytes; ii) was indispensable for the homeostatic sebum production (another key component of the skin barrier) of sebaceous glands; iii) influenced the biology of sweat glands; and iv) "tonically" suppressed maturation and degranulation of mast cells (Tóth et al. 2019). Moreover, we also demonstrated that "non-classical" **cannabinoid signaling** (e.g., via an adenosine A_{2A} receptor-coupled pathway), activated by several non-psychotropic plant-derived cannabinoids, led to significant **anti-inflammatory** actions and complex cellular anti-acne effects in human sebocytes (Oláh et al. 2016b; Oláh et al. 2014). Of further importance, in a previous study, we have demonstrated the existence of **a functional relationship between** one of the most important endocannabinoid (eCB)-degrading enzymes, fatty acid amide hydrolase (**FAAH**) (Tóth et al. 2019), and the highly **AD-relevant** Toll-like receptor 2 (**TLR2**) **signaling** (Kuo et al. 2013a). Namely, we found that the protein (but not mRNA) expression and activity of **FAAH** can be **up-regulated by TLR2** activation in human epidermal keratinocytes (Oláh et al. 2016a).

These findings collectively hint that cannabinoid signaling does indeed play a key role in epidermal (barrier) homeostasis. Thus, we intended to unveil novel aspects (including its impact on the mitochondrial biology and its putative interplay with the EVs) of the cannabinoid signaling in the cutaneous (patho)physiology.

RESULTS

1. Optimization of several experimental procedures

As planned in the research outline and the work plan, we started our study **by optimizing several experimental procedures**. Namely:

- ✓ We optimized staining protocols for FAAH as well as for occludin (IHC).
- ✓ Together with our collaborative partners (the group of prof. Jürg Gertsch), we determined the optimal culture conditions to measure eCB levels and FAAH-activity of cultured primary human epidermal keratinocytes (NHEKs), and the same procedures were also optimized for the analyses of intact skin samples.
- ✓ We optimized the assessment of several "mitochondrion-relevant" read-out parameters, such as enzyme activity assays, mitochondrial membrane potential, ATP production and mitochondrial ROS generation of NHEKs.
- ✓ Later on, via a newly established international collaboration, we managed to get access to a new thermosensitive fluorescent dye (MitoThermo Yellow), which is not commercially available yet, and started the adaptation of this measurement to our 2D and 3D cultures.
- ✓ Since due to some technical challenges, the first Seahorse experiments aiming to assess O_2 consumption of keratinocytes resulted in relatively poor reproducibility, we decided to complement the method by using a commercially available O_2 consumption measuring kit. Finally, the Seahorse experiments were performed within the confines of a newly established collaboration with Dr. Jakob Wikström (an expert in cutaneous mitochondrial biology) by a PhD student of the PI (Ms. Kinga Fanni Tóth), who spent one month in Dr. Wikström's laboratory at the Karolinska Institutet (Stockholm, Sweden) as a visiting scientist (see below).
- ✓ In order to get a deeper insight to the cutaneous cannabinoid signaling, another PhD student of the PI (Ms. Dorottya Ádám) spent one month in the laboratory of dr. Ellen H. van den Bogaard (an expert in reconstructed skin techniques) at the Radboud University (Nijmegen, Netherlands) as a visiting scientist. In course of the said period, she was able to master the establishment and handling of several reconstructed skin equivalent model systems, including AD as well as PSO-mimicking inflammatory models, which have recently been adapted to our laboratory.
- ✓ We optimized an ultracentrifugation-based isolation protocol to assess EVs from the supernatant of human keratinocytes and sebocytes, and could identify the presence of several eCBs.
- ✓ However, because the EV yield was relatively low, we established an alternative isolation protocol as well by using commercially available EV-isolation kits. To assess purity and reproducibility of the isolation, EVs were checked by transmission electron microscopy and the samples were also tested for the presence of several EV-specific markers (CD9, CD64 and CD81) and for the absence of a "purity" marker (β-tubulin). All of the tested samples were negative for β-tubulin. As expected, serum content of the sebocyte culture medium resulted in a huge EV background. These EVs were strongly positive to CD9, whereas CD81 positivity was less pronounced, and the samples appeared to be negative to CD64 by western blotting. Intriguingly, however, EVs harvested from primary human epidermal keratinocytes cultured under serum-free conditions were positive for CD64, but negative for the other two markers, suggesting that human keratinocytes may be most efficient in producing a special CD64 positive subset of EVs.

2. Investigation of the effects of κ-opioid receptor (KOR) on human epidermal keratinocytes

It has recently been shown that **κ-opioid receptor** (KOR) is down-regulated in lesional skin of patients suffering from AD (Tominaga et al. 2007) or PSO (Kupczyk et al. 2017). Since this correlated with the severity of itch, we hypothesized that homeostatic KOR signaling may act synergistically with the eCB

signaling in controlling (suppressing) cutaneous inflammatory processes. Our major findings on this topic were the following ones:

- ✓ KOR exerted remarkable anti-inflammatory effects, which supported the concept that its pharmacological activation could be a novel approach in the treatment of multiple inflammation-accompanied skin diseases, including not only PSO, but also AD.
- ✓ Importantly, the KOR-agonist nalfurafine had no detrimental impact on viability and proliferation of human keratinocytes even when applied at much higher concentrations than its potent anti-inflammatory dose.
- ✓ Finally, we compared KOR and prodynorphin (PDYN; the precursor of the major endogenous ligands of KOR) expression in the epidermis of healthy volunteers, and AD as well as psoriasis patients. Interestingly, our findings did not confirm the down-regulation of these molecules reported by others (Kupczyk et al. 2017; Tominaga et al. 2007) in the said diseases, which means that, at least in a subset of the patients, putative benefits of KOR-coupled signaling may still be exploitable by selective KOR agonists.
- ✓ These data have been presented at the annual meetings of the Hungarian Physiological Society (HPS; **1 poster**), the Hungarian Dermatological Society (HDS; **1 poster**), as well as at the 3rd Inflammatory Skin Disease Summit (ISDS 2018; **1 poster** and **a related citable abstract**), and **we started the preparation of a manuscript** summarizing our findings.

3. Role of the "classical" eCB-signaling in regulating keratinocyte biology

- ✓ By using several complementary experimental approaches (selective gene silencing, as well as receptor specific agonists and inverse agonists; immunoelectron microscopy of healthy human skin; calorimetry, immunohistomorphometry and *in situ* enzyme activity assays in organ-cultured full-thickness human skin [hSOC]; fluorescent/luminescent high-throughput screening methods on primary human epidermal keratinocytes) we showed that **homeostatic eCB signaling is an important negative regulator of the epidermal mitochondrial activity**.
- ✓ Moreover, we could also confirm that CB_1 cannabinoid receptor is expressed not only in the cell membrane (**cmCB_1**), but also in the mitochondria (**mtCB_1**) of the epidermal keratinocytes. Importantly, our data suggest that the two receptor sub-populations most probably play differential roles in regulating inflammatory responses and differentiation, and that (over)activation of mtCB_1, but not cmCB_1, may impair keratinocyte differentiation and hence occludin expression.
- ✓ Intriguingly, **in a preliminary study**, we found that activation of CB_1 receptor may differentially modulate **keratin 1** and **10 expression** in the human epidermis, suggesting that the impact of CB_1 on the keratinocyte differentiation might be more complex than as it was previously thought (**published** as a non-peer reviewed, but citable *Cover image*; Ramot et al., *Br. J. Dermatol.*, 2018).
- ✓ We assessed expression of **FAAH** in lesional and non-lesional epidermis of patients suffering from AD, as well as in the skin of appropriate healthy control subjects. We found that FAAH was expressed at a higher level in the lesional epidermis of AD patients. Because of the great inter-donor variability, this alteration did not reach the level of statistical significance. However, it supported the concept that dysregulation of the local homeostatic, anti-inflammatory eCB tone may contribute to the development of the symptoms of AD; therefore, we initiated the recruitment of AD patients to perform further functional analyses including eCB determination and *in situ* FAAH activity measurements by using our previously optimized protocols.
- ✓ Since we aimed to further investigate the putative role of eCB-dysregulation in the development of cutaneous inflammatory processes, besides AD patients, we analyzed skin samples of 4-4 subjects suffering from rosacea and PSO, i.e., two additional inflammation-accompanied skin diseases. We found that FAAH was tended to be up-regulated in rosacea, but remained largely unaltered in PSO. Thus, we decided to recruit both AD and PSO patients as well for our subsequent functional studies.

- ✓ We successfully completed the recruitment of healthy volunteers as well as of patients suffering from AD and PSO meeting our preset inclusion criteria (i.e., newly diagnosed patients with medium or severe lesions without previous treatment; 6 donors in each group). In our ongoing experiments the following end-points are being investigated:
    - Levels of the most important eCBs in the skin samples (HPLC-MS; in collaboration with the group of prof. Gertsch)
    - Activity of FAAH in the epidermis (specific activity assay; in collaboration with the group of prof. Gertsch)
    - Expressional alterations of FAAH and occludin (IF/IHC)
    - Expression of CB_1 cannabinoid receptors in the cell membrane ($cmCB_1$) as well as in the mitochondria ($mtCB_1$) of the keratinocytes (electron microscopy)
    - Putative alterations in the epidermal mitochondrial activity (*in situ* activity assays)
- ✓ To further assess the putative role of mitochondrial biology in AD, we treated primary human epidermal keratinocytes with interleukin (IL)-4 and IL-13 to mimic an AD-like cutaneous inflammation. As revealed by the Seahorse measurements (performed at the Karolinska Institutet by a PhD student [Ms. Kinga Fanni Tóth] of the PI), the AD-mimicking cytokine milieu increased the O_2 consumption of keratinocytes. Importantly, this could be prevented by the co-administration of a FAAH-inhibitor (URB597) in a $mtCB_1$-dependent manner, since the cell-penetrating CB_1 antagonist/inverse agonist AM251 (i.e., the one antagonizing both $mtCB_1$ and $cmCB_1$) abrogated the effect, whereas the equipotent, but extracellularly-restricted CB_1 antagonist/inverse agonist hemopressin (i.e., the one acting only on $cmCB_1$) failed to abolish it. These data strongly argue that AD-coupled inflammatory processes may up-regulate epidermal FAAH expression and activity, which in turn disturbs homeostatic mitochondrial activity in a $mtCB_1$-dependent manner.
- ✓ These findings were presented at **1 national** (annual meeting of the Hungarian Physiological Society [HPS]) and **3 international meetings** (4th Endocannabinoid Pharmacology meeting, 10th Targeting Mitochondria Conference, IACM 10th Conference on Cannabinoids in Medicine) in the forms of **1 poster** and **3 lectures** (**all of them invited, keynote lectures** delivered by the PI), and **1 *in extenso* manuscript** (Oláh et al., *Exp. Dermatol.*, 2020)**.**

4. Investigation of the pilosebaceous unit, a major contributor to the skin barrier

In order to further assess the role of the complex cannabinoid signaling in cutaneous intercellular communication, we decided to also investigate a special organ culture system, namely microdissected human hair follicles (HFs), where various cell types of the skin can be investigated simultaneously in their intact tissue microenvironment. Moreover, exploration of the effects of cannabinoid signaling on the HFs is a key question from the perspective of the putative side effect-free future clinical administration of any topically applied cannabinoid-based medications. Because a non-psychotropic phytocannabinoid, (-)-cannabidiol (**CBD**) is already assessed in various ongoing (phase Ib in rosacea), completed (phase II in AD [clinicaltrials.gov ID: NCT03824405] and in acne [clinicaltrials.gov ID: NCT03573518]), as well as planned (phase III in acne) clinical trials, we decided to also study its effects on the biology of human HFs. Interestingly, we found that CBD exerted differential effects on HF growth in a concentration-dependent manner, namely its low micromolar concentrations triggered the onset of the regressive catagen phase most likely via the activation of TRPV4 ion channels. However, when applied at nanomolar concentrations, CBD had no significant effect on the hair cycle, but exerted anti-inflammatory actions via activating adenosine receptors, highlighting the importance of "cannabinoid-associated" signaling pathways in mediating cutaneous effects of different cannabinoids. These results were successfully **published** (Szabó et al., *J. Invest. Dermatol*., 2020; **co-last-authored by the PI**).

Since the above data highlighted the putative involvement of **adenosinergic signaling** in mediating cellular effects of certain cannabinoids as well as in regulating human hair growth, we also aimed to

explore it in greater details. We found that adenosine treatment promoted the growing (anagen) phase of the hair cycle in an A_{2B} receptor-dependent manner, and **published** the data (Lisztes et al., *J. Invest. Dermatol.*, 2020).

Sebaceous gland dysfunction has recently been recognized as an important factor in the pathogenesis of AD (Shi et al. 2015), and we have previously shown that some eCBs are central orchestrators of sebaceous lipogenesis (Tóth et al. 2019). Thus, we also investigated the impact of the eCB signaling on the sebocytes' biology. We found that the major eCB synthesizing and degrading enzymes were expressed in human sebaceous glands, and the elevation of the eCB-tone (due to the inhibition of the eCB reuptake process) led to significant anti-inflammatory actions, and to a moderate increase of the sebaceous lipogenesis, which could be beneficial in alleviating the symptoms of AD. The **manuscript** summarizing the above findings was successfully **published** (Zákány et al., *J. Invest. Dermatol.*, 2018; **co-first-authored by the PI**).

Moreover, we could also demonstrate that human sebocytes metabolized two "eCB-related" substances, namely oleoylethanolamide (**OEA**) and palmitoylethanolamine (PEA), raising the possibility that besides the "classical" eCBs, OEA and PEA might also regulate sebaceous gland biology. Following this line, we found that **GPR119** (the main receptor of OEA) is expressed in human sebocytes *in vitro*, as well as in human sebaceous glands *in situ*, and its expression is decreased in acne patients arguing that disturbance of the homeostatic GPR119 signaling might contribute to the development of this disease. Furthermore, we could also demonstrate that the OEA (mostly, but not exclusively in a GPR119-dependent manner) promoted differentiation and hence sebaceous lipogenesis of human sebocytes. Further dissection of the mechanism of action revealed that lipogenic action of OEA was mediated by ERK1/2, Akt/PKB, CREB, and JNK, but was independent of STAT5. Moreover, OEA also induced pro-inflammatory actions. These findings were presented at **one national** (annual meeting of the **HDS**) and **two international** (IID 2018 and ISDS 2018) **conferences** in the form of **3 poster presentations** and **2** related **citable abstracts**. The manuscript summarizing all the available results has already been accepted for publication (Markovics et al., *J. Invest. Dermatol.*, 2020; **co-last-authored by the PI**).

Finally, we have recently shown that activation of the "non-classical" cannabinoid target **TRPV3** ion channels leads to strong pro-inflammatory response in human keratinocytes (Szöllősi et al. 2018), and it is up-regulated in the lesional epidermis of AD patients (Vasas et al. *under review*). Thus, to assess another aspect of the "non-classical" cannabinoid signaling, we investigated its expression and role in human sebocytes, and found that activation of **TRPV3 suppressed sebaceous lipogenesis, and induced up-regulation and release of several pro-inflammatory cytokines.** Taken together, our data suggested that TRPV3 antagonists may be beneficial in inflammation-accompanied dry skin dermatoses. These data have already been published (Szántó et al., *J. Invest. Dermatol.*, 2019; **co-first-authored by the PI**).

ADDITIONAL COLLABORATIVE PROJECTS

In course of the study, certain additional experiments were also performed, since, although they were not planned in the original proposal, they held out the promise to provide important and relevant data to better understand the complexity of cutaneous inflammation and pruritus in AD and in PSO. Moreover, it should also be noted that these additional side-projects provided invaluable benefit by enabling the PI to establish and further strengthen his national and international collaborative network. Newly established collaborations are highlighted by **bold red fonts**.

1. Investigation of selective serotonin reuptake inhibitors (SSRIs) in human keratinocytes

Since in a recent publication disturbance of the cutaneous serotoninergic signaling has been suggested to contribute to the development of AD symptoms (Rasul et al. 2016), we decided to assess the effects of selected selective serotonin reuptake inhibitors (SSRIs) in a keratinocyte model system. We found that fluoxetine (but, intriguingly, not the other tested SSRIs or serotonin) exerted remarkable anti-

inflammatory actions, and prevented the release of the itch-mediator endothelins from human keratinocytes. Importantly, findings of this side-project provided a valuable additional, highly "AD-relevant" experimental end-point (i.e., the endothelin release). Moreover, although high concentrations and/or long-term treatments of fluoxetine exerted anti-proliferative actions, by using complementary model systems (2D cultures of immortalized as well as primary human epidermal keratinocytes, reconstructed epidermal-equivalents, and full-thickness human skin organ culture) we could also demonstrate that its potent anti-inflammatory concentration has no impact either on the proliferation or on the differentiation of the keratinocytes. Having dissected the promising phenomenon, we also scrutinized the mechanism of action, and found that fluoxetine acts via a non-serotoninergic signaling pathway, most likely through inhibiting certain phosphodiesterases, and elevating intracellular levels of cAMP as well as inhibiting the mTOR pathway. **Preparation of an *in extenso* manuscript summarizing the above data is in progress**.

Collaborative partners involved in the project:

- ✓ Dr. August Wolff GmbH & Co. KG Arzneimittel (industrial collaborator)
- ✓ **Ellen H. van den Bogaard (Radboud University; reconstructed skin-equivalents)**

2. Investigation of the effects of nicotinic acid (NA) in human sebocytes

We also investigated the effects of nicotinic acid (NA; a member of the vitamin B3 complex) on sebocytes' biology. Interestingly, NA was proven to suppress excessive sebaceous lipogenesis induced by "pro-acne" agents via activating hydroxycarboxylic acid receptor 2 (HCA_2). The expression of this receptor on human sebocytes was previously unknown, thus, our findings highlighted a novel, druggable regulator of the lipid production of human sebocytes. These findings were presented at **1 national** (annual meeting of the Hungarian Physiological Society) and **2 international** (International Investigative Dermatology meeting 2018, 3rd Inflammatory Skin Disease Summit 2018) **conferences** in the form of **3 poster presentations** and **2 citable abstracts**, and **1** *in extenso* manuscript has also been published (Markovics et al., *JCMM*, 2019; **co-last-authored by the PI**).

Collaborative partners involved in the project:

- ✓ Christos C. Zouboulis (expert in sebaceous biology)
- ✓ **Zoltán Benyó (expert in HCA_2 receptor biology)**

3. Exploration of the anti-acne effects of honokiol (HNK), a plant-derived putative tribbles homolog 3 (TRIB3) activator

Within the confines of a newly established international collaboration, we assessed the effects of the plant-derived **tribbles homolog 3** (TRIB3; a key cannabinoid target gene in sebocytes) activator **honokiol** (HNK) in human sebocytes, and found that it exerted complex anti-acne effects. These data provided new evidence that direct modulation of the activity of certain cannabinoid target genes may be a promising tool in regulating cutaneous inflammatory processes. The results were presented at the annual meetings of the HPS and HDS as well as of at the annual meeting of the European Society for Dermatological Research (**3 posters** and **1 related citable abstract; all last-authored by the PI**). Moreover, we **started the preparation of a manuscript** summarizing the above findings.

Collaborative partners involved in the project:

- ✓ Christos C. Zouboulis (expert in sebaceous biology)
- ✓ **Jack L. Arbiser (expert in TRIB3 biology)**

4. Further exploration of the roles of TRPM3 ion channels in nociception

Within the confines of another collaboration, we also investigated the effects of certain volatile anesthetics (namely chloroform, halothane, isoflurane, and sevoflurane) on the thermosensitive nociceptor ion channel transient receptor potential melastatin 3 (TRPM3). We found that they inhibited

both the agonist-induced (pregnenolone sulfate and CIM0216), and heat-activated Ca^{2+} signals and transmembrane currents in a concentration-dependent manner in HEK293T cells overexpressing recombinant TRPM3. These data provided a better insight into the molecular mechanism of the analgesic effect of volatile anesthetics, and highlighted possible novel strategies to attenuate TRPM3-dependent nociception. The **manuscript** describing the above effects **has already been accepted for publication** in *Biochemical Pharmacology* (Kelemen et al., *Biochemical Pharmacology*, 2020). Moreover, by using wild-type as well as Trpm3$^{-/-}$ mice, we could also demonstrate that activators of TRPM3 evoked only nocifensive responses, but not itch in wild-type animals, and these nocifensive responses were abolished in the Trpm3$^{-/-}$ strain. Histamine and endogenous non-histaminergic pruritogens induced itch in both wild-type as well as Trpm3$^{-/-}$ mice to a similar extent. Genetic deletion or pharmacological blockade diminished Trpm3-mediated Ca^{2+} responses of sensory neurons, but did not affect responses evoked by pruritogenic substances. Collectively, our results demonstrated that, in contrast to other thermosensitive Trp channels, Trpm3 selectively mediated pain nociception but not itch sensation, and suggested that Trpm3 was a promising candidate to selectively target pain sensation (Kelemen et al. *Biochemical Pharmacology*, in revision).

Collaborative partners involved in the project:

- ✓ **Thomas Voets (expert in TRP channel biology)**

NON-EXPERIMENTAL PROJECT-RELATED ACTIVITIES

Although only 1 review paper was originally planned to be published in course of the 3-year period, we managed to publish **2 review papers** (**1 first- and 1 co-last-authored by the PI**) as well as **1 book chapter**. For details, see the relevant parts of the "**Dissemination, achievements**" section.

IMPACT, INNOVATION, FUTURE PERSPECTIVES

The current basic research project performed with the support of the FK_17 grant of the NRDIO aimed to unveil delicate details of the complex cannabinoid signaling and its putative translational potential in AD, PSO or in other inflammation-accompanied skin diseases. We believe that our above detailed results have the potential to encourage further R & D & I activities and subsequent future clinical trials. We are happy to report that a German company (whose name cannot be revealed yet due to the non-disclosure agreement) has recently expressed its interest in establishing a long-term relationship with our laboratory, and intends to initiate the innovation chain (e.g., management of intellectual property issues, feasibility studies, market research and positioning, marketing, etc.). If this relationship does indeed result in successful future clinical trials, it can be strongly hoped that our pre-clinical and clinical research efforts (besides resulting in definite commercial and economic values/income) will eventually result in obvious social impact, since the application of these novel products may improve quality of life of millions in Hungary and worldwide.

DISSEMINATION OF THE FINDINGS, MAJOR ACHIEVEMENTS

Although it was not part of the official work plan, we strongly believe that dissemination of our latest findings towards the society is crucially important. Thus, in the past years we regularly joined to the **Researchers' night events**, where we had the chance to present our most intriguing data in layman's terms to the public.

Since the long-term goal of the FK calls is to help the scientific development of the young PIs, and **to facilitate the establishment of their own teams**, it seems to be relevant to mention that in course of the project **the PI became supervisor of 3 PhD students, and formed his independent research team**. Moreover, one of the PhD students of the PI, Ms. Kinga Fanni Tóth, was recently awarded by the prestigious *Skin Science Travel Award* of the European Society for Dermatological Research, which enabled her to visit the Karolinska Institutet, where, within the confines of a **newly established collaboration** with the team of Dr. Jakob Wikström, she performed important experiments related to the current project (see above).

By the time of the submission of the application, the PI had 14 accepted manuscripts (IF: ~70) among which 6 was first-authored (IF: ~31). In the original work plan of the proposal, we planned to publish/submit **2 original papers** as well as **1 review paper** in course of the project, and to present our data at **1 national** and at **1 international meeting each year**. We believe that this plan was markedly outperformed, as during the course of this 3-year project, **both the number of the publications as well as the cumulative impact factor of the PI were almost doubled**, and the **majority** of the newly published papers were **first- or last-authored** by the PI. Moreover, it is also noteworthy that **the PI has been invited to give keynote lectures at international** (the 4th Endocannabinoid Pharmacology Meeting in 2018, the 10th Cannabinoid Conference of the International Association for Cannabinoid Medicines in 2019, and the 10th Targeting Mitochondria Conference in 2019) **conferences** indicating the increasing impact and international acknowledgement of his scientific work. Finally, it should also be mentioned that, as a special recognition of his expertise, during the course of the current project, **the PI was requested to join the editorial board of "Dermato"** (https://www.mdpi.com/journal/dermato/editors) a new dermatological journal of MDPI to be launched in the near future, and **to provide consultancy services to Botanix Pharmaceuticals Ltd.**, a company organizing the first human clinical trials using topically applicable CBD in acne (completed phase II; phase III is in preparation), AD (completed phase II), PSO (ongoing phase Ib), and rosacea (ongoing phase II).

LIST OF THE PROJECT-RELATED PUBLICATIONS

***In extenso* publications (10 [IF: 56.836]; among which 4 are first-authored [IF: 22.312], 4 are last-authored [IF: 22.421], and 2 are co-authored by the PI [IF: 12.103]; citations are given according to Google scholar [10/29/2020]):**

1) **Oláh A**, Szekanecz Z, Bíró T (2017): Targeting cannabinoid signaling in the immune system: "High"-ly exciting questions. *Fr. Immunol.* **8:**1487. doi: 10.3389/fimmu.2017.01487. **IF: 5.511.** Immunology: **Q1;** Citations: **52.** *This review paper focuses on summarizing the immunological effects of the cannabinoid signaling.*
2) Zákány N*, **Oláh A***, Markovics A, Takács E, Aranyász A, Nicolussi S, Piscitelli F, Allarà M, Pór Á, Kovács I, Zouboulis CC, Gertsch J, Di Marzo V, Bíró T, Szabó T (2018): Endocannabinoid tone regulates human sebocyte biology. *J. Invest. Dermatol*. **138(8):**1699-1706. doi: 10.1016/j.jid.2018.02.022. **IF: 6.29** *__Shared first-authorship.__ Dermatology: **D1;** Citations: **10.** *This paper describes the expression and functional roles of the major members of the ECS in human sebocytes in vitro and sebaceous glands in situ.*
3) Szántó M*, **Oláh A***, Szöllősi AG, Tóth KF, Páyer E, Czakó N, Pór Á, Kovács I, Zouboulis CC, Kemény L, Bíró T, Tóth BI (2019): Activation of TRPV3 inhibits lipogenesis and stimulates production of inflammatory mediators in human sebocytes – a putative contributor to dry skin dermatoses. *J. Invest. Dermatol*. **139(1):**250-253. doi: **10.1016/j.jid.2018.07.015. IF: 7.143** *__Shared first-authorship.__ Dermatology: **D1;** Citations: **12.** *This paper describes the lipostatic and pro-inflammatory role of TRPV3, an ionotropic cannabinoid receptor.*
4) Tóth KF, Ádám D, Bíró T*, **Oláh A*** (2019): Cannabinoid signaling in the skin: Therapeutic potential of the "c(ut)annabinoid" system. *Molecules* **24:**918. doi: 10.3390/molecules24050918**. IF: 3.267** *__Shared last authorship.__ Pharmaceutical Science: **Q1;** Citations: **40.** *This review paper summarizes the available knowledge on the cutaneous cannabinoid signaling.*
5) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, Bíró T#, **Oláh A#** (2019): Nicotinic acid suppresses sebaceous lipogenesis of human sebocytes via activating hydroxycarboxylic acid receptor 2 (HCA_2). *J. Cell Mol. Med.* **23:**6203–6214. doi: 10.1111/jcmm.14505. **IF: 4.868** *__Shared last authorship.__ Molecular Medicine: **Q1;** Citations: **6.** *This paper describes the lipostatic and anti-proliferative effects of nicotinic acid, and provides evidence that they are mediated via activating a previously unknown regulator of sebocyte function, namely hydroxycarboxylic acid receptor 2 (HCA_2).*
6) Szabó IL, Lisztes E, Béke G, Tóth KF, Paus R, **Oláh A***, Bíró T* (2020): The phytocannabinoid (-)-cannabidiol (CBD) operates as a complex, differential modulator of human hair growth: Anti-inflammatory submicromolar versus hair growth inhibitory micromolar effects. *J. Invest. Dermatol*. **140:**484-488. doi: 10.1016/j.jid.2019.07.690. **IF: 7.143 (according to JCR 2019)** *__Shared last authorship.__ Dermatology: **D1;** Citations: **4.** *This paper describes the differential effects of the non-psychotropic phytocannabinoid cannabidiol on human hair follicles.*
7) Lisztes E, Tóth BI, Bertolini M, Szabó IL, Zákány N, **Oláh A**, Szöllősi AG, Paus R, Bíró T (2020): Adenosine promotes human hair growth and inhibits catagen transition in vitro – role of the outer root sheath keratinocytes. *J. Invest. Dermatol*. **140:**1085-1088.e6. doi: 10.1016/j.jid.2019.08.456. **IF: 7.143 (according to JCR 2019).** Dermatology: **D1;** Citations: **2.** *This paper describes the role of the non-classical, purinergic branch of the cannabinoid signaling in human hair follicles.*
8) Markovics A, Angyal Á, Tóth KF, Ádám D, Pénzes Zs, Magi J, Pór Á, Kovács I, Törőcsik D, Zouboulis CC, Bíró T*, **Oláh A*** (2020): GPR119 is a potent regulator of human sebocyte biology. *J. Invest. Dermatol.* **140(10):**1909-1918.e8. doi: 10.1016/j.jid.2020.02.011. **IF: 7.143 (JCR 2019);** *__Shared last-authorship, corresponding author.__ **Dermatology: D1; Citations (Google scholar): 0.** *This paper describes the role of OEA and the novel cannabinoid receptor GPR119 in the regulation of human sebocyte biology*.

9) Kelemen B, Lisztes E, Vladár A, Hanyicska M, Almássy J, **Oláh A**, Szöllősi AG, Pénzes Zs, Posta J, Voets T, Bíró T, Tóth BI (2020): Volatile anaesthetics inhibit the thermosensitive nociceptor ion channel transient receptor potential melastatin 3 (TRPM3). *Biochemical Pharmacology.* **174 (2020) 113826:**1-11. doi: 10.1016/j.bcp.2020.113826. **IF: 4.96 (JCR 2019); Pharmacology: Q1; Biochemistry: Q1; Citations (Google scholar): 1.** *This paper describes the effects of volatile anesthetics on TRPM3 channels*.

10) **Oláh A***, Alam M*, Chéret J, Kis NG, Hegyi Z, Szöllősi AG, Vidali S, Bíró T, Paus R (2020) Mitochondrial energy metabolism is negatively regulated by cannabinoid receptor 1 in intact human epidermis. *Exp. Dermatol.* **29(7):**616-622. doi: 10.1111/exd.14110.
IF: 3.368 (JCR 2019); ****Shared first authorship.* **Dermatology: Q1; Citations (Google scholar): 0
In this paper, we demonstrate the expression and functional role of mtCB1 in human keratinocytes for the first time.

Book chapters:

1) Bíró T, **Oláh A**, Tóth BI, Szöllősi AG (2018) Endogenous Factors That Can Influence Skin pH. In. Surber C, Abels C, Maibach H (eds.) *pH of the Skin: Issues and Challenges*. Curr Probl Dermatol. Basel, Karger, vol. 54, pp. 54–63. doi: 10.1159/000489518. Citations: **1.** *In this book chapter we provide a concise overview of the endogenous factors involved in the development and maintenance of the acidic cutaneous pH (i.e., the "acid mantle"). Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

British Journal of Dermatology cover image (not peer-reviewed, but citable publication):

1) Ramot Y, **Oláh A**, Paus R (2018): Cover Image: Neuroendocrine treatment of inherited keratin disorders by cannabinoids? *Br. J. Dermatol.* **178(6):**1469. doi: 10.1111/bjd.16570. Citations: **11.** *In this paper, we present preliminary evidence showing that activation of CB1might differentially regulate keratin expression in intact human epidermis in situ. Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

Submitted manuscripts in the revision phase (2; both of them co-authored by the PI; IF: 12.103 [JCR 2019]):

1) Vasas N, Angyal Á, Pénzes Zs, Kistamás K, Nánási PP, Molnár Sz, Szegedi A, **Oláh A**, Tóth BI, Szöllősi AG, Bíró T: Transient receptor potential vanilloid 3 expression is increased in non-lesional skin of atopic dermatitis patients. ***Submitted to Journal of Investigative Dermatology*** **(IF: 7.143 [JCR 2019]).**
2) Kelemen B, Pinto S, Kim N, Lisztes E, Hanyicska M, Vladár A, Oláh A, Pénzes Zs, Shu B, Vriens J, Bíró T, Rohács T, Voets T, Tóth BI: The TRPM3 ion channel mediates pain but not itch evoked by endogenous pruritogenic mediators. ***Submitted to: Biochemical Pharmacology*** **(IF: 4.96 [JCR 2019]).**

Manuscripts in preparation (3; all 3 last-authored by the PI):

1) Tóth KF, Szabó-Papp J, Ádám D, Pénzes Zs, Niehues H, van den Bogaard EH, Bíró T, Kilić A, Soeberdt M, Abels C, **Oláh A**: The selective serotonin reuptake inhibitor fluoxetine exerts anti-inflammatory actions on human epidermal keratinocytes.
2) Ádám D, Tóth KF, Arany J, Sárkány F, Bíró T, Kilić A, Soeberdt M, Abels C, **Oláh A**: Activation of κ-opioid receptor (KOR) suppresses pro-inflammatory response of human epidermal keratinocytes.
3) Arany J, Tóth KF, Ádám D, Faragó P, Szilárd Póliska, Bíró T, Arbiser JL, Emanuela Camrea, Mauro Picardo, Zouboulis CC, **Oláh A**: The putative tribbles homolog 3 (TRIB3) activator honokiol suppresses lipogenesis, and exerts anti-proliferative as well as anti-inflammatory effects on human sebocytes.

Citable abstracts (6; 1 first-authored and 4 last-authored by the PI):

1) **Oláh A**, Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, Bíró T (2018): Nicotinic acid suppresses sebaceous lipid synthesis of human sebocytes via activating hydroxycarboxylic acid receptor 2 (HCA2). *J. Invest. Dermatol.* **138(5):**S224. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*
2) Tóth KF, Markovics A, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, Bíró T, **Oláh A** (2018): Endocannabinoid-like molecule oleoylethanolamide promotes sebaceous lipid synthesis. *J. Invest. Dermatol.* **138(5):**S224. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*
3) Ádám D, Tóth KF, Sárkány F, Soeberdt M, Abels C, **Oláh A**, Bíró T (2018): Activation of κ-opioid receptor (KOR) suppresses pro-inflammatory response of human epidermal keratinocytes. *Exp. Dermatol.* **27(Supplement 2):**38.
4) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, Bíró T, **Oláh A** (2018): Sebaceous lipogenesis of human sebocytes is suppressed by nicotinic acid via the activation of hydroxycarboxylic acid receptor 2 (HCA2). *Exp. Dermatol.* **27(Supplement 2):**27.
5) Tóth KF, Markovics A, Ádám D, Pénzes Zs, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, Bíró T, **Oláh A** (2018): GPR119 is a potent novel regulator of human sebocyte biology. *Exp. Dermatol.* **27(Supplement 2):**36.
6) Tóth KF, Ádám D, Arany J, Faragó P, Arbiser JL, Zouboulis CC, Bíró T, **Oláh A** (2019): The putative tribbles homolog 3 (TRIB3) activator honokiol suppresses lipogenesis, and exerts anti-proliferative as well as anti-inflammatory effects on human sebocytes. *J. Invest. Dermatol.* **139(9S) Supplement 2:**S319. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

Posters (13; 1 first- and 8 last-authored by the PI of the project) and lectures (3; all of them invited, keynote lectures [highlighted below with bold red fonts]), presented at national and international meetings:

1) **Oláh A**, Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, Bíró T (2018): Nicotinic acid suppresses sebaceous lipid synthesis of human sebocytes via activating hydroxycarboxylic acid receptor 2 (HCA2). *5th International Investigative Dermatology (IID) Meeting, 2018. 05.16-19., Orlando, Florida, USA* http://iid2018.org/ **POSTER presentation.**
2) Tóth KF, Markovics A, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, Bíró T, **Oláh A** (2018): Endocannabinoid-like molecule oleoylethanolamide promotes sebaceous lipid synthesis. *5th International Investigative Dermatology (IID) Meeting, 2018. 05.16-19., Orlando, Florida, USA* http://iid2018.org/ **POSTER presentation.**
3) Tóth KF, Faragó P, Ádám D, Sárkány F, Markovics A, Arbiser JL, Zouboulis CC, **Oláh A**, Bíró T (2018): A tribbles homolog 3 (TRIB3) aktivátor honokiol vizsgálata humán szebocitákon. *Annual meeting of the Hungarian Physiological Society (Szeged, Magyarország; 2018. június 27-30.)* http://www.regio10.hu/hu/?mod=webshop_cnt&cla=webshop_cnt&fun=showconflist&conf_id=4492 **POSTER presentation.**
4) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, Bíró T **Oláh A** (2018): A nikotinsav a „hydoxycarboxylic acid receptor 2" (HCA2) aktiválásával csökkenti a humán szebociták faggyúlipid-termelését. *Annual meeting of the Hungarian Physiological Society (Szeged, Hungary; 06/27/2018-06/30/2018)* http://www.regio10.hu/hu/?mod=webshop_cnt&cla=webshop_cnt&fun=showconflist&conf_id=4492 **POSTER presentation.**
5) Sárkány F, Ádám D, Tóth KF, Faragó P, Soeberdt M, Abels C, **Oláh A** Bíró T (2018): A κ opioid receptor (KOR) hatásainak vizsgálata humán epidermális keratinocitákon. *Annual meeting of the Hungarian Physiological Society (Szeged, Hungary; 06/27/2018-06/30/2018)*

http://www.regio10.hu/hu/?mod=webshop_cnt&cla=webshop_cnt&fun=showconflist&conf_id=4492 **POSTER presentation.**

6) **Oláh A** (2018): (Endo)cannabinoid signaling and stress-related disorders in the integumentary system - Is "stoned" skin less stressed? *4th Endocannabinoid Pharmacology Meeting (Bern, Switzerland; 10/25/2018-10/26/2018)* http://www.endocannabinoid-pharmacology.ch/2018.html **ORAL presentation (invited, keynote lecture).**

7) Tóth KF, Markovics A, Ádám D, Pénzes Zs, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, Bíró T, **Oláh A** (2018): A novel endokannabinoid oleoil-etanolamid hatásainak vizsgálata humán szebocitákon. *Annual meeting of the Hungarian Dermatological Society (Budapest, Hungary; 11/29/2018-12/01/2018)* *https://www.convention.hu/Rendezveny/Reszletek/MDT18/Koszonto* **POSTER presentation.**

8) Ádám D, Tóth KF, Sárkány F, Faragó P, Soeberdt M, Abels C, **Oláh A**, Bíró T (2018): A κ opioid receptor (KOR) hatásainak vizsgálata humán epidermális keratinocitákon. *Annual meeting of the Hungarian Dermatological Society (Budapest, Hungary; 11/29/2018-12/01/2018)* *https://www.convention.hu/Rendezveny/Reszletek/MDT18/Koszonto* **POSTER presentation.**

9) Ádám D, Tóth KF, Sárkány F, Soeberdt M, Abels C, **Oláh A**, Bíró T (2018): Activation of κ-opioid receptor (KOR) suppresses pro-inflammatory response of human epidermal keratinocytes. *3rd Inflammatory Skin Disease Summit (Vienna, Austria; 12/12/2018-12/15/2018)* *http://www.isds2018.org/* **POSTER presentation**.

10) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, Bíró T, **Oláh A** (2018): Sebaceous lipogenesis of human sebocytes is suppressed by nicotinic acid via the activation of hydroxycarboxylic acid receptor 2 (HCA2). *3rd Inflammatory Skin Disease Summit (Vienna, Austria; 12/12/2018-12/15/2018)* *http://www.isds2018.org/* **POSTER presentation**.

11) Tóth KF, Markovics A, Ádám D, Pénzes Zs, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, Bíró T, **Oláh A** (2018): GPR119 is a potent novel regulator of human sebocyte biology. *3rd Inflammatory Skin Disease Summit (Vienna, Austria; 12/12/2018-12/15/2018)* *http://www.isds2018.org/* **POSTER presentation**.

12) Tóth KF, Ádám D, Kis NG, Hegyi Z, Pénzes Zs, Gyetvai Á, Paus R, Bíró T, **Oláh A** (2019): A sejtfelszínen és mitokondriálisan kifejeződő CB1 receptor szubpopulációk szerepének vizsgálata epidermális keratinocitákon. *Annual meeting of the Hungarian Physiological Society (Budapest, Hungary; 06/05/2019-06/08/2019)* *http://www.eqcongress.hu/kongresszusadat/fame/* **POSTER presentation**.

13) Tóth KF, Ádám D, Arany J, Faragó P, Arbiser JL, Zouboulis CC, Bíró T, **Oláh A** (2019): The putative tribbles homolog 3 (TRIB3) activator honokiol suppresses lipogenesis, and exerts anti-proliferative as well as anti-inflammatory effects on human sebocytes. *49th Annual Meeting of ESDR (Bordeaux, France; 09/18/2019-09/21/2019)* *http://esdrmeeting.org/* **POSTER presentation**.

14) Tóth KF, Faragó P, Ádám D, Sárkány F, Arany J, Arbiser JL, Zouboulis CC, Bíró T, **Oláh A** (2019): A tribbles homolog 3 (TRIB3) aktivátor honokiol vizsgálata humán szebocitákon. *Annual meeting of the Hungarian Dermatological Society (Budapest, Hungary; 11/28/2019-11/30/2019)* *https://convention.hu/Rendezveny/Reszletek/MDT19/Koszonto* **POSTER presentation.**

15) **Oláh A** (2019): Cannabinoids and skin: The "c(ut)annabinoid" system as a novel player in regulating cutaneous mitochondrial biology. *10th Targeting Mitochondria Conference (Berlin, Germany; 10/27-29/2019)* https://www.targeting-mitochondria.com/ - **ORAL presentation (invited, keynote lecture).**

16) **Oláh A** (2019) Cannabinoids in dermatology: A "high" way to heal? *IACM 10th Conference on Cannabinoids in Medicine (Berlin, Germany; 10/31-11/02/2019)* http://cannabinoidconference.org/ - **ORAL presentation (invited, keynote lecture).**

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