**Innate Immunity, Microbiology, Inflammation**

**ABSTRACTS**

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**Drafty of a receptor-dependent step in cathelicidin activation of inflammation identifies a novel therapeutic target for psoriasis and rosacea**

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The skin immune system is regulated by bioactive lipids that initiate and amplify inflammation but control its efficient ending also called resolution. When dysregulated, bioactive lipid mediators contribute to skin pathologies by unresolved inflammation leading sometimes to chronic inflammation or fibrosis. Recently, age-associated alterations in inflammation and resolution programs were reported in aged mice allowing us to hypothesize that inflammation and its resolution could be impaired in aged human skin. Using PMAA-treated skin explants from young (24±9) and old (58±3) yd donors, we have performed a metabololipidomic study using LCMS-MS. We have shown that prostaeglandinE2 (PGE2), a pro-inflammatory mediator as well as g-hexatriene (LXa4), a pro-resolutive biomarker, were produced and temporally regulated in inflamed young skins. In contrast, a delayed and weaker inflammatory response with a seemingly defective production of specialized pro-resolving mediators was noticed in old skins. Using principal component analysis, we have also shown that in young skin arachidonic acid pathway was highly mobilized with subsequent biosynthesis of both pro- and anti-inflammatory mediators (PGE2, TXB2) and pro-resolving mediators (LXa4, LXb4). In old skins, the EPA/DHA pathways were rather mobilized without biosynthesis of final pro- and anti-resolving mediators. Hence, the metabololipidomic profiling of old skins uncovered an endogenous resolution program of inflammation that was associated with dysregulation and/or absence of pro-resolving mediators. Taken together, the present results seem to indicate a role for lipoxins to rebalance cutaneous inflammation during aging and to rescue failed resolution in aged skin.

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**Trichophyton rubrum infection on reconstructed human epidermis induces simultaneous epidermal barrier disruption and keratinocyte activation**

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Skin microbiome has an important role as host guardian, contributing to several physiological functions including skin barrier maintenance and protection against pathogenic microorganisms. It is postulated that skin microbiome communicates with skin cells regulating protein turnover and microorganism adhesion to keratinocytes. Prebiotics are widely used for improving the health of digestive tract that reflects itself on skin surface. Most ingredients used in topical use formulations might have an unknown prebiotic effect that contributes to its performance on skin. Little is known about the mechanisms triggered by specific ingredients that have prebiotic effect in skin gene expression. In this study, we tested different prebiotic technologies in a cellular model and showed that they are able to modulate significantly gene expression related to skin maintenance, differently modifying skin milieu depending on the technology used. Moreover, these ingredients interfere in microorganism adhesion to keratinocytes, suggesting that prebiotics and the microbiome are important to maintain skin health and that these technologies can be addressed to preserve skin integrity.

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**Drafty 103 characters a distinct molecular phenotype of human acral melanoma, by its correlated expression with IL-17A and IFN-g mediated immune genes, as well as MCR1-mediated signature peptides**

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β-defensin 103 highly expressed in stratum corneum and regulated by IL-17A and IFN-g, was recently identified as an MCR1 receptor agonist, which increases levels of pigmentation in mammals, and regulates melanoma cell migration. Our human melanoma research showed that high expression of DefB103B characterizes acral melanoma, which is associated with a poor prognosis, and is genetically different from other subtypes of melanoma. We first compared gene expression profiles of acral melanoma (n=10 for array, n=20 for PCR) to non-acral melanoma (n=21 for array, n=4 for array, n=7 for PCR) and non-acral skin (n=12 for array and PCR). Compared to non-acral melanoma, expression of DefB103B was increased in acral melanoma (p<0.05). In addition, the expression of DefB103B in acral melanoma was correlated with the number of CD11c+ dendritic cells in the tissue (r=0.77), the expression of IL-17A pathway genes (IL-17A = 0.83), IL-17F = 0.50, IL-23 (r=0.49), IL-19 (r=0.86), IL-20 (r=0.97). IFN-g pathway genes (IFN-g = 0.49), and MCR1-mediated signatures (MtF1 = 0.62), TYR (r=0.49) (p<0.05). Those correlations were not significant in normal skin (p>0.05). Thus, we propose that DefB103B is a novel access of keratinocytes to be a potential mechanism for abnormally dark pigmentation and invasive tumor progression of acral melanoma.

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**MicroRNA-17-92 cluster promotes the proliferation and the chemokine production of keratinocytes: Implication for the pathogenesis of psoriasis**

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MicroRNA-17-92 (miR-17-92) is a miRNA cluster that regulates cell growth and immunity, but the role of miR-17-92 in keratinocytes and its relation to skin diseases have not been well investigated. In the present study, we initially found that miR-17-92 cluster promotes proliferation of keratinocytes via suppression of cell cycle inhibitor C20 (CCND2) expression, miR-17-92 cluster facilitated the secretion of C-X-C motif chemokine ligand 9 (CXCL9) and C-X-C motif chemokine ligand 10 (CXCL10) from keratinocytes by inhibiting suppressor of cytokine signaling 1 (SOCS1) expression. Moreover, miR-17-92 cluster was positively correlated with the disease severity in psoriasis individuals (p=0.03). At last, miR-17-92 cluster was increased in keratinocytes by cytokines through the activation of signal transducers and activators of transcription 1 (STAT1) signaling pathway. Our findings demonstrate that cytokine-induced overexpression of miR-17-92 cluster can promote the proliferation and the immune function of keratinocytes and thus may contribute to the development of psoriasis. Moreover, miR-17-92 cluster as a potential therapeutic target for psoriasis and other skin diseases with similar inflammatory pathogenesis.

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**Prebiotic stimulant alters gene expression in skin**

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Skin microbiome has an important role as host guardian, contributing to several physiological functions including skin barrier maintenance and protection against pathogenic microorganisms. It is postulated that skin microbiome communicates with skin cells regulating protein turnover and microorganism adhesion to keratinocytes. Prebiotics are widely used for improving the health of digestive tract that reflects itself on skin surface. Most ingredients used in topical use formulations might have an unknown prebiotic effect that contributes to its performance on skin. Little is known about the mechanisms triggered by specific ingredients that have prebiotic effect in skin gene expression. In this study, we tested different prebiotic technologies in a cellular model and showed that they are able to modulate significantly gene expression related to skin maintenance, differently modifying skin milieu depending on the technology used. Moreover, these ingredients interfere in microorganism adhesion to keratinocytes, suggesting that prebiotics and the microbiome are important to maintain skin health and that these technologies can be addressed to preserve skin integrity.