Health supplement Spirulina induces inflammatory cytokine production via monocye derived dendritic cells and classical monocyte activation in Dermatomyositis (DM) patients. We sought to evaluate whether Spirulina’s immunostimulatory effects differ in healthy controls (HC) compared to DM. We performed ELISA on Spirulina stimulated HC and DM PBMC supernatants, demonstrating similar effects in both HC and DM with Spirulina significantly increasing TNFα and IFNγ levels. Inhibition of TNFα or IFNγ significantly decreased Spirulina’s immunostimulatory effects on both TNFα (p<0.0001) and IFNγ (p<0.05) at 0.3 mg/ml Spirulina. Using flow cytometry, we investigated Spirulina’s immunostimulatory effects at the cellular level, demonstrating that TNFα and IFNγ secretion, Spirulina has the greatest effect on monocyte-derived macrophages (Mo/Mac) and dendritic cells (DC) in DM and HC. At concentrations of 0.3, 1, and 3 mg/mL of Spirulina, the percent of MoDCs secreting IFNγ increased from a mean (SEM) of 0.11% to 96.40% and 96.90% (1.80) (p<0.0001) respectively. The percent of MoDCs secreting IFNγ was increased (p<0.0001) and pre treatment with TLRA inhibitor suppressed CM activation (p<0.05). Moreover, the MFI of CMs secreting IFNγ increased significantly (p<0.05). TLRA or TBK1 inhibition decreased MFI for both MoDC and CMs (p<0.05 and p<0.001 respectively). These data demonstrate that Spirulina induces DM and MoDC activation in DM, likely via TLRA or TBK1 activation.

Hyperthermia controls DAB2 transcription in macrophage through inducing the separation of c-Jun and c-Fos heterodimers

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Sporotrichosis is an emergent subcutaneous mycosis of humans and some animals caused by dimorphic fungi of the Sporothrix schenckii. Hyperthermia can effectively treat sporotrichosis by regulating the phenotypic regulation of macrophages which is critical for controlling tissue inflammation and resolution. The adaptor protein disabled homolog 2 (DAB2), a regulator of phenotypic polarization in macrophages, have been identified to inhibit an inflammatory phenotype of the macrophages. However, whether and how hyperthermia act on the immune regulation mechanism through macrophages to DAB2 is needed more research and complement. In this study, mouse bone marrow derived primary macrophages (BMDMs) and cell line ANA-1 were used to investigate the regulation of DAB2 gene transcription by hyperthermia in vitro. Immunofluorescence was used to examine sub-localization of AP-1 complex within the cells under the 42°C conditions. Chemokine immunoprecipitation was used to detect whether 42°C stimulation affect the binding of AP-1-complex to DAB2 gene. Conditional DAB2 knockout mice were used to evaluate the role of DAB2 in Sporotrichosis. Our results show that 42°C stimulation downregulated the expression of c-Jun and c-Fos, and led to the separation of c-Jun and c-Fos dimers, causing the downregulated transcription of DAB2. In conclusion, topical hyperthermia treatment can inhibit the transcription of DAB2 gene, promote macrophage M1 polarization, and promote the treatment of sporotrichosis via AP-1 complex.

Systemic hyperinflammation as a driver of maculopapular drug exanthema in severely ill COVID-19 patients

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Coronavirus disease 2019 (COVID-19) has been associated with cutaneous findings, some being the result of drug hypersensitivity reactions. Here, we utilize imaging mass cytometry (IMC) to characterize the cutaneous immune response in maculopapular drug rashes (MDR), including those associated with COVID-19 infection (COVID MDR). For comparison, skin from healthy volunteers and patients with drug rash with eosinophilia and systemic symptoms (DRESS) was analyzed. Results demonstrated that COVID MDR are characterized by a more prominent infiltration of cytotoxic CD8+ T cells and highly activated, phenotypically shifted monocyte/macrophages (Mo/Mac) clusters in comparison to MDR and DRESS. RNA sequencing transcription of the affected skin also demonstrated a more robust cytotoxic response in lesional COVID skin. Serum proteomic profiling of COVID MDR patients revealed up-regulation of various inflammatory mediators (IL-4, IL-5, IL-8, IL-18, IL-6, TNF, and IFNγ), eosinophil and Monocyte-attracting chemokine MCP-2, MCP-3, MCP-4 and CCL11. Analyses of cytokine networks demonstrated a relatively milder cytokine storm in DRESS compared to COVID MDR, while MDR did not exhibit such features. These results suggest different immune responses in COVID MDR and DRESS, which impacts MDR development in severely ill COVID-19 patients.

Multiplexed skin immunophenotyping of new-onset dermatomyositis following first time use of Spirulina by patients

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The rise in the use of natural supplements to improve wellbeing and boost immune function has led to a rise in the use of herbal products such as Spirulina platensis. Our group has previously shown that Spirulina use is temporally associated with both new-onset and acute exacerbations of dermatomyositis (DM). We have also previously shown that Spirulina is capable of activating the TLRA and STING pathways, as well as inducing TNFa, IFNb, and IFNγ production. Here, we sought to characterize the cutaneous inflammatory infiltrate in Spirulina-induced dermatomyositis (Spir-DM). We performed high-gene in situ, single-cell level analysis of lesional biopsies of DM and Spir-DM skin using Imaging Mass Cytometry (IMC). We utilized two separate panels of 17 metal-conjugated antibodies against various surface markers, intracellular cytokines, and phosphorylated signaling molecules of interest. Significance was determined by the Mann-Whitney test. Our data show similar normal counts of 17 cell populations, including macrophages, dendritic cells, T and B cells (±0.05). Total cytokine and activated pathway signal intensity was also similar between both groups for type 1 IFN and JAK-STAT pathways (<0.05). Using a heatmap of cell types plotted against intracellular markers, we sought to identify cytokines or inflammatory pathways that may be differentially up- or down-regulated in Spir-DM patients. We similarly found no significant differences at the canonical cell-type level, however, there was notable heterogeneity in both groups. While the precise trigger for autoimmunity induced by Spirulina requires further interrogation, we believe these data suggest Spirulina induces immunophenotypically similar DM when compared to DM triggered by other causes, with little difference in the inflammatory infiltrate.

Demystification of the effects of docosahexaenoic acid on the PPAR signaling pathway in psoriasis

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Psoriasis is a multifactorial skin disease that is distinguished histologically by the hyperproliferation of keratinocytes. n-3 polysaturated fatty acids (n-3 PUFAs), particularly docosahexaenoic acid (DHA), are known to have numerous anti-inflammatory effects in several pathologies, including psoriasis. The beneficial actions of DHA in psoriasis are primarily mediated by its interactions with the receptors activated via peroxisome proliferators (PPARs), as well as by its secretion of active anti-inflammatory metabolites. The aim of this study was therefore to assess the influence of DHA on the main characteristics of psoriasis, namely hyperproliferation and abnormal cell differentiation of lesional keratinocytes, through the PPAR signaling pathway, using a tissue-engineered psoriatic model. Psoriatic skin substitutes were produced according to self-assessed medical criteria of psoriasis and incubated in medium supplemented with 10 μM DHA in comparison with regular medium. Three different psoriatic cell populations were used. The supplementation of the culture media with DHA regulated the expression of cell differentiation proteins in psoriatic substitutes. Moreover, the added DHA was correctly incorporated into the membrane phospholipids of the epidermis and metabolized into eicosapentaenoic acid (EPA) in psoriatic substitutes supplemented with DHA. Also, the addition of DHA to the culture medium decreased the synthesis of lipid mediators derived from n-6 PUFAs, known to be overexpressed in psoriasis. Finally, DHA supplementation positively restored the expression of PPAR receptors, which is deregulated in the pathology and causes a decrease in the synthesis of TNF-α. Ultimately, our results show that DHA has beneficial effects in attenuating the proinflammatory features which are achieved through the signaling pathway of PPARs.

FABPs-induced Th17 polarization in atopic march

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Atopic March (AM) represents a typical progression of allergic diseases that often begin early in life, with which has a role for the strongest evidence for systemic involvement of atopic dermatitis (AD). However, the mechanism underlying the development of AM in patients with AD is still unknown. To elucidate the possible mechanisms which might be engaged in AM, we performed gene expression analysis was done with the skin biopsy specimens, blood samples in AD, AM, and healthy controls. Metabolic pathways-related genes were one of the most enriched in AM samples compared with AD and healthy controls. Interestingly, the genes that were overrepresented in AM were elucidated to interact with AD skin. Furthermore, we found that increased fatty acid binding protein 5 (FABP5) expression was observed in human skin samples and T cells with AM patients, in accordance with increased IL-17A level, when compared with AD samples and healthy controls. Knock-down of FABPs expression in A549 cells inhibited IL-17A expression and FABP5 expression and IL-17A level. Taken together, the results indicate that ‘fatty acid binding protein 5’ might be as a possible biomarker to explain the progression of atopic march in atopic dermatitis patients, acting by directly promoting Th17 inflammation.