pathologies. We have recently shown that resveratrol can prevent carcinogenesis via an anti-inflammatory action through a modulation of miRNA. This inflammation could also promote tumoral progression through a modulation of the immune response. Thus, the objectives of this study were to evaluate the potential effect of resveratrol in the immune response in mice with melanoma. Our results highlight that resveratrol modulates differentiation of lymphocytes Th17, which exerts protumoral activity via interleukin-17 production. Indeed, naïve CD4 T cells derived from C57BL/6 mice displayed reduced capability to differentiate into Th17 cells *in vitro* after resveratrol treatment. Moreover in a mouse model of melanoma (B16F10), resveratrol prevented tumor growth and angiogenesis in an IL-17-dependent manner. This phenomenon could be due to a strong inhibition of the expression of the Th17-specific transcription factor Rorc. This work brings a new mechanism by which resveratrol prevents cancer related inflammation through a modulation of the immune cells and interleukin production.

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O29

Nrf2/HO-1 pathway alleviates epithelial-mesenchymal transition by inhibiting HMGB1 expression in pulmonary fibrosis

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Pulmonary fibrosis (PF) is a chronic, interstitial lung disease with unknown cause, characterized by the activation of accumulated myofibroblasts and deposition of extracellular matrix (ECM). Epithelial-mesenchymal transition (EMT) is considered to be one of the major hypotheses behind the formation of PF. High mobility group box1 (HMGB1) plays an important biological role in infection, inflammation, and immune responses. Nuclear factor E2-related factor 2 (Nrf2) is an important transcription factor for the regulation of oxidative stress. However, there is no direct evidence regarding the relationship between the Nrf2/HO-1 antioxidant system and HMGB1 in lung fibrosis. In our studies, the PF model was induced with bleomycin in both wild type (WT) mice and $Nrf2^{-/-}$ mice. Rat type II alveolar epithelial cells (RLE-6TN) and the human alveolar epithelial cell line A549 were treated with the Nrf2 activator, sulforaphane, or transfected with Nrf2 and HMGB1 siRNAs to explore their relationship in TGF-β-induced PF. This research showed that bleomycin-induced fibrosis was more severe in $Nrf2^{-/-}$ mice compared to WT mice. In the *in vitro* experiments, sulforaphane-treated cells had significantly attenuated TGF-β-induced epithelial-mesenchymal transition accompanied by downregulated expression of HMGB1. In contrast, silencing Nrf2 by siRNA enhanced TGFβ1-induced EMT with increased expression of HMGB1. However, when HMGB1 was silenced by siRNA, sulforaphane could not reduce the progression of EMT in either RLE-6TN cells or A549 cells. These findings suggest that the inhibitory effect of HMGB1 on EMT in PF is regulated by the Nrf2/HO-1 antioxidant pathway.

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O30

Natural compounds affecting neutrophil migration

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Hydrogen peroxide (H_2O_2) has recently been identified as the earliest messenger released by damaged tissues and is crucial for the chemoattraction of neutrophils to sites of injury and infection. However, how neutrophils sense and respond to H_2O_2 remains unresolved. Recently, we have identified the transient potential receptor melastatin-2 ion channel (TRPM2) as having a key role in directing the chemotaxis of neutrophils towards hydrogen peroxide (H_2O_2), in both *in vitro* and *in vivo* models. We isolated neutrophils from wild-type and $TRPM2^{-/-}$ mice and we observed that the genetic deletion of TRPM2 results in a reduction in both the speed and directionality of the neutrophil migration up a gradient of H_2O_2. We tested a diverse group of natural products, including a range of terpenes, alkaloids and flavonoids, for their effects on this H_2O_2-induced neutrophil chemotaxis using the Ibidi-chemotaxis system, which allows live-cell imaging *in vitro* of migration over time. From our screen, we have identified: beta-carotene, artemisinin, ferulic acid and N-acetylcysteine as compounds which reduce neutrophil chemotaxis in a comparable way to TRPM2 deletion, leading to the suggestion that they may be acting as TRPM2 inhibitors. Moreover, our compounds induce a more pronounced reduction in chemotaxis than the currently available TRPM2 inhibitors, which lack potency and selectivity. The natural compounds we have tested may have clinical applications; for example, in the treatment of inflammatory conditions, such as sepsis, which are characterised by excessive and damaging neutrophil migration.

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Session 11: Translating novel pathways – Gastrointestinal

O31

Can colonic metabolites be responsible for the hypotensive effect of orally given quercetin?

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Epidemiologic data suggest protective effects of higher flavonoid intake on cardiovascular diseases. Some human and animal studies reported a decrease in arterial blood pressure after quercetin administration. The mechanism of this effect is not yet well-understood since the closes metabolites of quercetin are either inactive or present in very low plasma concentrations.

In this study, a series of colonic quercetin metabolites was analysed. First, the effects on isolated rat aorta were evaluated. Subsequently, the efficient metabolites were also tested *in vivo* on normotensive and hypertensive rats and *in vitro* on mesenteric artery. Screening in aorta clearly showed 3-(3-hydroxyphenyl) propionic acid to be the most efficient. These results were confirmed *in vivo*, where this metabolite decreased arterial blood pressure in hypertensive rats. Further mechanistic experiments confirmed that this effect was based on vasodilation of vessels, no negative effects on the heart were observed. Interestingly, additional experiments showed that two other metabolites with lower effects in the aorta, were also able to reduce blood pressure in rats. Interestingly, these metabolites seemed to have better effects on resistance vessels than