Study of redox signaling in vascular homeostasis: development of protective strategies for lymphatic vascular diseases

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Redox signaling is implicated in many different physiological and pathological processes. In particular aberrant redox signaling, usually induced by excessive production of reactive oxygen species (ROS) and/or by decreases in antioxidant activity, leads to endothelial dysfunction and alteration of vascular function such as hyperpermeability (Lee & Griendling, 2008). Vascular harmful events as ROS and inflammation induce vascular remodeling by influencing phenotype modulation of vascular smooth muscle cells, aberrant growth of vascular cells, cell migration, endothelial permeability and extracellular matrix reorganization. Among the others the modulation of lymphatic permeability may be important for the trafficking of immune cells and inflammatory signals may increases permeability causing lymphedema (Cromer et al., 2014).

The knowledge of the mediators and mechanisms leading to redox imbalance in lymphatic endothelium can be important for the definition of targets for novel preventive and/or therapeutic strategies.

Among the stimuli that increase ROS production are inflammatory mediators, in particular cytokines. IL-1ß for example promotes ROS production in a time- and dose-dependent manner via NADPH oxidase. The exposure of lymphatic endothelium to an inflammatory environment can predispose to lymphedema (Rockson, 2013).

Antioxidant can play a role and be beneficial in the prevention and or treatment lymphedema and other vascular diseases. Consistent with epidemiological investigations and animal studies, clinical studies suggest that polyphenol-rich natural sources may also have a beneficial effect on vascular function in humans. The aim of this study was to evaluate the effect of combination of phytocomplexes (called MIX, provided by Aboca SpA) on lymphatic endothelial cell permeability induced by IL-1β and the molecular mechanisms underneath.

The results obtained on human dermal lymphatic endothelial cells documented that IL-1β induced lymphatic endothelial hyperpermeability, evaluated by FITC-dextran transcellular passage. The phytocomplex MIX (derived by *Taraxacum officinalis, Fagopyrum esculentum, Solidago virgaurea, Orthosiphon stamineus, Ruscus aculeatus*) significantly reduced the cytokine induced effect. Reduced permeability was associated with the maintenance of tight junctions and cell-cell localization of occludin and zonula occludens-1, evaluated by immunofluorescence analysis. Moreover, MIX reduced the expression of inflammatory key elements such as inducible nitric oxide synthase (NOS) and cyclooxygenase-2, while it not affect the levels of endothelial NOS The upregulation of antioxidant enzymatic systems (catalase and superoxide dismutase-1) and the downregulation of pro-oxidant markers (p22 phox subunit of NADPH oxidase) were also evident, with concomitant reduced ROS levels.

In conclusion, MIX shows a good activity in reducing IL-1β induced lymphatic endothelial hyperpermeability and protective effect in oxidative stress moving the balance toward detoxification pathways

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