Keywords: Desmethylated tocotrienols, Mammary tumors, Cancer therapy, HER-2/neu transgenic mice

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Inflammation and Immunity Oral Presentations

Inflammation and Immunity 1:

Oxidative stress as a cause for autoimmune hemolytic anemia; supporting evidences from genetically modified mice

T. Konno, N. Ohtsuki, N. Kibe, S. Tsunoda,
Y. Iuchi, J. Fujii*
Yamagata University, Japan

Autoimmune hemolytic anemia (AIHA) is the symptom in which antibodies against red blood cells (RBC) are produced and trigger the destruction of RBCs, resulting in hemolytic anemia. We recently found elevation of reactive oxygen species (ROS) levels in RBCs, and augmented production of autoantibodies to RBCs in SOD1-knockout C57BL/6 mice. Since both anemia and autoimmune responses in SOD1-deficient mice are totally rescued by local expression of human SOD1 in erythroid cells, these phenotypes are attributable to oxidative stress in RBC. A causal connection between ROS and AIHA was further confirmed by using an AIHA-prone NZB mouse. ROS levels in RBC were originally high in young NZB mice and further increased during aging. Now we have strong evidence implying involvement of ROS in the development of AIHA by making genetically-modified congenic NZB mice. We prepared both human SOD1-trangenic (hSOD1-Tg) NZB mice, which express human SOD1 protein in erythroid cells specifically, and SOD1-deficient (SOD1-KO) NZB mice by back-crossing eight times to NZB mice. The severity of AIHA phenotypes, such as autoantibody production and anemia, and levels of intracellular ROS and oxidative stress markers were positively correlated among the mice. While SOD1 deficiency showed elevated oxidative stress and accelerated mortality, transgenic expression of human SOD1 protein in RBC suppressed ROS levels and concomitantly decreased the autoantibody levels and the death rate. Thus, oxidative stress-mediated autoantibody production may be a more general mechanism for AIHA and related autoimmune diseases. Thus we have now firm evidence that imply involvement of oxidative stress in the autoimmune response in NZB mice. The results obtained in our studies support the hypothetical role of ROS in triggering the autoimmune reaction, and propose a novel approach to mitigate the progression of AIHA by antioxidants.

Keywords: superoxide dismutase, knockout mouse, autoantibody, red blood cell

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Inflammation and Immunity 2:

Modulation of TH1/TH17 equilibrium in vitro by indicaxanthin from *Opuntia ficus indica* (L. Mill)

M. Allegra*[1], L. Rattazzi[2], A. Attanzio[1], L. Tesoriere[1], M.A. Livrea[1], F. D'Acquisto[2]
[1]*Università di Palermo, Italy,* [2]*Queen Mary University of London, UK*

Indicaxanthin is a betalainic phytochemical from Cactus Pear Fruit (*Opuntia Ficus Indica*, L. Mill). We have recently showed that this compound is a reducing and amphipathic molecule, able to penetrate cells and membranes and counteract oxidative damage in vitro. Moreover, it behaves as a signalling molecule and modulates specific redox-dependent pathways in vitro (1). Remarkably, indicaxanthin is highly bioavailable: the ingestion of three cactus pear fruits generates, in humans, an indicaxanthin plasma concentration of 7μM after 3 h (2).

In the light of the above reported properties of indicaxanthin, we have here investigated the effects of the pigment on T effector function, differentiating splenocytes in Th0, Th1 and Th17 skewing conditions in presence or absence of indicaxanthin 15μM. Differentiated cells were analysed by flow cytometry (FACS) intracellular staining while cell supernatants were screened by multiplex cytometer beads assay (CBA).

Our CBA results show that indicaxanthin inhibits both IFN-gamma and IL-17 production in Th17 conditions. Interestingly, these effects were accompanied by a marked increase in IL-6 levels and a significant reduction in IL-10, together suggesting a modulation of T regulatory differentiation and/or function.

FACS intracellular staining of gated T cells in Th17 condition indicated a reduced percentage of IL-17 and a parallel increase in IFN-gamma-producing cells in indicaxanthin-treated cells compared to control. Consistent with this, indicaxanthin almost doubled the number of IFN-gamma+ T cells in splenocytes differentiated in Th1 skewing conditions.

Together these results indicate that indicaxanthin exerts an immunomodulatory effect on both antigen-presenting cells and T cells in vitro. In addition, our data suggest that indicaxanthin might either induce a robust Th1-mediated protective immunity against extracellular pathogens or suppress a wide variety of Th17-driven autoimmune disorders such as multiple sclerosis or rheumatoid arthritis.