

RESUMO

Role of Endoplasmic Reticulum stress in sensitization induced dendritic-like cell maturation/toxicity

The pathogenesis of allergic contact dermatitis, the most common manifestation of immunotoxicity in humans, is intimately connected to hapten-induced maturation of dendritic cells (DC). The molecular mechanisms driving this maturational program are not completely known, however, initial danger signals such as the generation of reactive oxygen species (ROS) were shown to play a critical role. Recent evidence linking ROS production, endoplasmic reticulum (ER) stress and the pathogenesis of several inflammatory diseases led us to analyze, in the present work, the ability of the skin sensitizer 1-fluoro-2,4-dinitrobenzene (DNFB) to evoke ER stress in DC-like THP-1 cells and the concomitant consequences to their immunobiology. We found that DNFB triggers a ROS-dependent activation of the PERK-eIF2 α -ATF4 unfolded protein response (UPR) branch conferring cytoprotection and modulating the maturation/proinflammatory cell status in a biphasic manner. Early DNFB induction of ATF4 positively modulates autophagy-related genes MAP1LC3B and ATG3 and stabilizes the transcription factor Nrf2, causing a strong induction of the HMOX1-detoxifying gene. Moreover, we observed that in a first phase, DNFB-induced ATF4 upregulates IL8 mRNA levels while blocking CD86, IL1B, IL12B, and CXCL10 transcription. Later, following ATF4 decay, HMOX1 and IL8 transcription drastically decrease and CD86, IL1B, and IL12B are upregulated. Overall, our results evidence a connection between sensitizer-induced redox imbalance and the esta-

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blishment of ER stress in DC-like cells and provide new insights into the role of UPR effectors such as ATF4 to the complex DC maturational program.



PALAVRAS-CHAVE: allergic contact dermatitis, ROS, ER stress, dendritic cell maturation, ATF4, autophagy