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Role of anti-mitochondrial antibodies in pemphigus autoimmunity

Current understanding of pemphigus vulgaris (PV) does not explain acantholysis in patients lacking desmoglein antibodies. PV IgGs enter keratinocytes (KCs) and specifically bind to mitochondrial proteins, which is associated with mitochondrial damage triggering apoptosis and acantholysis. Using a protein microarray approach, we have previously demonstrated that mitochondrial proteins most commonly targeted in PV are involved in oxidative phosphorylation, O_2 respiration, production/inactivation of reactive oxygen species (ROS), and tricarboxylic acid cycle. In this study, we sought to identify changes in the vital mitochondria functions in KCs treated with the sera from PV patients and healthy donors. PV sera significantly increased proton leakage from KCs, suggesting that PV IgGs increase ROS production and reduce the ability of KCs to respond to stress. Indeed, measurement of intracellular ROS production by the c-H_2DCFDA-AM dye labeling of cultured KCs showed a drastic increase of cell staining in response to treatment by PV sera, which was confirmed by FACS analysis. Exposure of KCs to PV, but not normal, sera also caused dramatic changes in the mitochondrial membrane potential detected with the JC-1 dye. This observation indicated that binding of PV IgGs to mitochondrial target proteins disrupts the electron transfer chain resulting in loss of electrochemical gradient across the inner membrane. The results of this studyhelp explain the mechanism of therapeutic action of mitochondria-protecting drugs, such as nicotinamide, minocycline and cyclosporine, in PV patients and suggest novel avenues for development of personalized therapies based on the pharmacological correction of mitochondrial abnormalities in individual PV patients.

Biography

Sergei A. Grando is a Board Certified Dermatologist with more than 30 years experience. He is a leading expert and researcher in eczema and other autoimmune blistering diseases. He is conducting a clinical trial for the treatment of pemphigus with a non-hormonal medication. He has published more than 225 papers, monographs and book chapters, and has been awarded numerous research grants from the National Institutes of Health and other funding agencies. He was awarded as a Doctor of the Year in 2010, International Pemphigus and Pemphigoid Foundation and Vice Chair, a medical advisory board of the International Pemphigus and Pemphigoid Foundation.

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