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Endoplasmic Reticulum Calcium, Stress and Cell-to-Cell Adhesion

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Abstract

Darier's Disease (DD) is caused by mutations in the endoplasmic reticulum (ER) Ca^{2+} ATPase ATP2A2 (protein SERCA2). Current treatment modalities are ineffective for many patients. This report shows that impaired SERCA2 function, both in DD keratinocytes and in normal keratinocytes treated with the SERCA2-inhibitor thapsigargin, depletes ER Ca^{2+} stores, leading to constitutive ER stress and increased sensitivity to ER stressors. ER stress, in turn, leads to abnormal cell-to-cell adhesion via impaired redistribution of desmoplakin, desmoglein 3, desmocollin 3 and E-cadherin to the plasma membrane. This report illustrates how ER Ca^{2+} depletion and the resulting ER stress are central to the pathogenesis of the disease. Additionally, the authors introduce a possible new therapeutic agent, Miglustat.

Dariers Disease

DD, caused by mutations in the ER Ca^{2+} ATPase ATP2A2 (Sakuntabhai, et al., 1999), is an uncommon (1:30,000) blistering skin disease. Patients with DD suffer from impaired cell-to-cell adhesion, defective keratinocyte differentiation, and non-physiologic keratinocyte apoptosis. Histologically, DD manifests with suprabasal clefting in the epidermis, acantholysis, rounded dyskeratotic keratinocytes (“corps ronds”), hyperkeratosis and parakeratotic keratinocytes in the stratum corneum (“grains”). Current treatments, such as retinoids, do not ameliorate the underlying defect in ER Ca^{2+} sequestration, and are ineffective for many patients.

This report, by Savignac et al (EDITOR, PLEASE ADD REFERENCE), advances our understanding of DD in several important ways. First, it illustrates how ER stress impairs the formation of both adherens junctions and desmosomes, contributing to DD pathogenesis. Second, it expands our understanding of how ER Ca^{2+} signaling may control, not only keratinocyte growth and differentiation, but also keratinocyte cell-to-cell adhesion. Lastly, it introduces a possible new therapeutic agent, Miglustat.

Defects in Cell-to-Cell Adhesion in Dariers Disease

Defects in desmoplakin redistribution have been associated with the impaired cell-to-cell adhesion seen in DD (Dhitavat, et al., 2003, Hobbs, et al., 2011). Defective desmoplakin redistribution after SERCA2 Ca^{2+} depletion is mediated by Protein Kinase C alpha (PKCalpha) (Hobbs, et al., 2011). PKCalpha also may act on desmoplakin to direct the “hyperadhesive” desmosomal state (Hobbs and Green, 2012), rearrange desmosome components during wound healing (Garrod, 2013), and modulate desmosomal susceptibility

to autoimmune attack in Pemphigus Vulgaris (Cirillo, et al., 2010). More recently, cell-to-cell adhesion defects in DD also have been associated with defects in E-cadherin redistribution (Celli, A., et al., 2011). The current report demonstrates that both structural components are disturbed in DD. Because both desmoplakin and E-cadherin have been shown to have signaling as well as structural roles (Kowalczyk and Green, 2013, Tu, et al., 2012), it is likely that interactions among adhesion components involve multiple feedback loops between each other and the SERCA2-controlled ER Ca^{2+} store.

Er Stress: A Double-Edged Sword

This report also highlights the importance of ER stress. Mild and self-limited ER stress, due to transient release and refill of ER Ca^{2+} stores, is an important physiologic signal for epidermal permeability barrier repair and antimicrobial peptide synthesis (Celli, A., et al., 2011, Park, et al., 2011). However, once ER Ca^{2+} depletion passes a critical threshold, the ER Unfolded Protein Response (UPR) is triggered, and apoptotic mechanisms are initiated in many cell types (Oakes, et al., 2003). This report identifies ER stress, induced by ER Ca^{2+} depletion due to SERCA2 dysfunction, as an important contributor to DD pathogenesis.

Miglustat in Dariers Disease

Finally, this report demonstrates that treatment of DD keratinocytes with Miglustat improves desmoplakin and E-cadherin redistribution and improves (although it does not normalize) cell-to-cell adhesion. The authors propose that Miglustat acts as a chaperone that allows adhesion molecules to escape from the ER stress-induced UPR, thus enabling them to reach the plasma membrane and form adherens junctions and desmosomes. Miglustat, used clinically for Gaucher disease, also acts to inhibit glucosylceramide synthase (reviewed in Venier and Igdoura (Venier and Igdoura, 2012)), and an additional potential therapeutic pathway may be through its modulation of the ceramide/sphingolipid pathway previous described in DD pathogenesis (Celli, A, et al., 2012). Lastly, since glucosylceramide synthesis is required for epidermal permeability maintenance (Jennemann, et al., 2007), some caution should be used in extrapolating these results from monolayer keratinocytes to a multilayered epidermis or to patients. As the authors note, however, therapeutic options for DD are limited, and Miglustat may be the first in a series of agents that treat DD by facilitating redistribution of adhesion molecules to the plasma membrane.

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Key Points

1. Patients with DD, caused by a mutation in the endoplasmic reticulum ATPase SERCA2, suffer from impaired cell-to-cell adhesion, defective keratinocyte differentiation, and non-physiologic keratinocyte apoptosis.
2. Impaired SERCA2 function depletes ER Ca^{2+} stores, leading to constitutive ER stress. ER stress, in turn, leads to abnormal cell-to-cell adhesion via impaired redistribution of desmoplakin, desmoglein 3, desmocollin 3 and E-cadherin to the plasma membrane.
3. Miglustat, an agent already used as a pharmacologic chaperone and ceramide modulator, improves cell junction formation and enhances keratinocyte adhesion strength in DD keratinocytes.