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Review

Reactive oxygen species, Ca^{2+} stores and acute pancreatitis; a step closer to therapy?

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ABSTRACT

Disruption of Ca^{2+} homeostasis can lead to severe damage of the pancreas, resulting in premature activation of digestive enzymes, vacuolisation and necrotic cell death, features typical of acute pancreatitis (AP). Therefore a fine balance between Ca^{2+} release from internal stores, Ca^{2+} entry and extrusion mechanisms is necessary to avoid injury. Precipitants of AP induce Ca^{2+} overload of the pancreatic acinar cell that causes mitochondrial dysfunction, *via* formation of the mitochondrial permeability transition pore (MPTP), loss of ATP production and consequent necrosis. Oxidative stress has been shown to occur in the development of AP and may modify Ca^{2+} signalling events in the acinar cell. However, the precise pathophysiological involvement is currently unclear and antioxidant therapy in the clinic has largely proved ineffective. Possible reasons for this are discussed, including evidence that ROS generation may determine cell death patterns. In contrast, recent evidence has indicated the potential for AP therapy *via* the prevention of Ca^{2+}-dependent mitochondrial damage. Multiple approaches are indicated from preclinical findings; 1) inhibition of Ca^{2+} release by IP_3R blockade, 2) inhibition of Ca^{2+} entry through Orai1 blockade and 3) prevention of MPTP formation. Clinical trials of drugs which prevent mitochondrial dysfunction induced by Ca^{2+} overload of pancreatic acinar cells are imminent and may provide patient benefit for a disease that currently lacks specific therapy.

Contents

1. Introduction: acute pancreatitis

The exocrine pancreas is a highly specialised secretory organ capable of synthesising, storing and releasing large quantities of digestive enzyme precursors into the small intestine, necessary for the breakdown of food. Homeostasis of the functional unit, the acinar cell, is therefore paramount for the smooth running of physiological processes; disruption can lead to severe damage of the pancreas, resulting in premature activation of zymogens, vacuolisation and necrotic cell death, features typical of acute pancreatitis (AP). This severe inflammatory disease, which currently affects approximately 50 per 100,000 individuals per year, is triggered predominantly by alcohol excess and gallstones,

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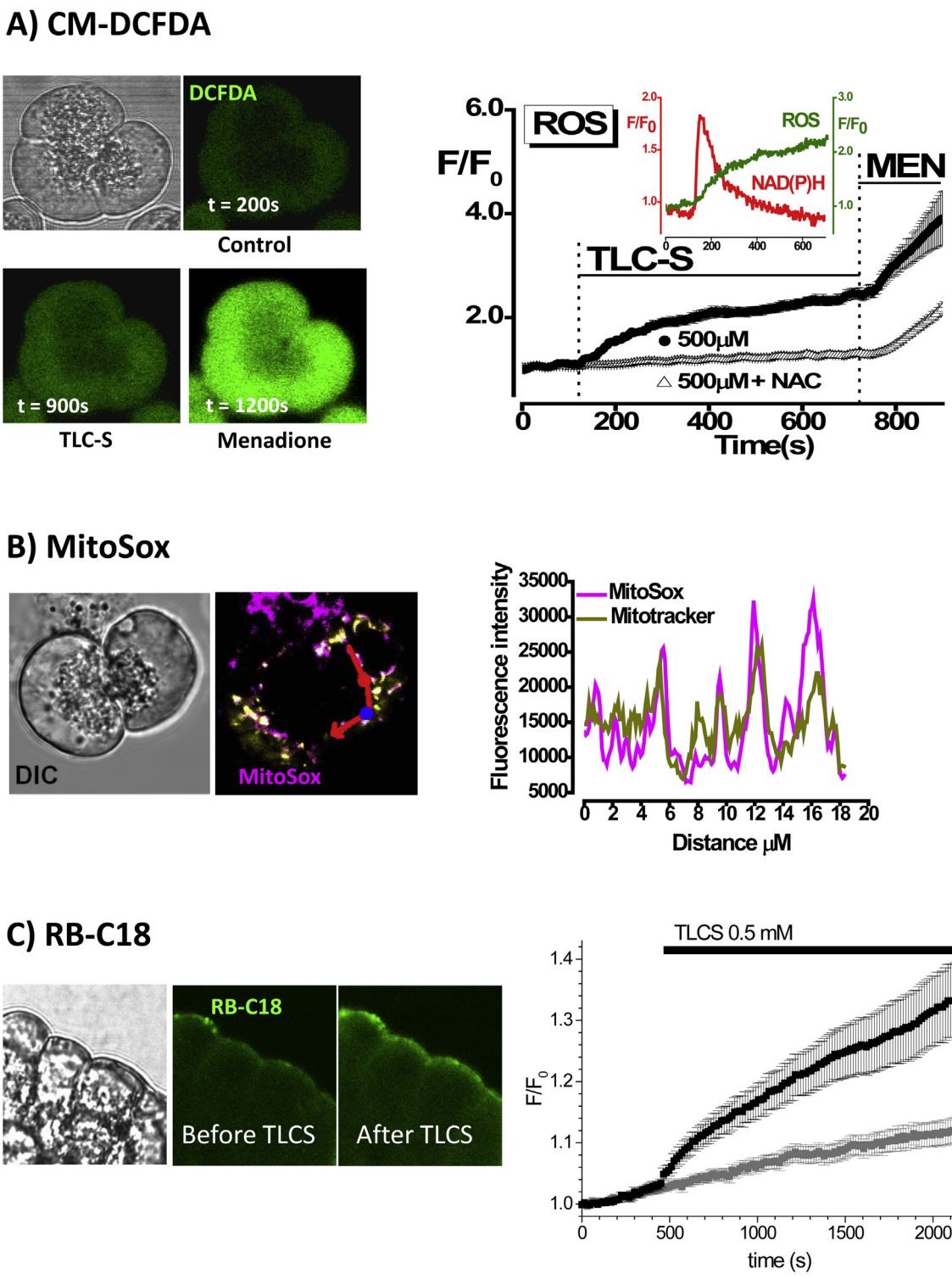

Fig. 1. Detection of ROS in primary human and mouse pancreatic acinar cells using confocal microscopy. A) Typical images and graphs showing Ca^{2+}-dependent rises of ROS induced by the bile acid taurolithocholic acid sulphate (TLCS), measured with CM-DCFDA in human and murine acinar cells, that were inhibited by the antioxidant N-acetylcysteine (NAC) [7], B) Co-localisation studies using MitoSox and Mitotracker indicated that bile acid- induced ROS generation occurred in the mitochondria [7], C) TLCS-induced ROS increases measured with a novel lipophilic probe, RB-C18, recently developed for detecting near-membrane responses [16].

although diverse precipitants are recognised potentially suggesting a common mechanism [1]. Severe cases of AP involve a systemic inflammatory response syndrome (SIRS) that may result in multiple organ damage and death of the patient. A prominent feature of the development of AP is a disruption of calcium signalling within the acinar cell [2–4]; overload of cytosolic calcium ($[Ca^{2+}]_c$) leads to significant damage of the mitochondria, critically affecting their ability to produce ATP, thereby promoting cell death [5]. Importantly, the extent of pancreatic necrosis, which may develop in patients within days of symptom onset, is a major determinant of disease progression; the presence of necrosis dramatically raises the mortality rate in AP [1,6]. Sustained rises of $[Ca^{2+}]_c$ have been