



Editorial

Deficiency of NDUFC2: Cause or bystander in acute coronary syndromes?☆

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Acute coronary syndromes (ACS) usually result from the acute thrombotic complications of an unstable coronary artery plaque and continues to be, despite preventive and therapeutic advances, a leading cause of death [1]. An important goal in ACS is to understand novel molecular mechanisms that explain plaque instability, which might lead to the discovery of novel therapeutic targets. In this regard, the role of mitochondrial dysfunction in the development of atherosclerosis has so far been largely neglected.

Mitochondria are the main source of intracellular reactive oxygen species (ROS). Their accumulation can trigger oxidative stress and inflammation, resulting in a vicious cycle that contributes to the progression of atherosclerosis and plaque rupture. So far, the question of the relevance of mitochondrial dysfunction in ROS accumulation, leading to plaque instability, remains largely unsolved. The mitochondrial antioxidant complex might be a crucial novel target for innovative therapies in ACS.

There are four interacting mechanisms involved in the pathogenesis of ACS in humans [2]: ischemia-related injury, reperfusion-related injury, distal embolization, and microvascular dysfunction. The accumulation of ROS favored by myocardial ischemic or reperfusion damage may contribute to ischemia-reperfusion injury and microvascular dysfunction. The molecular mechanisms that lead to ROS accumulation during an ACS are still elusive, and basic research in this fields promises to address one of the unmet needs in the treatment of ACS.

NADH dehydrogenase [ubiquinone] 1 subunit (NDFUFC2) is one of the 45 subunits composing mitochondrial complex I (CI) encoded by the *Ndufc2* gene. NDFUFC2 is known as a NADH:ubiquinone oxidoreductase, and is the first and largest complex of the mitochondrial respiratory chain. In particular, NDFUFC2 plays a key role in CI assembly and activity (Fig. 1). CI exerts important functions, since it processes NADH to produce electrons and reduce molecular oxygen to form H₂O. CI contributes about 40% of the driving force of the proton that is responsible

for ATP synthesis through ATP synthase, and is one of the main source of mitochondrial anion superoxide [3]. A dysfunctional CI determines an increase in the accumulation of mitochondrial ROS and deleterious cellular effects, which may be the basis of various pathological conditions, including ACS [3,4].

Several studies have shown that NDUFC2 inhibition by high-salt diet promotes cerebrovascular accidents in an animal model of spontaneous hypertension and stroke [5]. Furthermore, human subjects carrying an *ndufc2* gene variant associated with reduced level of protein expression features a significant increase in the risk of juvenile ischemic stroke [5]. A dysfunctional *ndufc2* gene is also involved in the pathogenesis of diabetes and of a few types of cancer [6,7]. In particular, the pharmacological stimulation of NDUFC2 restores the gene expression of mitochondrial energy metabolism and suppresses cardiac fibrosis in the border zone of the infarcted heart [8].

The study by Raffa et al., published in the current issue of *International Journal of Cardiology*, shows that mitochondrial structural and dysfunction is involved in ACS development through deficiency of NADH dehydrogenase [ubiquinone]. In this study, *ndufc2* gene silencing in human endothelial and smooth muscle cells upregulated the expression of genes involved in atherogenesis [(such as intercellular adhesion molecule 1 (ICAM) and vascular cell adhesion molecule 1 (VCAM)] and plaque destabilization [CD40 ligand and metalloproteinase (MMP) type 9]. Furthermore, a significant reduction of *ndufc2* gene expression is present in peripheral blood mononuclear cells (PBMCs) of ACS patients. Therefore, the deficiency of NADH dehydrogenase [ubiquinone] resulting from the reduction of NDUFC2 is either causal or an epiphenomenon of ACS and related infarct size and of the coexisting microvascular damage.

This is an important research line for at least two reasons. First of all, it provides new insights on the pathways that control ROS production in ACS, giving one of the first demonstrations of an active signaling role for NDUFC2, which acts as a ROS scavenger in the main players of atherogenesis – namely endothelial and smooth muscle cells. From this standpoint, it would also be interesting to investigate protein expression and identify additional cofactors for NDUFC2 that can play potential roles during early stages of atherogenesis and plaque destabilization.

Secondly, and more practically relevant, it might lead to the development of NDUFC2 as an ACS biomarker, as well as a target for new therapies against plaque development and rupture through

☆ This editorial refers to the accepted manuscript "The reduction of NDUFC2 expression is associated with mitochondrial impairment in circulating mononuclear cells of patients with acute coronary syndrome" by S. Raffa et al.

DOI of original article: <https://doi.org/10.1016/j.ijcard.2019.02.027>.

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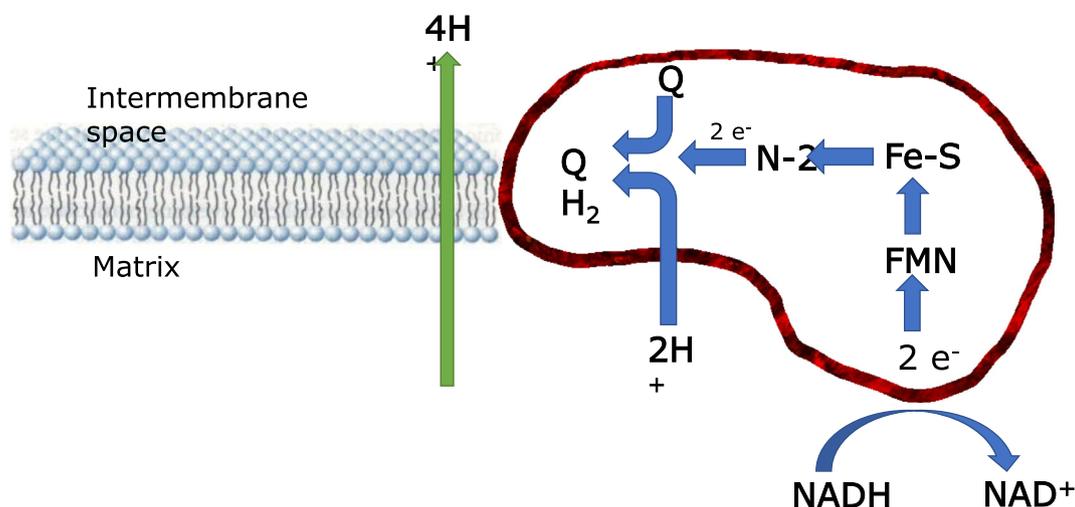


Fig. 1. NADH ubiquinone oxidoreductase (NDUFC2). Schematic representation of NDUFC2 activity within the inner mitochondrial membrane. NDUFC2 activity consists of redox reactions which take place in the hydrophilic domain of complex I. NADH initially binds to complex I and transfer two electrons to the flavin mononucleotide (FMN) prosthetic group. This reaction causes the conversion of nicotinamide adenedine dinucleotide (NAD) from reduced (NADH) to oxidized (NAD⁺). The electrons are then transferred to coenzyme Q10 (ubiquinone) via a series of iron-sulfur (Fe-S) clusters, which results into the transfer of 2 electrons from NADH to intermediate molecules such as flavin mononucleotide (FMN), Fe-S and QH. This electron flow causes stoichiometrically the flux of 4 protons (H⁺) into the matrix, resulting in significant increase of mitochondrial membrane potential and decrease of anion superoxide.

pharmacological or molecular biology strategies. Should the role of NDUFC2 as causative in ACS be found in large controlled trials in patients, through the demonstration that its inhibition reduces the incidence and/or severity of ACS, this could pave the road to new weapons to combat the occurrence or consequences of myocardial infarction.

The Authors disclose no conflict of interest related to the content of this article.

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