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HFWM: Sera from myocarditis patients caused iron depletion in cultured human cardiomyocytes

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Background

Cardiomyocytes are the main cells affected in the course of myocarditis. They are particularly sensitive to changes in iron homeostasis and reactive oxygen species (ROS). Iron is crucial for the maintenance of optimal energy metabolism, but also plays an important role in inflammation and ROS production. We hypothesize that iron homeostasis might be involved in the pathogenesis of myocarditis.

Purpose

The aim of the study was to assess differences in profiles of the expression of key genes involved in iron homeostasis, cardiac remodeling, and protection against ROS in human cardiomyocytes (HCMs) cultured in the presence of sera from patients with acute myocarditis and after 6 weeks of recovery, and also to compare the results with healthy controls.

Methods

In HCMs cultured for 48 hours with sera from 11 patients and 7 controls we analyzed expression of light and heavy ferritin chains [FTL, FTH], transferrin receptor 1 [TfR1], galectin 3 [LGALs3], TGFβ signaling [TGFβ1, TGFβ2, TGFβ3], glutathione peroxidase [GPX] and superoxide dismutase [SOD1] at the mRNA level using RT- qPCR.

Results

We found a significant increase in an expression of TfR1 (p<0,01) in HCMs exposed to sera from myocarditis patients, in comparison to those treated with sera from healthy controls. Additionally, elevated expression of TfR1 in cells correlated with serum levels of total iron (R=-0.52; p<0.05), CRP (R=0.67; p<0.05), and NT-proBNP (R=0.55; p<0.05), suggesting increased iron demand in HCMs and its possible relation to inflammation and hemodynamic dysfunction in patients. Moreover, we observed elevated expression of FTH and FTL (both p<0.01) and its strong correlation with expression of TfR1 as well as with increased levels of CRP in sera. It could be explained by the double role of ferritin in iron storage and in inflammation.

In the context of remodeling potential HCMs treated with myocarditis sera, in comparison to those treated with
sera from healthy controls, displayed augmented expression of galectin 3 (p<0,01) and disturbances in TGFβ genes. Interestingly, upregulation of galectin 3 was related to changed iron homeostasis, reflected by correlations with TfR1 (R=0,77; p<0,05), FTH (R=0,92; p<0,05) and FTL (R=0,76; p<0,05).

Additionally, HCMs treated with sera from myocarditis patients showed increased expression of ROS defensive genes such as GPX and SOD1 (both p<0,01), and also strongly correlated with expression of TfR1, FTH, and FTL. Thus, it is possible that an impairment in iron homeostasis in the course of myocarditis may exaggerate oxidative stress.

A similar pattern of gene expression profile was observed in HCMs treated with sera collected after 6 weeks of clinical recovery, suggesting that the negative impact of sera was preserved.

Conclusions
Malfunctioning of cardiomyocytes in myocarditis might be related to derangements in the expression of genes involved in iron homeostasis, cardiac remodeling, and ROS protection