Impaired glucose and lipid metabolism affects mitochondrial function in experimental diabetes-induced cardiac remodelling: role of MMP-2

1)Gliozzi M. 2)Scarano F. 3)Saverio N. 4)Scicchitano M. 5)Musolino V. 6)Carresi C. 7)Maiuolo J. 8)Maretta A. 9)Muscoli C. 10)Mollace V.

IRC-FSH - Department of Health Sciences - UniCZ

Diabetes is a metabolic, heterogeneous disorder characterized by a complex pathogenesis which can be related to genetic susceptibility, obesity, sedentary lifestyle and hypercaloric dietary supply. Cardiovascular diseases, such as diabetic cardiomyopathy, are the main causes of death among people with diabetes. Despite this evidence, to date, the exact role of impaired glucose and lipid metabolism in triggering molecular mechanisms underlying diabetic cardiomyopathy is not well established. Therefore, the aim of our study was to investigate the effect of hyperglicaemia or hypercholesterolemia on the early stages of cardiac remodeling in a rat model of diabetes.

To better clarify these aspects, rats were fed with a normocaloric diet (NPD group) or with a high fat diet (HFD group), respectively. One month later, streptozocin (STZ, 35 mg/Kg, i.p.) was administered in a subgroup of both NPD and HFD rats to induce diabetes. After 60 days, we observed that hyperglicaemia or hypercholesterolemia significantly increased the diameter of the left ventricular chamber in diastole (LVEDd) and in systole (LVESd) and these pathological conditions reduced ejection fraction (EF) and fractional shortening (FS) compared to control (NPD). Unexpectedly, cardiac dysfunction was less marked in diabetic rats fed with an hyperlipidemic diet (HFD+STZ) suggesting an adaptative response to injury of diabetic heart in the presence of hyperlipidemia. This response was characterized by a modulation of matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases responsible for both physiological and pathophysiological tissue remodeling.

In particular, we observed an activation of all myocardial MMP-2 isoforms (intracellular full-length-MMP-2, N-terminal truncated intracellular MMP-2 and extracellular MMP-2) in NPD as well as in HFD and HFD+STZ rats as compared with diabetic rats not affected by hyperlipidemia. This profile of activation was also accompanied by a different intracellular localization of NT-MMP-2 among groups. Recent evidence shows that under physiological conditions, NT-MMP-2 is involved in the regulation of cardiomyocyte calcium levels and is preferentially localized into a subdomain of the endoplasmic reticulum (ER), mitochondria-associated membrane (MAM), than into mitochondria, thus ensuring the maintenance of normal mitochondrial function. On the other hand, it has been hypothesized that stress conditions can cause the translocation of MMPs from MAM to mitochondria, triggering free radical overproduction and cardiomyocyte apoptosis.

Here, we demonstrated for the first time that MMP-2 accumulated in mitochondria of cardiomyocytes in the setting of hyperglicaemia (NPD+STZ) as well as of hyperlipidemia (HFD). The migration into mitochondrial matrix triggered superoxide anion overproduction by NADPH oxidase and promoted apoptotic cell death. Hyperlipidemia prevented the cardiac damage observed in the presence of high blood glucose levels; indeed, in HFD+STZ rats, we observed a co-localization of

MMP-2 with ER and a down-regulation of NADPH oxidase, suggesting a reduced free radical overproduction and a preserved mitochondrial function.

In conclusion, our results highlight the importance of MMP-2 as a potential pharmacological target in order to counteract myocardial oxidative damage in diabetes.