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Acute cardiac dysfunction induced by Ionizing radiation exposure: the mitochondrial side

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Exposure to ionizing radiation (IR) is a cause of cardiac dysfunction whose severity relates among other factors to the increased reactive oxygen species production (ROS). Mitochondria, being the primary source of ROS and of energetic substrates for the myocardium, are the possible mechanisms of IR related cardiac dysfunction. To evaluate the possible involvement of mitochondria to mediate the effects of IR exposure on cardiac function, in C57BL/6 mice subjected to IR exposure by X-ray (4 Gy), we performed echocardiography at basal, and 3 and 24 hours post IR exposure. Mice were sacrificed and heart samples collected at each time point for analysis of mitochondria morphology by transmission electron microscopy (TEM) and biochemistry. At 3 h post-IR, we observed increased left ventricle diastolic diameter (LVDd: 39.5±0.3 vs 35±0.15 mm; p<0.05 vs Basal) with reduced ejection fraction (EF: 45%±2 vs 66%±4; p<0.05 vs Basal). At 24h post-MI, we found a recovered LVDd (36.2±0.4 vs 35±0.15 mm; ns) and ameliorated cardiac contractile function (EF: 60%±3 vs 66%±4; ns). Morphological analysis by TEM (Fig 1) reveled that, at 3 hours post IR exposure, mitochondria were reduced in number, showing crista disarrangement with intra-vacuolization and fragmentation. At 24 h post-IR mitochondria number and morphology are recovered with normal cristae and absence of vacuolization. Morphological changes were accompanied by molecular modifications involved in mitochondria induced apoptosis (Cyt C), mitophagy (p62) and mitochondrial mass (SOD). In particular, Cyt C release was dramatically increased into cytosolic fraction at 3 h post IR and reduced at 24 h. Similarly, p62 was increased in response to stress at 3 h with a partial reduction at 24 h. Inversely, SOD level was reduced at 3h but normalized at 24h as compared to basal, indicating recovering of mitochondrial mass. Mitochondria damage was also evaluated by expression of the different complexes (I to IV) composing the mitochondria respiratory chain through RT-PCR. At 3 h post-IR complex I,II,III and IV are all reduced as well ATPase expression. At 24 hours post-IR, complexes expression and ATPase were recovered. A recently described modulator of mitochondrial survival, GRK2, was investigated in related in vitro model. In H9C2, over-expression of GRK2, induced a rightward shift in time for mitochondrial alterations and ROS production, which occurred after 8 hours after IR. Opposite, GRK2 silencing lead to anticipated mitochondrial impairment and no recovery occurred at 8h. Mechanistically, IR exposure produced interaction of GRK2 with MFN1 and 2, key molecules of mitochondrial recovery process, at 3h post IR. IR induces an acute cardiomyopathy that is associated to an altered mitochondrial morphology and function.
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