Abstract: P490

**GRK2 is a novel early marker of cardiotoxicity in response to doxorubicin**

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**Topic(s):**
Basic Science - Cardiac Diseases: Biomarkers

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**Background:**
Doxorubicin (DOXO) is common anticancer drug, whose efficacy is limited by a cumulative dose-dependent cardiotoxicity which can lead to severe heart failure and death. The current goal of cardio-oncology research is the identification of early markers of cardiotoxicity to promptly start an effective therapy. In this context, the G protein coupled receptor kinases type 2 (GRK2) is an useful marker of cardiac injury since its levels and activity are elevated in damaged heart. Moreover, it has been shown that myocardial GRK2 expression and activity are mirrored by lymphocyte levels of this kinase and can predict late ventricular remodeling as early as 3 days after Myocardial Infarction proposing this kinase as early biomarker of cardiac injury.

**Purpose:**
The aim of the study is to evaluate the role of GRK2 as early marker of cardiac dysfunction induced by DOXO.

**Methods:**
In vitro, GRK2 and Cleaved Caspase 3 levels were analyzed in cardio- myoblasts (H9C2) after treatment with DOXO 5 uM, by western blot. In vivo, C57B WT mice were treated with a single intraperitoneal injection of DOXO (20 mg/ Kg). Heart and blood from mice were collected at 24, 48 and 72h after treatment. The levels of GRK2 were evaluated by western blot in whole heart lysate and in PBMCs isolated from mice blood. Cardiac gene expression of ANF and MCP-1 was evaluated by Real time PCR.

**Results:**
In cardio-myoblasts, GRK2 levels were reduced in response to DOXO at 1 hour from starting treatment while Cleaved caspase 3, marker of damage, increased in a time dependent manner only after 3 hours from starting treatment. Similarly, in vivo, GRK2 levels were decreased in whole heart lysates from mice treated with DOXO compared with controls, at 24, 48 and 72h, when the transcriptional levels of ANF and MCP-1, were not still increased by DOXO administration. Also in PBMCs from mice blood, the levels of GRK2 were reduced after 24, 48 and 72h from starting treatment, reflecting the GRK2 cardiac reduction.

Conclusion DOXO induces an early decrease of GRK2 levels in cardiac cells. This reduction occurs in a pre-damage phase suggesting the potential role of GRK2 as early markers of cardiotoxicity. Moreover, the correlation between GRK2 levels in the heart and its expression in PBMCs, suggest that this protein could be easily detectable from peripheral blood to indirectly evaluate its expression levels in the heart. These data suggest that the reduction of GRK2 levels in PBMC could be an early marker of DOXO induced toxicity since it arises before the activation of DOXO-dependent damage.
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Methods: In vitro, GRK2 and Cleaved Caspase 3 levels were analyzed in cardiomyoblasts (H9C2) after treatment with DOXO 5 uM, by western blot. In vivo, C57B WT mice were treated with a single intraperitoneal injection of DOXO (20 mg/Kg). Heart and blood from mice were collected at 24, 48 and 72h after treatment. The levels of GRK2 were evaluated by western blot in whole heart lysate and in PBMCs isolated from mice blood. Cardiac gene expression of ANF and MCP1 was evaluated by Real time PCR.

Results: In cardiomyoblasts, GRK2 levels were reduced in response to DOXO at 1 hour from starting treatment while Cleaved caspase 3, marker of damage, increased in a time dependent manner only after 3 hours from starting treatment. Similarly, in vivo, GRK2 levels were decreased in whole heart lysates from mice treated with DOXO compared with controls, at 24, 48 and 72h, when the transcriptional levels of ANF and MCP-1, were not still increased by DOXO administration. Also in PBMCs from mice blood, the levels of GRK2 were reduced after 24, 48 and 72h from starting treatment, reflecting the GRK2 cardiac reduction.

Conclusion: DOXO induces an early decrease of GRK2 levels in cardiac cells. This reduction occurs in a pre-damage phase suggesting the potential role of GRK2 as early markers of cardiotoxicity. Moreover, the correlation between GRK2 levels in the heart and its expression in PBMCs, suggest that this protein could be easily detectable from peripheral blood to indirectly evaluate its expression levels in the heart. These data suggest that the reduction of GRK2 levels in PBMC could be an early marker of DOXO induced toxicity since it arises before the activation of DOXO-dependent damage.