New role of EPAC1 in Anthracycline-induced cardiotoxicity and anticancer therapy

Authors:
A Belhadef1, M Ribeiro1, M Mazever1, M Laudette2, B Crozatier1, F Lezoualc’h2, J-P Benitah1, A-M Gomez1, C Lemaire1, E Morel1, 1University of Paris-Sud 11, UMR-S 1180 - Chatenay-Malabry - France, 2Institute of Cardiovascular and Metabolic Diseases, INSERM U1048 - Toulouse - France,

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Introduction: Doxorubicin (Dox) is an anthracycline commonly used to treat many types of cancer; unfortunately this chemotherapeutic agent induces many side effects such as cardiotoxicity leading to dilated cardiomyopathy (DCM). The cardiotoxicity of Dox has been related to reactive oxygen species generation, DNA intercalation, topoisomerase II inhibition and bioenergetics alterations leading to cardiomyocyte death.

Objectif: Nowadays the challenge is to find new treatment options aiming at reducing Dox cardiotoxicity. Epac (exchange protein directly activated by cAMP) signaling could be worth investigating as Epac activates small G proteins which are known to be involved in Dox-induced cardiotoxicity.

Methods: We investigated the time/dose-dependent Dox effect on Epac signaling in both in vivo mice model (C57Bl63/ Knock-out Epac1 mice, iv injections, 12mg/kg cumulative dose) and in vitro (primary culture of neonatal rat cardiomyocytes (NRVM, 24h, Dox 1µM).

Results: In vivo, Dox-treated mice developed a DCM associated with Ca2+ homeostasis dysfunction (increase of Ca2+ waves and Ca2+ leaks). In vitro, as measured by flow cytometry and western blot, Dox (1µM) induced DNA damages and cell death in NRVM. This cell death is associated with apoptotic features including mitochondrial membrane permeabilization, caspase activation and cell size reduction. The inhibition of Epac1 (ESI09, CE3F4) decreased Dox-induced DNA damage, loss of mitochondrial membrane potential, apoptosis and finally cardiomyocyte death. Moreover, in vivo, Epac1 KO mice were protected against Dox-induced cardiotoxicity by unaltered cardiac function (no DCM) and calcium homeostasis at 15 weeks post-treatment.

Conclusion: Inhibition of Epac1 could be a valuable therapeutic strategy to limit Dox-induced cardiomyopathy during cancer chemotherapy. Indeed, preliminary data show also that preventing Dox-induced cardiotoxicity, the inhibition of Epac1 can also potentiate cancerous cells death.