Three tyrosine kinase inhibitors cause cardiotoxicity by inducing endoplasmic reticulum stress and inflammation in cardiomyocytes

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一、簡述論文摘要及重大發現:

This study investigates the cardiotoxicity caused by tyrosine kinase inhibitors (TKIs) which are commonly used in cancer treatment. By profiling the phenotype and transcriptome of human cardiomyocytes treated with eight TKIs. They found that three of TKIs, afatinib, ponatinib, and sorafenib, can induce ER stress, pro-inflammation, and cardiac fetal gene expression, leading to impaired cardiac function and cell death. Moreover, they showed that inhibition of either PERK or IRE1α axes of the ER stress pathway blocks the expression of cardiac fetal and pro-inflammatory genes which may be a potential therapeutic target to mitigate the cardiotoxicity induced by TKIs. Overall, the findings highlight the need for careful monitoring and management of cardiovascular risk in cancer patients receiving TKIs.

二、對論文內容的提問、缺點與評論:

In this study, by using Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) and Neonatal rat cardiac myocytes (NRCM), they not only investigate the mechanisms of TKIs-mediated cardiac damage but also provide the potential therapeutic target to mitigate the TKIs-induced cardiotoxicity. However, owing to cardio-oncology being kind of like a triangle relationship between anti-cancer drugs, heart, and cancer, it would be better if the author could mention whether cancer will participate or affect the TKIs-induced cardiotoxicity in the heart. Therefore, I think an in vivo experiment using tumor-bearing mice is needed, to clarify whether the existence of cancer would affect the phenotype, the transcriptome, and the mechanisms of cardiotoxicity in TKIs treated mice in the heart. More importantly, they must examine whether inhibiting the potential therapeutic target they proposed won't affect the anti-tumor effects of TKIs in mice.

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Abstract

Background Tyrosine kinase inhibitors (TKIs) are anti-cancer therapeutics often prescribed for long-term treatment. Many of these treatments cause cardiotoxicity with limited cure. We aim to clarify molecular mechanisms of TKI-induced cardiotoxicity so as to find potential targets for treating the adverse cardiac complications.

Methods Eight TKIs with different levels of cardiotoxicity reported are selected. Phenotypic and transcriptomic responses of human cardiomyocytes to TKIs at varying doses and times are profiled and analyzed. Stress responses and signaling pathways that modulate cardiotoxicity induced by three TKIs are validated in cardiomyocytes and rat hearts.

Results Toxicity rank of the eight TKIs determined by measuring their effects on cell viability, contractility, and respiration is largely consistent with that derived from database or literature, indicating that human cardiomyocytes are a good cellular model for studying cardiotoxicity. When transcriptomes are measured for selected TKI treatments with different levels of toxicity in human cardiomyocytes, the data are classified into 7 clusters with mainly single-drug clusters. Drug-specific effects on the transcriptome dominate over dose-, time- or toxicity-dependent effects. Two clusters with three TKIs (afatinib, ponatinib, and sorafenib) have the top enriched pathway as the endoplasmic reticulum stress (ERS). All three TKIs induce ERS in rat primary cardiomyocytes and ponatinib activates the IRE1α-XBP1s axis downstream of ERS in the hearts of rats underwent a 7-day course of drug treatment. To look for potential triggers of ERS, we find that the three TKIs induce transient reactive oxygen species followed by lipid peroxidation. Inhibiting either PERK or IRE1α downstream of ERS blocks TKI-induced cardiac damages, represented by the induction of cardiac fetal and pro-inflammatory genes without causing more cell death.

Conclusions Our data contain rich information about phenotypic and transcriptional responses of human cardiomyocytes to eight TKIs, uncovering potential molecular mechanisms in modulating cardiotoxicity. ER stress is activated by multiple TKIs and leads to cardiotoxicity through promoting expression of pro-inflammatory factors and cardiac fetal genes. ER stress-induced inflammation is a promising therapeutic target to mitigate ponatinib- and sorafenib-induced cardiotoxicity.

Keywords Cardiotoxicity, Tyrosine kinase inhibitor, Transcriptomics, Endoplasmic reticulum stress, Inflammation

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