Metformin attenuates the cardiotoxicity of ibrutinib through AMPK and PI3K-Akt pathway

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Introduction

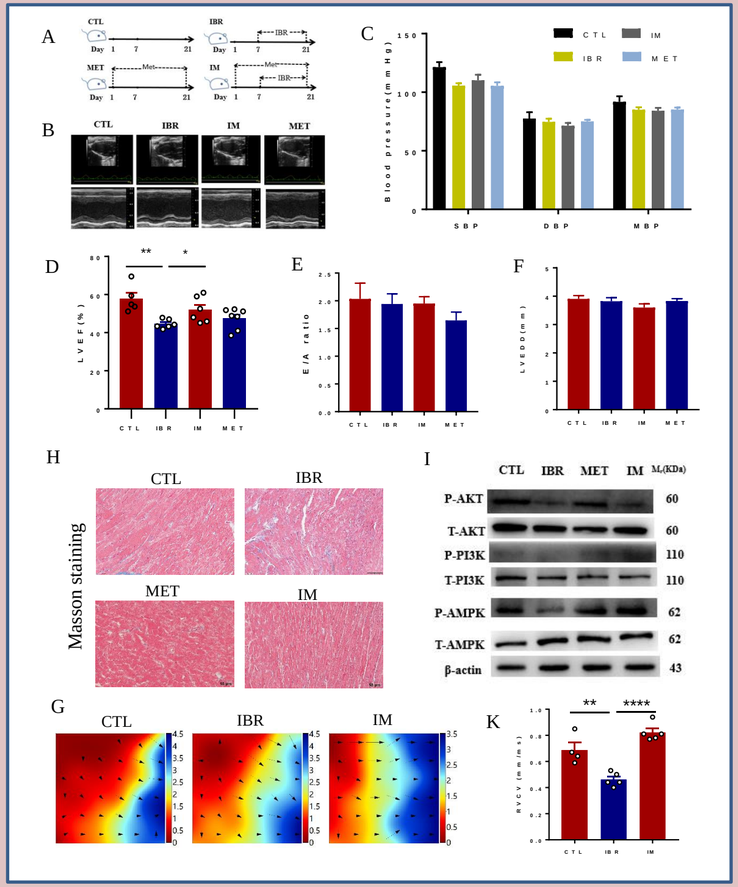
Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor that has shown significant efficacy in B-cell lymphoma. However, it is highly associated with adverse cardiovascular events, such as atrial fibrillation, ventricular arrhythmia, and sudden cardiac death. These cardiotoxicities limit its clinical application. Previous studies have shown that ibrutinib can inhibit AMPK and PI3K-Akt pathway. In this study, we hypothesized that metformin (an AMPK activator) can reduce ibrutinib-induced cardiotoxicity.

Methods

12 weeks old male mice were selected and divided into 4 groups: 1) control group (n=8); 2) ibrutinib group (30 mg/kg/d; i.p. n = 8,2 weeks); 3) metformin group (200mg/kg/d; p.o. n = 8,3 weeks); 4) ibrutinib + metformin group (n = 8,3 weeks). All animals were subjected to follow-up experiments after three weeks. Evaluate the structure and function of the heart by echocardiography; detect the surface electrocardiogram and hemodynamic changes in each group of mice; detect the cardiac conduction function and the ventricular arrhythmia induction by endocardial electrophysiological experiments and epicardial electrical conduction mapping to evaluate the ventricular electrical remodeling. To observe the cell morphology by HE staining, Masson staining to measure ventricular fibrosis to evaluate the ventricular structural remodeling in mice. To observe the AMPK protein expression and the PI3K-Akt pathway in the ventricle by Western Blot.

Conclusion

Metformin, an AMPK activator, can ameliorate the cardiotoxicity induced by ibrutinib through AMPK and PI3K-Akt pathway.



Results

Ibrutinib treatment caused a significant decline in left ventricular ejection fraction (LVEF) compared to control group, which was ameliorated with metformin (200 mg/kg) co-treatment. Ibrutinib significantly reduces the right ventricular conduction velocity (CV), while the combined use group can increase the right ventricular conduction velocity; Ventricular morphological changes were detected using Masson's trichrome staining. Extensive interstitial fibrosis of ventricular cardiomyocytes were observed in the ibrutinib group, and ibrutinib + metformin group significantly attenuated these changes. Western Blot results show that ibrutinib treatment can inhibit AMPK phosphorylation and inhibit the PI3K-Akt pathway, while the combined use group can reduce these changes.

Figure 1: (A) Schematic diagram of 21-day modeling of C57BL/6J mice (B-F) Echocardiography and hemodynamics in each group (H) Masson staining of left ventricle (I) Western blot analysis of changes in protein expression levels (G) Mapping image of right ventricle (K) conduction velocity of right ventricular CTL: control IBR: ibrutinib IM: ibrutinib + metformin MET: metformin