Dynasore, a Dynamin Inhibitor, Induces PAI-1 Expression in MeT-5A Human Pleural

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摘要

Abstract

Plasminogen activator inhibitor-1 (PAI-1) is a primary regulator of plasminogen activation that plays an essential role in regulating the physiological thrombotic/fibrinogenic balance. The elevation of PAI-1 expression by human pleural mesothelial cells has been reported to contribute to pleural fibrosis and pleurodesis. In this study, we examined the effects on PAI-1 expression of dynasore, a cell-permeable inhibitor of dynamin, and its mechanisms in a human pleural mesothelial cell line (MeT-5A). The results indicated that dynasore enhanced transforming growth factor (TGF)-beta(1)- and TNF-alpha-induced PAI-1 protein expression in a concentration-dependent manner. Furthermore, dynasore significantly up-regulated PAI-1 protein and its messenger RNA expressions. Interestingly, Smad2/3 activation was induced by TGF-beta(1) but not by dynasore. Among signaling inhibitors, a c-Jun NH(2)-terminal kinase (JNK) inhibitor (SP600125) markedly attenuated dynasore-stimulated PAI-1 protein production. Consistently, dynasore strongly increased JNK phosphorylation. On the other hand, there was no enhancement effect by dynasore on TGF-beta(1)-induced matrix metalloproteinase-2 activation. These findings suggest that dynasore may stimulate PAI-1 protein expression and enhance TGF-beta(1) activity through activation of JNK-mediated signaling in human pleural mesothelial cells. Given the profibrotic effect of dynasore, further in vivo studies may be conducted to evaluate its potential as a pleurodesing agent.