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LY294002 and Rapamycin promote coxsackievirus-induced cytopathic effect and apoptosis via inhibition of PI3K/AKT/mTOR signaling pathway

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Abstract Coxsackievirus B3 (CVB3) is a common human pathogen for acute myocarditis, pancreatitis, non-septic meningitis, and encephalitis; it induces a direct cytopathic effect (CPE) and apoptosis on infected cells. The Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT/PKB)/mammalian target of Rapamycin (mTOR) signaling pathway regulates several cellular processes and it is one of the most important pathways in human networks. However, the effect and mechanism of PI3K/AKT/mTOR signaling pathway in CVB3 infected cells are poorly understood. In this study, we demonstrate that inhibition of PI3K/AKT/mTOR signaling pathway increased CVB3-induced CPE and apoptosis in HeLa cells. The activity of downstream targets of PI3K and mTOR is attenuated after CVB3 infection and inhibitors of PI3K and mTOR made their activity to decrease more significantly. We further show that LY294002 and Rapamycin, the inhibitor of PI3K and mTOR respectively, promote CVB3-induced CPE and apoptosis. Taken together, these data illustrate a new and imperative role for PI3K/AKT/mTOR signaling in CVB3 infection in HeLa cells and suggest an useful approach for the therapy of CVB3 infection.

Keywords LY294002 · Rapamycin · Coxsackievirus-induced cytopathic · Apoptosis

Introduction

Coxsackievirus B3 (CVB3), a small and nonenveloped positive-strand RNA *Enterovirus* in the *Picornaviridae* family, encodes four capsid protein and seven nonstructural proteins [1]. CVB3 infection has been know as the most common causes of viral myocarditis-associated heart failure in infants, children, and young adults [2, 3]. Moreover, CVB3 can also infect other organs, including pancreas, spleen, and brain, involving in the pathogenesis of pancreatitis, aseptic meningitis, and encephalitis [4, 5]. Although more and more research on mechanism of CVB3 infection and CVB3-related human illness [6, 7], there is no specific therapeutics available to efficiently inhibit CVB3 infection currently.

HeLa cells are highly proliferative and susceptible to productive CVB3 infections [8], which made HeLa cells to be the most common human model for studying CVB3 infection and apoptosis in vitro. It has been reported that CVB3 infection can induce a direct cytopathic effect and apoptosis in HeLa cells and mouse hearts [9–11]. The possible mechanisms include activation of caspase-3 [12], phosphorylation, and activation of the extracellular signal-regulated kinase (ERK1/2) [13], activation of protein kinaseB/AKT(PKB/AKT) [14]. However, the specific genes or signaling proteins responsible for CVB3-induced CPE and apoptosis are still poorly understood.

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