

SARS-CoV-2 and the Possible Role of Raf/MEK/ERK Pathway in Viral Survival: Is This a Potential Therapeutic Strategy for COVID-19?

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Keywords

COVID-19 · Raf/MEK/ERK signaling · RNA viruses · Viral life cycle · Viral survival

In late 2019, a sudden rise in respiratory-related disease cases in China triggered the identification of its source as a novel corona virus, termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused by novel SARS-CoV-2 is named as COVID-19 by the World Health Organization [1]. The culprit virus belongs to the *Coronaviridae* family of coronaviruses that caused 2 other outbreaks, namely, severe acute respiratory syndrome (SARS) in 2002 [2] and Middle East respiratory syndrome in 2012 [3]. As the survival of every virus depends on its host cell, the understanding of cellular functions such as signaling pathways that are essential for viral replication may be suitable to define targets for antiviral therapy and pave the way toward effective drugs against essential cellular activities supporting viral replication [4]. In this regard, we have focused on the Raf/MEK/ERK signaling pathway, which is probably one of the most well-known signal transduction pathways among biologists because of its implication in a wide variety of cellular functions such as cell proliferation, cell

cycle arrest, and apoptosis [5]. The mechanism of this pathway is initiated by G protein-coupled receptors, which leads to the phosphorylation of downstream molecules and activates the serine threonine kinase Raf (dual specificity kinase MEK and MAPK/ERK). ERK phosphorylates various substrates, transforms the signals, and follows different functions in cells [6]. Hence, it is not surprising that several DNA and RNA viruses inherit this pathway, apart from an initial activation upon viral attachment, for various steps in the viral life cycle [7]. Consequently, the kinetic of pathway activation is highly dynamic [8]. For example, herpes simplex type-1 virus-induced activation of the Raf/MEK/ERK pathway is used for cytoskeleton rearrangement during entry [9], JC polyomavirus requires ERK activation for viral transcription [10], and influenza A virus hijacks Raf/MEK/ERK activity for efficient viral ribonucleoprotein export [11, 12]. Ebola virus glycoprotein-induced cytotoxicity depends on ERK activation [13], and hepatitis C virus relies on Raf/MEK/ERK-mediated upregulation of cytosolic phospholipase A2 for efficient particle production [14]. Flaviviruses, including yellow fever virus, Saint-Louis encephalitis virus, and dengue virus, as well depend on Raf/MEK/ERK-mediated signaling for efficient replication

[15, 16]. It has been shown that activated ERK1/2 enhanced the infectivity of human immunodeficiency virus, whereas treatment of cells with the MEK1/2 inhibitor PD98059 significantly inhibited human immunodeficiency virus infectivity [17, 18]. Treating cells with UO126, a highly selective inhibitor of both MEK1 and MEK2, also significantly inhibited the propagation of influenza A virus, Borna disease virus, coxsackievirus B3, and HCMV [11, 19–21]. Thus, it appears that the MEK1/2 inhibitors have a broad effect on propagations of viruses from various families (positive-strand and negative-strand RNA viruses, retroviruses, and DNA viruses) [22]. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. Similar to SARS and Middle East respiratory syndrome, the SARS-CoV-2 genome encodes nonstructural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (such as spike glycoprotein), and accessory proteins. The 4 nonstructural proteins mentioned above are key enzymes in the viral life cycle, and the spike glycoprotein is indispensable for virus-cell receptor interactions during viral entry [23]. By analyzing the effects of transiently expressed viral spike protein (S) of SARS-CoV, it was revealed that the S protein plays an important role in virus-stimulated cyclooxygenase-2 (COX-2) expression [24]. COX-2 is a prostaglandin synthetase involved in inflammation [25] that is highly regulated by different factors including cytokines [26]. The upstream calcium-dependent PKCa that modulates the downstream Raf/MEK/ERK pathway is induced by the SARS-CoV S protein. It was revealed that ERK is involved in S protein-induced activation of the COX-2 promoter and the production of COX-2 protein in HEK293T cells. This result helps explain the function of SARS-CoV S protein in SARS pathogenesis [24]. More information on relevant MAPK signaling induced by coronavirus was obtained for murine coronavirus. It was revealed that infection of cultured

cells with murine coronavirus resulted in activation of the Raf/MEK/ERK signal cascade, and inhibition of the MAPK signaling pathway by UO126 or knockdown of MEK and ERK by small interfering RNAs significantly impaired murine coronavirus progeny production. The treatment did not affect virus entry or cellular and viral mRNA production. However, synthesis of viral genomic and sub-genomic RNAs was severely suppressed by UO126 treatment. This study indicated that the MAPK signaling pathway is involved in murine coronavirus RNA synthesis [22]. Selective RAF inhibitors are well tolerated, and severe toxicities occur infrequently in noninfected cells. Among the common grade 1–2 adverse events are dermatological affections (50–70%), fatigue (30–50%), diarrhea (10–30%), and nausea (10–20%) [27]. Considering the role of the Raf/MEK/ERK signaling pathway in the pathogenesis of various viruses, it is probable that the activation of this signaling pathway by COVID-19 has an important role in the survival of this virus. In this regard, drugs that inhibit the Raf/MEK/ERK signaling pathway may be potential antiviral candidates for the treatment of COVID-19.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

M. Ghasemnejad-Berenji: literature review and writing the manuscript. S. Pashapour: literature review and revising the manuscript.

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