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Review

Development of cellular signaling pathway inhibitors as new antivirals against influenza

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ABSTRACT

Influenza virus exploits a number of cellular signaling pathways during the course of its replication, rendering them potential targets for new therapeutic interventions. Several preclinical approaches are now focusing on cellular factors or pathways as a means of treating influenza. By targeting host factors, rather than viral mechanisms, these novel therapies may be effective against multiple virus strains and subtypes, and are less likely to elicit viral drug resistance. The most promising candidates are inhibitors of intracellular signaling cascades that are essential for virus replication. This article reviews novel approaches and compounds that target the Raf/MEK/ERK signaling pathway, NF-κB signaling, the PI3K/Akt pathway and the PKC signaling cascade. Although these new antiviral strategies are still in an early phase of preclinical development, results to date suggest they offer a new approach to the treatment of influenza, supplementing direct-acting antiviral drugs.

Contents

1. Introduction

The number of intracellular signaling pathways that have been found to be essential for influenza virus replication has steadily increased over the past decade (Ludwig and Planz, 2008; Ludwig et al., 2003; Pleschka, 2008). In addition to influenza virus, other RNA and DNA viruses must interact with intracellular signaling mechanisms to ensure productive infection (Ludwig and Planz, 2008; Ludwig et al., 2006; Planz et al., 2001; Pleschka, 2008; Seth et al., 2006). Intracellular signaling pathways are therefore increasingly being studied as targets for novel antiviral therapies. Pathways that are required for the virus to cross intracellular barriers, such as the nuclear membrane, are most suitable for antiviral intervention. Influenza viruses must pass these barriers during the initial phase of replication, when the viral ribonucleoproteins

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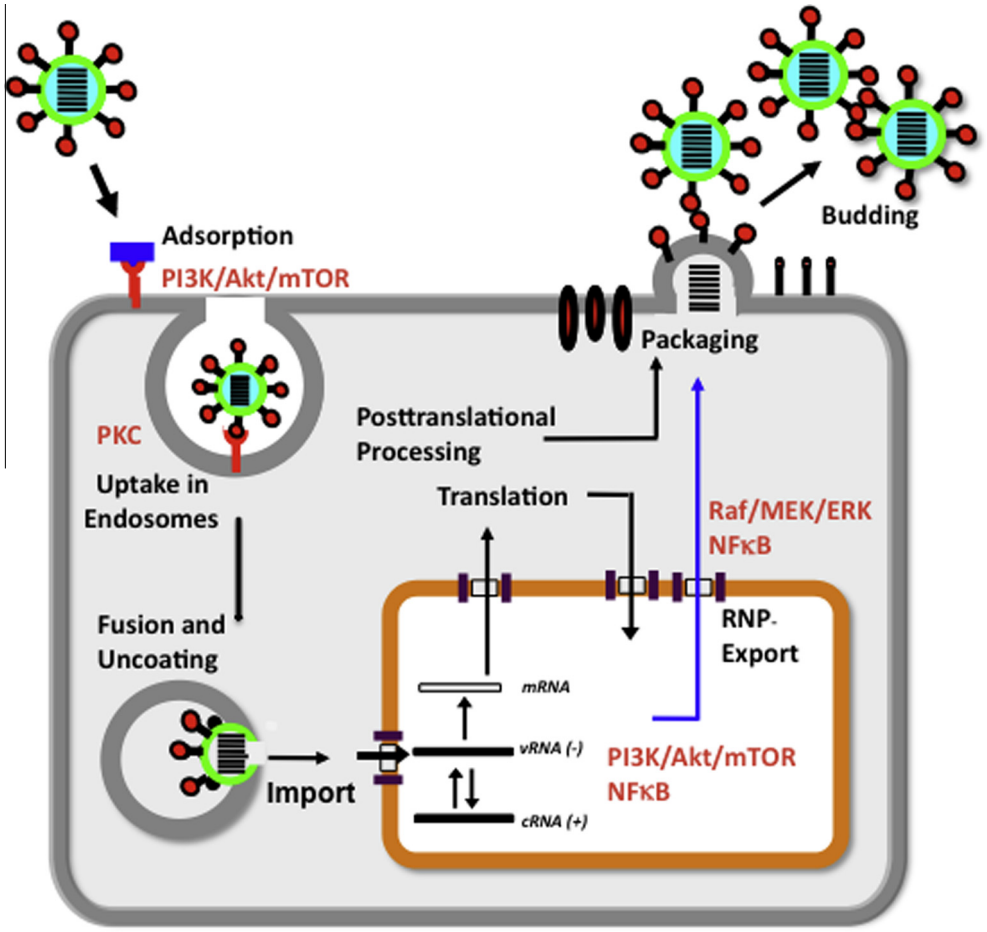

Fig. 1. Influenza virus replication cycle. Involvement of cellular Raf/MEK/ERK, NFκB, PI3K/Akt/mTOR and PKC pathways during the replication of influenza virus. Detailed information is given also in Table 1. Figure modified from (Ludwig et al., 2003).

(RNPs) are transported from the cytoplasm to the nucleus, and later in the replication cycle, when virus particles are released from the infected cell.

A potential advantage of antiviral strategies that target intracellular signaling pathways is that they are less likely to induce viral resistance than those that directly target viral replication, as has already been shown for several compounds (Ludwig et al., 2004; Mazur et al., 2007). However, development of resistance is dependent on multiple factors, including the specific pathway inhibited, its role in influenza virus replication and the level of pathway inhibition (i.e., at the global regulatory level vs. the specific effector level). On the other hand, potential adverse effects of inhibitors of intracellular signaling pathways must also be taken into consideration, since they interfere with the host cell machinery and with substantial cellular functions.

Intracellular signaling pathways are currently being evaluated as targets for many different medical indications. The most advanced development has occurred in the area of antitumor therapy, with an increasing number of compounds now in clinical studies or licensed for the treatment of human malignancies. As a consequence, there is an enormous amount of information about these compounds, as regards their pharmacokinetic and pharmacodynamic properties and adverse effects in humans. It would therefore be of great interest to investigate the antiviral potential of those compounds that have successfully passed Phase I clinical trials for other medical indications, and are suitable for oral administration. Because the target of influenza therapy is the respiratory epithelium, agents that could be delivered by aerosol are also of interest.

This article describes the potential of intracellular signaling pathways as targets for novel influenza therapies, focusing on the Raf/MEK/ERK signaling pathway, NF-κB signaling, the PI3K/Akt pathway and the PKC signaling cascade. In each case, a summary of the basic physiological features of the pathway is followed by a brief review of compounds that inhibit the pathway and have been shown to reduce influenza virus replication, including their *in vitro* and *in vivo* antiviral activity, safety and tolerability in patients, current developmental status and prospects for introduction into clinical use.

2. Development of Raf/MEK/ERK inhibitors against influenza virus infection

2.1. The Raf/MEK/ERK signaling pathway

The Ras-dependent Raf/MEK/ERK signaling pathway belongs to the family of so-called mitogen-activated protein kinase (MAPK) cascades and is one of the best studied signal transduction pathways. Since the discovery of MAP kinases more than 30 years ago a huge number of articles have been published on this topic. Almost all growth factors and cytokines that act through receptor tyrosine kinases, cytokine receptors or G-protein-coupled receptors initiate signaling via the Raf/MEK/ERK pathway (Fig. 1). Typically, ligand binding to receptor tyrosine kinases induces dimerization of the receptor and auto-phosphorylation of specific tyrosine residues in the C-terminal region. This generates binding sites for adaptor proteins, such as growth factor receptor-bound protein 2 (GRB2), which recruit the guanine nucleotide exchange