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Review Article

Targeting Host Cell Factors for Development of Antiviral therapeutics

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ABSTRACT

Suitable antiviral medications are unavailable to treat the sick animals suffering from viral infections. To reduce the impact of viral diseases of livestock, controlling the spread of virus is of great importance. Vaccines with good efficacy exist for some but not against all animal viral diseases. However, vaccines cannot be used to provide instantaneous protection during epidemics. Antiviral compounds could be used as a rapid control tool to serve this purpose. Infection of cells with viruses results in the activation of a variety of intracellular signaling pathways that are in part exploited by the virus to ensure efficient replication. The dependencies of the virus on these signaling pathways can be exploited to develop novel antiviral drugs that disrupt signal transduction. Receptor tyrosine kinase (RTK), Raf/MEK/ERK and NF–κB, are important signaling pathways that are required for efficient virus propagation and have attracted some attention as suitable targets for antiviral interventions. These studies are in preclinical phase and will certainly lead to paradigm changes in antiviral drug development. Targeting host cell factor might have an additional advantage in terms of drug resistance because the virus cannot easily replace the missing cellular functions by mutations. Although limited experiments have been performed in animals, encouraging results for Foot–and–mouth disease virus (FMDV) suggest that use of antiviral agents up to 12 h post–infection provides significant protection. Such antiviral drugs can complement emergency vaccination or be applied to treat valuable zoological collections and breeding stocks.

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INTRODUCTION

As an obligate intracellular parasite, virus has to rely on host cell machinery for its effective replication (Beaud, 1995; Ludwig et al., 2006; Saito, 2006). The role of different viral proteins in its replication cycle is well characterized. However, there is a significant gap in knowledge about the host cell factors used by the virus during its replication. Accumulating evidences suggest involvement of various host cell factors at different steps of virus replication cycle and each essential steps of replication cycle is considered as a potential site for antiviral intervention (Borgeling et al., 2014; Dierkes et al., 2014). Virus encoded protein targets are attractive but can lead to selection of drug resistant variants over a period of time due to mutations (Poland et al., 2009).

There are some antiviral medications approved by US Food and Drug Administration (FDA) that are used for both prophylactic and therapeutic treatment of viral infection in human beings (http://www.fda.gov/drugs/drugsafety). However, most of the currently available antiviral agents target viral components; repeated use of which leads to emergence of drug resistant virus variants due to mutations (Bloom et al., 2010; Fry and Gubareva, 2012; Hamelin et al., 2010; Hayden, 2009; Hayden, 2006; Hayden and de Jong, 2011; Hayden and Hay, 1992; Ismail et al., 2012; Pawlotsky, 2012; Ujike et al., 2010). For example, in case of influenza virus, the first group of antivirals comprises ion channel or M2 inhibitors which include Amantadine (approved in 1966) and Rimentadine (approved in 1993) and second group comprises neuraminidase inhibitors which include Oseltamivir (Tamiflu) and Zanamivir (Relenza) (both were approved in 1999. The M–2 inhibitors have limited use in medical practice because of lack of their activity against influenza B viruses and also rapid emergence of drug resistant variants. Neuraminidase inhibitors came with great success, but by 2009, resistant mutants have been reported in both seasonal and pandemic H1N1 suggesting an alternative strategy to be design that do not have a tendency to easily induce drug resistance in viruses due to preexisting selection pressure. The cellular factors that are required for virus replication but at the same time are dispensable for host cell metabolism may be such targets for antiviral interventions as virus cannot easily replace missing cellular functions by mutations (Edinger et al., 2014; Ehrhardt et al., 2010; Eierhoff et al., 2009; Fry and Gubareva, 2012; Kumar et al., 2011b; Ludwig, 2011; Ludwig et al., 2006; Pleschka et al., 2001).

Roles of host signaling pathways in virus replication

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Living system respond to the environmental stimuli by encoding and transmitting the received information in form of a chain of events called signal transduction that in turn results in change in the behavior of the cell (Port et al., 2013). The cellular signals that are activated upon virus infection might be due to

i. interaction of viral surface proteins with cellular receptors
ii. Accumulation viral proteins or RNA inside cell and
iii. Overloading of host cell protein synthesizing machinery due to viral proteins (Yu et al., 2014).

In addition, many viral proteins not present in infectious virus but produced during replication in host cell, might also activate signaling pathways. The fate of the signal transduction pathway initiated by the cells might be:

i. Antiviral
ii. Virus supportive
iii. Both antiviral and virus supportive and
iv. No role in virus life cycle.

Infection of cells with viruses results in the activation of a variety of intracellular signaling pathways that are in part exploited by the virus to ensure efficient replication. These dependencies may be used to develop novel antiviral drugs by disrupting signal transduction (Kumar et al., 2011b).

The most characterized host cell signaling pathway for virus infection are; receptor tyrosine kinase (RTK) (Naskar et al., 2011; Ubee et al., 2011), Mitogen activated protein kinase (MAPK) (Pleschka et al., 2001), Phosphatidylinositol 3–kinase (PI3K) (Ehrhardt et al., 2006) and Nuclear factor–kappaB (NF–κB) (Kumar et al., 2008). Following activation of the cell signaling pathways, there is an upregulation of the genes responsible for cytokines production (Kang et al., 2013; Stoppelenburg et al., 2014) which ultimately produce an antiviral state. However, inhibition of these pathways has been shown to inhibit virus replication suggesting that the virus exploits the component/s of signaling pathways to support its own replication (Fujioka et al., 2013). The virus supportive activity of such signaling pathways can be exploited to develop novel antiviral therapeutics (Chinnakannan et al., 2014).

Receptor tyrosine kinases (RTKs) signaling

Receptor tyrosine kinases are a group of growth factor receptors that undergo autophosphorylation as ligand binds at its tyrosine (Tyr) residues (Schlessinger, 2000). These phosphorylated tyrosines then recruit Src homology–2 (SH2) and phosphotyrosine–binding (PTB) domain–containing proteins to activate downstream signaling pathways, such as the, PI3K, Ras/ERK/MAPK and JAK/STAT pathways (Pawson, 1995). Together, the complex signaling network triggered by RTKs leads to regulation of immune response, metabolism, cell growth, and migration, and cell differentiation. RTKs have been extensively studied in various cancers to develop anticancer therapeutics. Recently RTKs and other tyrosine kinases have also been shown to play important roles in virus replication. For example, RTK inhibitor genistein was found to block replication of HIV–1, herpes simplex virus type 1 (HSV–1), and arenavirus (Stantchev et al., 2007; Vela et al., 2008; Sharma et al., 2011). Src family kinases are known to be important for assembly and maturation of the dengue virus and West Nile virus (Hirsch et al., 2005). The Raf/MEK/ERK and PI3K pathways which are downstream of RTKs play important roles in influenza virus replication (Ludwig et al., 2006). Specific RTK inhibitors (RTKIs), known as tyrphostin AG879 and tyrphostin A9, have shown strong antiviral activity against influenza A virus by inhibiting multiple steps of the virus life cycle viz: (i) inhibiting export of the vRNP complex across nuclear membrane via Crm1–dependent nuclear export pathway (ii) inhibition of the viral RNA synthesis (NF–kappaB independent), and (iii) inhibition of the virus release by impairing a lipid biosynthesis enzyme, farnesyl biophosphate synthase (FPPS) (Kumar et al., 2011a). Diverse interventions targeting RTK (TrkA) can impede not only influenza virus replication but also impair replication of several other viruses such as Rotavirus, Coronavirus, Sendai virus, Arenavirus and Herpessimplex virus–1 (HSV–1), thus validating this specific RTK as a candidate for drug target (Kumar et al., 2011a).

MAP kinase pathway

Mitogen activated protein kinase (MAPK) cascades are important signaling pathways that convert extra–cellular signals into cellular responses (reviewed in reference (Houliston et al., 2001). They regulate proliferation, differentiation, cell activation and immune responses. Four different members, organized in separate cascades have been identified so far: (i) ERK (extra–cellular signal regulated kinase), (ii) JNK (Jun–N–terminal kinase), (iii) p38 and (iv) ERK5. For each MAPK, different isoforms are known. All these enzymes are activated by phosphorylation, mediated by an upstream MAPK kinase (MAPKK, MEKs or MKKs). It is induced by extra–cellular agents, including pathogens such as RNA viruses and DNA viruses (Pleschka, 2008). Influenza virus infection induced ERK activation leads to virus–induced cytokine production and airway inflammation (Mizumura et al., 2003), however at the same time it supports viral replication by facilitating vRNP export (Pleschka et al., 2001; Marjuki et al., 2006) suggesting its dual role in influenza virus life cycle.

NF–κB pathway

Classic NF–κB comprises a heterodimer of 50–kDa protein named p50/ NF–κB1 and a 65–kDa protein called p56/RelA. This heterodimer is the most common form of NF–κB in different cell types (Ludwig et al., 2006). In resting stage, NF–κB heterodimer resides in the cytoplasm in a complex with inhibitory protein (IκB) and can not enter to the nucleus. Various NF–κB inducing signals ultimately lead to activation of IκB kinase β (IKK–β) which in turn promotes phosphorylation of IκB resulting in ubiquitination and proteosome–mediated degradation of IκB. Following degradation of IκB, NF–κB enters to the nucleus and activates transcription of several pro-inflammatory cytokine genes (Ludwig et al., 2006). Influenza A virus nucleoprotein (NP), hemagglutinin protein (HA) and matrix protein (M) activate NF–κB pathway. Over accumulation of these proteins induce ER stress response which in turn promotes degradation of the inhibitory protein (IκB) and hence activation of NF–κB pathway (Flory et al., 2000, Mogensen and Paludan, 2001). Nimerjahan et al., 2004, showed the preliminary role of NF–κB influenza in virus propagation. However the first direct evidence suggesting requirement of

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NF–κB for efficient influenza virus replication came from a study by Kumar et al., 2008. Using two known inhibitors of NF–κB [Bay11–7082 which inhibit phosphorylation of IkB and Pyrrolidine dithiocarbamate (PDTC), which inhibit ubiquitin–proteosome–mediated degradation of IkB] and siRNA knockdown of p65, authors identified that NF–κB signaling differentially regulates influenza virus RNA synthesis and NF–κB subunit p65 enhances vRNA synthesis but not cRNA synthesis (Kumar et al., 2008). Highly pathogenic avian influenza virus of H5N1 subtypes in human and birds leads to bleeding and overproduction of cytokines (cytokine storm/hypercytokinemia) preferentially by attacking endothelial cells. The H5N1 (highly pathogenic influenza virus)-induced overproduction of cytokines depends on functional NF–κB signaling whereas low pathogenic strains are much weaker and less NF–κB dependent (Schmolke et al., 2009). Viruses have also evolved strategies to counteract these responses. Influenza A virus not only suppress IFN–β induction but also suppress type I IFN signaling involving NF–κB dependent induction of inhibition of cytokine signaling–3 (SOCS–3) protein expression which block JAK/STAT activation ultimately resulting in inhibition of antiviral response (Pauli et al., 2008).

Phosphatidylinositol 3–kinase (PI3K) pathway

Phosphatidylinositol 3–kinase (PI3K) has been shown to be activated in response to dsRNA intermediate and mediates activation of transcription factor interferon regulatory factor–3 (IRF–3), a protein with antiviral functions (Ehrhardt et al., 2006). Inhibition of the PI3K pathway using chemical inhibitors results in decrease of viral titers due to reduced uptake of the virus particles (entry) into the host cell (Ehrhardt et al., 2006). Additionally, with mechanism unknown, inhibition of PI3K pathway has also been reported to inhibit viral RNA synthesis, vRNP export and viral protein synthesis (Shin et al., 2007).

Host cell signaling pathways have been shown to play dual role in virus replication. For example, influenza virus NS1 protein inhibit the dsRNA–responsive transcription factors, whereas on another hand, it activates PI3K pathway to suppress the onset of premature virus–induced caspase activation and apoptosis (Ehrhardt et al., 2007) by inhibiting JNK (c–jun N terminal kinase) pathway via ASK1 (apoptosis signal–regulating kinase 1) (Lu et al., 2010). However, further studies are required to dissect the complex host–pathogen interactions.

These studies are in preclinical phase and will certainly lead to paradigm changes in antiviral drug development. Targeting host cell factor might have an additional advantage in terms of drug resistance because the virus cannot easily replace the missing cellular functions by mutations.

Genome–wide screens to search host cell factors required for virus replication

Completion of human genome project in 2003 has lead to accumulation of knowledge about host genes involved in virus replication. Several approaches have been used to identify host cell factors required for virus replication (Coombs et al., 2010; Li et al., 2009; Naito et al., 2007; Moncorge et al., 2010). The RNA interference (RNAi)–based genome–wide screening is considered as most powerful approach to study host cell factors involved in virus replication (Watanabe et al., 2010). RNAi involves suppression of a host gene by delivering 20–25 nucleotide long dsRNA homologous of the gene under question. Several independent studies using genome–wide RNAi screens have identified several human genes involved in influenza virus replication (Hao et al., 2008). The data from all these genome–wide screens have been analyzed (Watanabe et al., 2010) which indicated that out of 1449 human genes identified for influenza virus, 128 genes have been found in at least two screens. These host genes have been analyzed in several different ways which includes (i) PANTHER classification system which categorized genes associated with defined molecular functions (kinases, transcription factors, mRNA splicing proteins, ribosomal proteins, nucleic acid binding proteins and hydrogen transporters). (ii) Analysis by reactome, a curated knowledge of biological pathways and several other events (Golgi–to–ER transport, translation initiation, processing of mRNA, regulation of gene expression, etc). Further analysis by using GeneGo (GeneGo Inc, MI) followed by integration of information on the viral and cellular interaction partners from other sources (Konig et al., 2010), deduced a network of host–influenza virus interaction which revealed that each step of influenza virus life cycle is closely associated with multiple host cell factors. Several of these host cell factors identified using RNAi were previously known to support influenza virus replication but several others need to be defined for their precise role. However, the genome–wide screens do not cover all human genes and may represent false positive or false negative results due to poor knockdown efficiency or cytotoxicity of the siRNAs. More detailed functional analyses of these human genes identified in genome–wide screens will allow finding novel cellular pathways and/or hosting genes sets important for influenza virus replication.

Antivirals of livestock

During acute or lethal infection of livestock, with diseases like Foot–and–mouth disease (FMD), sheep and goat pox, Peste des Petits Ruminants (PPR), usually two strategies are adopted for control and eradication. First is vaccination and second is stamping out (mass slaughter) policy around the infected area. Since it takes time when the vaccination induces protective antibody (at least 14 days) and that the animals can still be infected during this period, the stamping out policy has been used in several outbreaks in the past. Moreover, the vaccination may have adverse economic consequences because of value loss of vaccinated products and trade restrictions that apply to vaccinated premises for a longer time (Kumar et al., 2013).

Therefore, as an alternate, use of antiviral agents has been proposed (Goris et al., 2008; Lefebvre et al., 2013) which may provide instantaneous protection upon administration (Backer et al., 2013). Antiviral agents could be used either to bridge the period between vaccination and full immunity (immunity–gap) or as an independent control measure (Raheel et al., 2013). Promising *in vitro* and *in vivo* results have been obtained with compound like 5–[(4–bromophenyl) methyl]–2–phenyl–5H–imidazo[4,5–c]pyridine (BPIP) against classical swine fever virus (CSFV), where a reduced transmission of the virus was observed from infected to susceptible animals (Vrancken et al., 2009). Some other antiviral agents such as ribavirin

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(Goris et al., 2008), 5–Fluorouracil (Sierra et al., 2000), 5–Azacytidine (Sierra et al., 2000), 2'–C–Methylcytidine (Goris et al., 2007) and T–1105 have also been studied for their antiviral properties against FMD virus (FMDV). Although limited experiments have been performed, a study on FMDV suggests that animals can be protected against FMDV infection up to 12 h post–infection (Charleston et al., 2011; Goris et al., 2008). Such antiviral drugs can complement emergency vaccination or be applied to treat valuable zoological collections and breeding stocks in endemic and previously disease–free regions (Goris et al., 2008).

To address the gaps in the current control measures, alternative methods need to be investigated, developed and marketed. Emerging evidences suggest the potential use of both specific and non–specific antiviral agents for rapid inhibition of virus replication and the early onset of protection against the disease. The success of such antiviral agents, however, depends on the efficacy, specificity, safety, drug–resistance profile and the cost of treatment involved.

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