Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Review

Energy metabolic disorder is a major risk factor in severe influenza virus infection: Proposals for new therapeutic options based on animal model experiments

Hiroshi Kido, Ph.D., M.D., Irene L. Indalao, M.Sc., Hyejin Kim, Ph.D., Takashi Kimoto, Ph.D., Satoko Sakai, B.Sc., Etsuhisa Takahashi, M.Sc.*

Division of Enzyme Chemistry, Institute for Enzyme Research, Tokushima University, Kuramoto-cho 3-18-15, Tokushima 770-8503, Japan

ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form
20 February 2016
Accepted 24 February 2016
Available online 4 April 2016

Keywords:
Influenza virus
Cytokine storm
Metabolic disorder
Energy metabolism
Multiorgan failure

ABSTRACT

Severe influenza is characterized by cytokine storm and multiorgan failure. Influenza patients with underlying diseases show a rapid progression in disease severity. The major mechanism that underlies multiorgan failure during the progressive stage of infection, particularly in patients with underlying risk factors, is mitochondrial energy crisis. The relationship between the factors that determine infection severity, such as influenza virus, cytokines, cellular trypsin as a hemagglutinin processing protease for viral multiplication, accumulation of metabolic intermediates and ATP crisis in mitochondria, is termed the "influenza virus–cytokine–trypsin" cycle. This occurs during the initial stages of infection, and is interconnected with the "metabolic disorders–cytokine" cycle in the middle to late phase of infection. Experiments using animal models have highlighted the complex relationship between these two cycles. New treatment options have been proposed that target the ATP crisis and multiorgan failure during the late phase of infection, rather than antiviral treatments with neuraminidase inhibitors that work during the initial phase. These options are (i) restoration of glucose oxidation in mitochondria by diisopropylamine dichloroacetate, which inhibits infection-induced pyruvate dehydrogenase kinase 4 activity, and (ii) restoration of long-chain fatty acid oxidation in mitochondria by L-carnitine and bezafibrate, an agonist of peroxisome proliferation-activated receptors-β/δ, which transcriptionally upregulates carnitine palmitoyltransferase II. The latter is particularly effective in patients with influenza-associated encephalopathy who have thermolabile and short half-life compound variants of carnitine palmitoyltransferase II.

*Corresponding author. Tel.: +81 88 633 7423; fax: +81 88 633 7425.
E-mail addresses: kido@tokushima-u.ac.jp (H. Kido), c201256039@tokushima-u.ac.jp (I.L. Indalao), h-kim@tokushima-u.ac.jp (H. Kim), kimoto@tokushima-u.ac.jp (T. Kimoto), ssakai@tokushima-u.ac.jp (S. Sakai), etaka@tokushima-u.ac.jp (E. Takahashi).

http://dx.doi.org/10.1016/j.resinv.2016.02.007
2212-5345/

Contents

1. Introduction

Influenza A virus (IAV), a single-stranded negative-sense RNA virus, is the most common infective pathogen in humans, causing significant morbidity and mortality especially in infants and the elderly [1,2]. Multiorgan failure (MOF) with vascular hyperpermeability can occur during the progressive stage of seasonal influenza virus pneumonia and influenza-associated encephalopathy (IAE) [3,4]. Several underlying diseases have been recognized as risk factors for mortality following H1N1 pdm09 infection [5], including chronic lung disease, immune suppression, cardiac disease, neurological disease, metabolic disease, diabetes mellitus, and asthma. However, the pathogenetic relationship between these risk factors and the severity of the outcome of the IAV infection remains elusive.

We previously reported that the "influenza virus–cytokine–trypsin" cycle is one of the major underlying mechanisms of vascular hyperpermeability and MOF in severe influenza [6]. Severe influenza causes a marked increase in the levels of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β. This potentially fatal immune response has been termed the cytokine storm. Such hypercytokinemia alters the cellular redox state through different cytokine receptors and reduces the expression of four complex I subunits, oxygen consumption [7,8] and ATP synthesis in mitochondria, as well increasing mitochondrial O_2^- production and the intracellular calcium concentration $[Ca^{2+}]_i$ [9] (Fig. 1). ATP depletion causes dissociation of zonula occludens-1, an intracellular tight junction component, from the actin cytoskeleton and thus increases junctional permeability [10]. These cytokines also upregulate trypsin through activation of nuclear factor-kappa B (NF-κB) and activator protein 1 (AP-1) [6,11], which mediates the post-translational proteolytic cleavage of viral envelope hemagglutinin (HA) and is crucial for viral entry and replication [12] in various organs and endothelial cells. Trypsin also increases $[Ca^{2+}]_i$ [6] and Cl^- and K^+ secretion [13] via the protease-activated receptor (PAR)-2, resulting in loss of zonula occludens-1 in endothelial cells and severe edema in

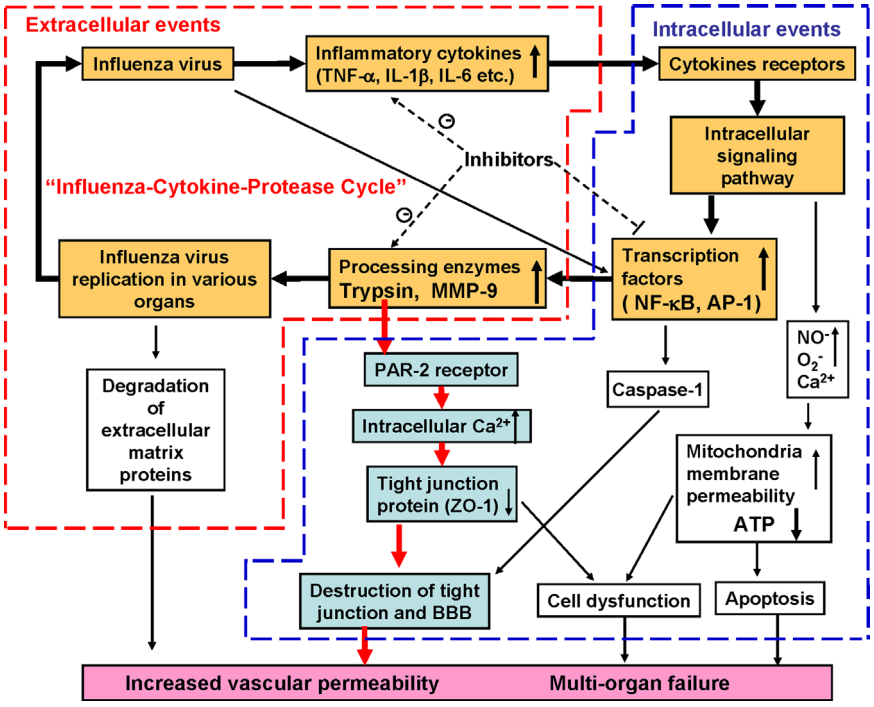

Fig. 1 – The "influenza virus–cytokine–trypsin" cycle hypothesis, which may affect the pathogenesis of vascular hyperpermeability and tissue destruction in severe influenza. AP-1, activator protein 1; BBB, blood–brain barrier; PAR-2, protease-activated receptor 2; ZO-1, zonula occludens-1.