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Review

Novel reassortant influenza viruses between pandemic (H1N1) 2009 and other influenza viruses pose a risk to public health

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ABSTRACT

Influenza A virus (IAV) is characterized by eight single-stranded, negative sense RNA segments, which allows for gene reassortment among different IAV subtypes when they co-infect a single host cell simultaneously. Genetic reassortment is an important way to favor the evolution of influenza virus. Novel reassortant virus may pose a pandemic among humans. In history, three human pandemic influenza viruses were caused by genetic reassortment between avian, human and swine influenza viruses. Since 2009, pandemic (H1N1) 2009 (pdm/09 H1N1) influenza virus composed of two swine influenza virus genes highlighted the genetic reassortment again. Due to wide host species and high transmission of the pdm/09 H1N1 influenza virus, many different avian, human or swine influenza virus subtypes may reassert with it to generate novel reassortant viruses, which may result in a next pandemic among humans. So, it is necessary to understand the potential threat of current reassortant viruses between the pdm/09 H1N1 and other influenza viruses to public health. This study summarized the status of the reassortant viruses between the pdm/09 H1N1 and other influenza viruses of different species origins in natural and experimental conditions. The aim of this summarization is to facilitate us to further understand the potential threats of novel reassortant influenza viruses to public health and to make effective prevention and control strategies for these pathogens.

Contents

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1. Introduction

As a key mechanism for rapid novel virus creation, reassortment of influenza viruses can introduce phenotypic changes by allowing a direct exchange of genetic materials between co-infecting viral strains. For a long time, pigs have been considered as mix vessels to generate novel pandemic influenza viruses due to their susceptibility to avian and human influenza viruses [1]. Although there is no concrete evidence to prove that 1957 and 1968 pandemic influenza viruses were regenerated in pigs by reassortant events those pigs still pose a high risk to public health. This threat was borne out in 2009 when the first influenza pandemic of the 21st century was caused by a novel reassortant H1N1 swine influenza virus with genetic segments from both avian-like Eurasian swine viruses and North American swine viruses [2]. The 2009 pandemic H1N1 influenza virus spread to over 215 countries and caused hundreds of thousands of people deaths [3]. After the pandemic was over, the pdm/09 H1N1 influenza virus turned into a seasonal one to continue to circulate in humans.

Since 2009, the pdm/09 H1N1 influenza virus repeatedly jumped back to pigs all around the world. Some swine-origin pdm/09 H1N1 influenza isolates displayed higher pathogenicity in mice than the human-origin isolates through eliciting a stronger innate immune reaction and pro-oxidation stimulation [4]. In addition, the pdm/09 H1N1 influenza virus was found to spread to turkeys continuously and caused a progressive drop in egg production [5]. In China, this virus also has transmitted to dogs although there was no obvious clinical symptoms can be observed [6]. The virological and serological surveillance of the pdm/09 H1N1 influenza virus infection clearly demonstrated the transmission of this virus to cats both in China and the U.S.A [7–9]. Other than this, the pdm/09 H1N1 influenza virus was also found to be able to infect wild animals including American badger, Bornean binturong and black-footed ferret in the U.S.A [10]. Interestingly, there is no evidence so far to indicate that chicken can be infected by the pdm/09 H1N1 influenza virus. In total, these findings suggested that the pdm/09 H1N1 influenza virus not only circulated in humans but also crossed the species barrier to result in expansion of its host range. Due to the fact that many different influenza viruses existed in the same host, these different viruses thus have extremely high potential to generate many novel reassortant viral variants. Considering that the majority of the human populations is immunologically naive to enzootic swine, canine and avian influenza viruses and the pdm/09 H1N1 influenza virus is able to induce an effective human-to-human transmission, the continuous interaction among this virus and swine influenza viruses (SIVs), canine influenza viruses (CIVs) and avian influenza viruses (AIVs) thus need to be ascertained to evaluate possible threats to human populations by creating novel reassortant influenza viruses. This opinion has been well confirmed by the good genetic compatibility between the pdm/09 H1N1 influenza virus and many different avian influenza viruses *in vitro* [11]. In this review, we summarized the biological characteristics of reassortant influenza viruses between the pdm/09 H1N1 influenza virus and other influenza viruses of different species-origins in natural and experimental conditions to help us further understand the potential threats of newly-generated reassotant influenza viruses to humans and make effective prevention and control strategies accordingly.

2. Natural reassortant influenza viruses from different species

2.1. Reassortant influenza viruses in pigs

Frequent transmission of the pdm/09 H1N1 influenza virus to pigs from humans had been confirmed by serologic surveillance in many countries [12,13]. H1N1, H1N2 and H3N2 SIVs were the major viral subtypes circulating among pigs worldwide. In swine influenza lineage, classical swine (CS) H1N1 influenza virus and European avian-like (EA) H1N1 influenza virus were predominant prevalence in pigs [14]. The CS virus may originate from 1918 pandemic H1N1 influenza virus [15]. The EA virus was first isolated from pigs in Italy in 1979 [16] and appeared in China in the 1990s [17]. Recently, some avian-origin influenza viruses including H5N1, H9N2, H6N6, H4N8 and others frequently jumped back into pig populations [18]. However, these avian-origin influenza viruses did not establish in pigs and then did not cause adverse consequences yet. Genetic analyses revealed that these avian-origin influenza viruses were likely derived from those residential in aquatic birds and was believed to be transient viral variants [19,20]. Because avian influenza viruses hardly adapt to pigs, these viruses may need a long term to evolve or reassert with swine adapted influenza viruses in order to establish in pigs [21,22]. The avian H5N1 and H9N2 influenza viruses spread more prevalently than other avian influenza viruses in pigs. However, infection of these viruses showed slight or no clinical symptoms in pigs [23]. Some human H1N1 and H3N2 influenza viruses also can infect pigs [24,25] and gave rise to numerous reassortant viruses including those like double reassortant (DR) H1N2 or H3N2, triple reassortant (TR) H1N1, H1N2 or H3N2 influenza viruses [26–29]. Some of these reassortant influenza viruses caused endemic in pigs. These reassortant influenza viruses could provide gene(s) to interact with other swine or human-origin influenza viruses to generate novel influenza viruses. Due to the high transmission of the pdm/09 H1N1 influenza virus in humans, novel reassortant viruses hybridizing the internal genes of the pdm/09 H1N1 influenza virus in pigs thus may pose a high threat to public health.

Since 2011, the H3N2 variant (H3N2v) generated by TR influenza viruses and the pdm/09-origin influenza viruses (containing a matrix protein derived from the pdm/09 influenza viruses (pM) and other genes from endemic H3N2 (TR) influenza viruses [30]) in pigs has caused more than 340 human infection cases in the U.S.A., emphasizing the role of pigs in the generation of reassotant influenza variants with the potential to infect humans [31,32]. Between 2011 and 2012, H3N2 (H3N2pM-like) and H3N1 reassortant influenza viruses between a pdm/09-like H1N1 and TR H3N2-like influenza viruses were isolated in pigs in South Korean. *In vivo* experiment demonstrated that both the H3N2pM-like and the novel H3N1 reassortants can replicate efficiently in mice and ferrets. All the reassortant H3N1 strains exhibited growth advantage