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TRANSFUSION CLINIQUE ET BIOLOGIQUE

Transfusion Clinique et Biologique 23 (2016) 28–38

Update article

Viral metagenomics and blood safety

La métagénomique virale : un nouvel outil au service de la sécurité transfusionnelle

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Available online 9 January 2016

This manuscript has been written in memory to Jean Jacques Lefrère.

Abstract

The characterization of the human blood-associated viral community (also called blood virome) is essential for epidemiological surveillance and to anticipate new potential threats for blood transfusion safety. Currently, the risk of blood-borne agent transmission of well-known viruses (HBV, HCV, HIV and HTLV) can be considered as under control in high-resource countries. However, other viruses unknown or unsuspected may be transmitted to recipients by blood-derived products. This is particularly relevant considering that a significant proportion of transfused patients are immunocompromised and more frequently subjected to fatal outcomes. Several measures to prevent transfusion transmission of unknown viruses have been implemented including the exclusion of at-risk donors, leukocyte reduction of donor blood, and physicochemical treatment of the different blood components. However, up to now there is no universal method for pathogen inactivation, which would be applicable for all types of blood components and, equally effective for all viral families. In addition, among available inactivation procedures of viral genomes, some of them are recognized to be less effective on non-enveloped viruses, and inadequate to inactivate higher viral titers in plasma pools or derivatives. Given this, there is the need to implement new methodologies for the discovery of unknown viruses that may affect blood transfusion. Viral metagenomics combined with High Throughput Sequencing appears as a promising approach for the identification and global surveillance of new and/or unexpected viruses that could impair blood transfusion safety.

Keywords: Viral metagenomics; High Throughput Sequencing; Viral discovery; Blood-borne viruses; Emerging viruses; Blood safety

Résumé

Le risque transfusionnel infectieux lié aux virus connus (VHB, VHC, VIH et HTLV) peut être considéré à ce jour comme maîtrisé, en raison des mesures préventives prises par la plupart des pays à ressources élevées. En revanche, le risque potentiel persistant est lié à l'émergence d'agents infectieux, et en particulier viraux, non encore identifiés. Ceci est d'autant plus important qu'une proportion significative des patients transfusés sont immunodéprimés et donc plus exposés à des formes infectieuses graves dont l'issue peut être fatale. Plusieurs mesures visant à prévenir la transmission par transfusion de virus inconnus sont mises en œuvre tels que l'exclusion des donneurs à risque, la déleucocytation des plasmas, et le traitement physico-chimique des différents composants sanguins. Cependant, il n'existe pas à ce jour de méthode universelle pour l'inactivation des pathogènes, qui soit applicable à tous les types de composants sanguins et, tout aussi efficace pour toutes les familles virales. Par ailleurs, parmi les procédures d'inactivation des génomes viraux disponibles, certaines d'entre elles sont reconnues pour être moins efficaces sur les virus non

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http://dx.doi.org/10.1016/j.tracli.2015.12.002
1246-7820/

enveloppés, et non optimales pour inactiver des titres viraux élevés dans les pools de plasma ou les produits dérivés. Il apparaît donc indispensable de mettre en place de nouveaux outils pour la détection d'agents viraux inconnus susceptibles d'affecter la sécurité infectieuse du receveur. La métagénomique virale associée au séquençage haut débit constitue une approche prometteuse pour l'identification et la surveillance d'agents viraux nouveaux ou inattendus qui pourraient compromettre la sécurité transfusionnelle.

Mots clés : Métagénomique virale ; Séquençage haut débit ; Découverte de virus ; Virus transmis par le sang ; Virus émergents ; Sécurité transfusionnelle

1. Introduction

In developed countries, blood and organ donors are routinely screened for a range of blood-borne viruses (HIV, HBV, HCV and HTLV in some countries) with highly sensitive screening tests. This has dramatically improved the safety of blood supply. However, transmission by transfusion of unknown or unsuspected viruses, responsible for persistent and asymptomatic viremia, remains a continuing threat. This is particularly relevant considering that a significant proportion of transfused patients are immunocompromised and more frequently subjected to fatal outcomes. Several measures to prevent transfusion transmission of unknown viruses have been implemented including the exclusion of at-risk donors, leukocyte reduction of donor blood, and physicochemical treatments of the different blood components aimed to inactivate infectious agents potentially present in blood. However, up to now there is no universal method for pathogen inactivation, which would be applicable for all types of blood components (currently there is no method applicable for red blood cell concentrates) and, equally effective for all viral families [1]. Several inactivation procedures are available but some of them are recognized to be less effective on non-enveloped viruses, such as human parvovirus B19 (B19 V), Hepatitis A (HAV) or Hepatitis E (HEV) viruses [2]. Moreover, recent publications have also confirmed that some viral reduction methods (solvent/detergent and heat treatment) are inadequate to inactivate high viremic titers of these viruses in plasma pools or derivates [3,4]. Given this, the threat for blood safety due to emerging viruses is of crucial importance. Thus, it remains imperative to improve the blood product safety, not only by surveillance of well-characterized viral pathogens (HBV, HCV, HIV, B19 V) but also, by implementing new methodologies for discovery of unknown viruses that may affect blood transfusion safety.

The recorded emergence of infectious diseases has risen significantly since the last three decades. In a period of 64 years (1940–2004) the emergence of 335 infectious diseases (all pathogens combined) was reported. Emerging infectious diseases (EIDs) are dominated by zoonoses, the majority of which (72%) has wildlife origin. The increasing and ongoing documentation of novel animal viruses identified worldwide predicts that additional animal pathogens may jump species barrier to potentially become novel human infectious diseases in the near future, some perhaps highly pathogenic. Viruses account for 25–44% of all EIDs [5] and are the pathogen class most likely to emerge [6] with an estimated number of undiscovered mammalian viruses of at least 320,000 [7]. This estimation suggests that zoonotic EIDs represent a serious threat to human health and emphasizes the importance to evaluate the factors that are involved in the contact between human and animals, responsible for the emergence of "zoonotic-human" infections [5]. Among some recent examples of viral emergence by host switching, with great impact on the public health, are the HIV pandemic (Europe, 1981; Central Africa, 1983), Severe Acute Respiratory Syndrome (SARS) caused by coronavirus (SARS-CoV, China, 2003) and Middle East Respiratory Syndrome (MERS) caused by MERS coronavirus (MERS-CoV, Saudi Arabia, 2013). Other examples include the extreme genetic variability of RNA influenza viruses like the emergence of highly virulent types like H5N1 (since 2003, China), pandemic H1N1 (Veracruz, Mexico, 2009–2010) and more recently a more virulent H7N9 influenza A virus (2013, China). These examples demonstrate that emergent diseases can easily overcome country boundaries, and even continents by means of infected travelers or international trade of livestock or plants. Many factors can contribute to the emergence and the spread of a novel infectious agent [8], as the increasing contact between humans and wildlife habitats mainly due to agricultural practices and the globalization of travel and trade. Other important factors include climate changes that promote vector expansion (mosquitoes, ticks) and mass human migrations (due to wars, natural disasters, poverty, and desertification) [9]. For these reasons, there is now a clear increased risk of arbovirus emergence in the future due to environmental and climate changes, extensive tropical urbanization and to the colonization of this expanding habitat by highly anthropophilic mosquitos (i.e. Chikungunya and dengue viruses both transmitted by *Aedes aegypti).* To date, dengue viruses are internationally recognized as an existing threat to blood safety due to a known transfusion-transmission and severe/fatal disease in recipients [10]. As all arboviruses are potentially transmissible by transfusion due to their capacity to induce an asymptomatic viremic phase, this represents new risks for blood safety.

In the last years, very broad and sensitive high throughput techniques based on metagenomics were developed to detect and characterize previously unknown or variant viruses associated with several human diseases. These methods based on the random amplification of genomes include pan-viral microarrays and High Throughput Sequencing (HTS) [11]. By overcoming conventional methods of viral identification, metagenomics, which gives access to all nucleic acids present in a given sample, allows the description of viral communities and their diversity in environmental [12,13], human [14–16] and animal samples [17–19] using HTS. Metagenomic sequencing has also demonstrated its usefulness in investigations when infectious diseases have