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Interferon α/β receptor knockout mice as a model to study bluetongue virus infection

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ABSTRACT

Bluetongue is an arthropod-borne disease caused by a virus of the genus *Orbivirus*, the bluetongue virus (BTV), which affects ruminant livestock such as cattle, sheep, and goats and wild ruminants such as deer, and camelids. Recently, adult mice with gene knockouts of the interferon α/β receptor (IFNAR−/−) have been described as a model of lethal BTV infection. IFNAR(−/−) mice are highly susceptible to BTV-1, BTV-4 and BTV-8 infection when the virus is administered intravenously or subcutaneosuly. Disease progression and pathogenesis closely mimics signs of bluetongue disease in ruminants. In the present paper we review the studies where IFNAR(−/−) mice have been used as an animal model to study BTV transmission, pathogenesis, virulence, and protective efficacy of inactivated and new recombinant marker BTV vaccines. Furthermore, we report new data on protective efficacy of different strategies of BTV vaccination and also on induction of interferon α/β and proinflammatory immune responses in IFNAR(−/−) mice infected with BTV.

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1. IFNAR(−/−) mice as a model to study viral infections

Blocking IFN-α/β activity in mice leads to a dramatically increased sensitivity to many viruses. Mice lacking the type I interferon (IFN) receptor (IFNAR (−/−)) were generated to elucidate the physiological role of the type I IFN system by Müller and colleagues (Muller et al., 1994). These mice were unresponsive to the antiviral action of natural murine type I IFN, a mixture of IFN-α and IFN-β. Comparative cytofluorometry revealed no abnormalities in the major lymphocyte subsets in terms of expression of CD3, CD4, CD8 (thymocytes and splenocytes) and major histocompatibility complex (MHC) class I and class II antigens (thymocytes, splenocytes, and peritoneal macrophages). IFNAR(−/−) mice showed no overt anomalies but were unable to cope with viral infections.

The lack of a type I IFN system allows the virus to replicate more efficiently and IFNAR(−/−) mice have been used as a laboratory animal model to study the immune response, determinants of virulence, vaccine development, or pathogenicity of Crimean-Congo hemorrhagic fever virus (Bereczky et al., 2010; Zivcec et al., 2013), human T cell leukemia virus type I (Delebecque et al., 2005), Schmallenberg virus (Wernike et al., 2012), West Nile virus (Winkelmann et al., 2012), poliovirus (Ida-Hosonuma et al., 2005; Ohka et al., 2007), Theiler's virus (Fiette et al., 1995), La Crosse virus (Pavlovic et al., 2000), measles virus (Mrkic et al., 1998; Volker et al., 2013), hepatitis B and C viruses (Aly et al., 2011; Chen et al., 2013), or Rift valley fever virus (Bouloy et al., 2001; Lopez-Gil et al., 2013; Lorenzo et al., 2010). All these data, and the presence of an otherwise intact immune system in these mice suggest that IFNAR(−/−) mice could be a good animal model to study bluetongue virus (BTV) infections and to evaluate vaccine strategies against this virus.

2. Bluetongue and type I interferon

The innate immune response is the first line of defense against viruses resulting in the production of IFNα/β and other proinflammatory cytokines that control de infection (Randall and Goodbourn, 2008). BTV infection induces type I IFN in cells in culture and ruminants (Foster et al., 1991; Fulton and Pearson, 1982; Huismans, 1969; Jameson and Grossberg, 1978, 1981; MacLachlan and Thompson, 1985). Although the induction of type I IFN after BTV infection was described more than 40 years ago, the mechanism of IFNα/β induction has remained unknown for several years. Recent studies showed that BTV induced IFN-α/β in skin lymph and in blood in vivo (Ruscanu et al., 2012). Although BTV replicated in a substantial fraction of the conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs) in vitro, only pDCs responded to BTV by producing a significant amount of IFN-α/β. BTV replication in pDCs was not mandatory for IFN-α/β production since it was still induced by UV-inactivated BTV, and the induction of IFN-α/β in

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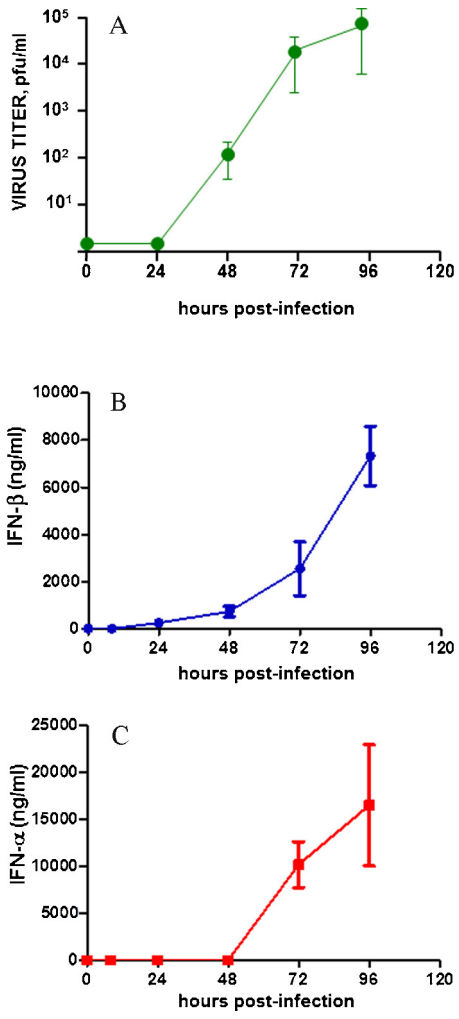

Fig. 1. Production of IFN-α and IFN-β measured in serum of IFNAR(−/−) mice infected with BTV-4. Mice were infected subcutaneously with 10^3 PFU per mouse of BTV-4 (MOR2009/09) (A) Titers of virus recovered in blood after infection. Virus was extracted from blood and the titer was determined by plaque assay in Vero cells. Each point represents the mean values of the viral titer of five animals, and standard deviations are shown as error bars. (B) Kinetic of IFN-β production in serum of infected mice detected by ELISA (Verikine Mouse IFN-β ELISA kit, PBL interferon source, USA). (C) Kinetic of IFN-α production in serum of infected mice detected by ELISA (Verikine Mouse IFN-α ELISA kit, PBL interferon source). Levels of IFN-α and IFN-β were measured for each group of five mice in pools of sera collected at 12, 24, 48, 72, or 96 h.p.i., by ELISA.

pDCs occurred via a novel TLR-independent and Myd88-dependent pathway (Ruscanu et al., 2012). However, this is not the only way of IFN-α/β induction. Another study showed that both viral RNA sensors RIG-I and MDA5 are upregulated by BTV infection of the epithelial bronchial human cell line A549 and that viral recognition by RIG-I and MDA5 is the driving force for the activation of IFN regulatory factor 3 (IRF3) and consequently the induction of IFN-α/β. In addition, this study showed that virus replication is essential for IFN-β induction in A549 cells (Chauveau et al., 2012).

These two different ways of type I IFN induction can explain the fact that BTV is a potent interferon inducer in wild type mice without virus replication (Jameson et al., 1978) but in IFNAR(−/−) mice there is a strong correlation between BTV replication, viremia, and the induction of IFN-α and IFN-β. The kinetics of IFN-α and IFN-β production measured in sera of IFNAR(−/−) mice infected subcutaneously with 10^3 PFU of BTV-4 (MOR2009/09) per mouse are shown in Fig. 1. IFN-β is detected in serum at 48 h post-infection when BTV is detected at low levels in blood (titers up to 10^2 PFU/ml). IFN-α is detected in serum at 72 h post-infection when the viremia is in the upper level (titers up to 8×10^4 PFU/ml). In both cases, the production of IFN increases to a maximum at 96 h post-infection, before the death of the animals. The IFN production peak also coincides with the viremia peak in sheep infected with several strains of BTV and this high concentration of IFN induces a decrease in the viremia of the infected animals (Foster et al., 1991). Although the infection of IFNAR(−/−) mice with BTV induces a strong production of IFN-α/β in response to viral infection, the absence of receptor in these animals does not allow the type I IFN signal transduction and the antiviral defense, increasing the susceptibility of IFNAR(−/−) mice to viral infections.

3. IFNAR (−/−) mice as a model to study BTV virulence

Bluetongue (BT) is an arthropod-borne disease caused by a virus of the genus *Orbivirus*, the BTV, which affects ruminant livestock such as cattle, sheep, and goats and wild ruminants such as deer, and camelids. For years, different groups have tried to establish a laboratory animal model to facilitate the studies of pathogenesis, immune response and vaccination against BTV. Natural hosts are expensive and require specialized animal facilities with biosafety level 3 for these studies. It is known that BTV infects mouse embryos (Bowen et al., 1982). Furthermore, experimental studies showed that BTV grew in suckling mice inoculated intracerebrally and the growth was faster in mice at 1 day than at 2 weeks of age (Narayan and Johnson, 1972). In contrast, adult mice are nor susceptible to BTV infection and viremia is not observed in mice inoculated either intravenously or subcutaneously (Calvo-Pinilla et al., 2009a). Previous studies showed that lesions caused by bluetongue virus infection of the central nervous system in sheep and mice vary with age of the host suggesting that the character of the lesions appears to be influenced by the stage of immunological maturity of the infected animals (Richards and Cordy, 1967). All these studies suggest that the cellular receptor is not a limitation for BTV to infect mice and the possible limitation for the productive infection in mice could be the innate immune response against BTV generated for the animal that establishes an antiviral state.

Recently, our laboratory has shown that adult mice deficient for type I IFN receptor (IFNAR(−/−)) are highly susceptible to infection with serotypes 4 (BTV-4) and 8 (BTV-8) of BTV when the virus is administered intravenously (Calvo-Pinilla et al., 2009a). The fisrt characterization of this model was developed in IFNAR(−/−) mice with a C57BL/6 genetic background and intravenously infected. Afterwards, we observed that IFNAR(−/−) mice with a 129 genetic background showed the same susceptibility to BTV infection and no differences were found between subcutaneous and intravenous infection in the survival rates and appearance of clinical signs and viremia (Calvo-Pinilla et al., 2009b, 2012). Recently, we have also characterized this murine model for serotype 1 (BTV-1). IFNAR(−/−) mice infected with serotypes 1, 4 or 8 showed the same clinical signs characterized by ocular discharges, apathy and the disease progression led to animal death. Infectious virus was recovered from the spleen, lung, thymus, lymph nodes and blood. The appearance of viremia after BTV infection in IFNAR(−/−) mice was dependent on the viral dose, althought the highest titers observed in blood were not dose-dependent (Fig. 2). The differential virulence of serotypes 1, 4, and 8 was maintained in this animal model. Some BTV serotypes such as serotype 8 exhibit enhanced virulence in cattle (Saegerman et al., 2008), in contrast to BTV-4 that usually exhibits subclinical infections in this species. In infected IFNAR(−/−) mice, BTV-1 and BTV-8 killed 100% of the animals with a dose as low as 10 PFUs per mouse. In contrast 10^3 PFUs of BTV-4 were needed to kill 100% of the mice. The highest titers of virus

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