VETERINARY RESEARCH

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# Immunosuppression abrogates resistance of young rabbits to Rabbit Haemorrhagic Disease (RHD)

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## Abstract

Rabbit Haemorrhagic Disease (RHD) is caused by a calicivirus (RHDV) that kills 90% of infected adult European rabbits within 3 days. Remarkably, young rabbits are resistant to RHD. We induced immunosuppression in young rabbits by treatment with methylprednisolone acetate (MPA) and challenged the animals with RHDV by intramuscular injection. All of these young rabbits died within 3 days of infection due to fulminant hepatitis, presenting a large number of RHDV-positive dead or apoptotic hepatocytes, and a significant seric increase in cytokines, features that are similar to those of naïve adult rabbits infected by RHDV. We conclude that MPA-induced immunosuppression abrogates the resistance of young rabbits to RHD, indicating that there are differences in the innate immune system between young and adult rabbits that contribute to their distinct resistance/susceptibility to RHDV infection.

## Introduction, methods and results

Rabbits of the species *Oryctolagus cuniculus* are the natural hosts of the Rabbit Haemorrhagic Disease Virus (RHDV). This virus targets the liver of rabbits and causes the death of millions of wild and domestic adult rabbits worldwide [1-3]. Usually, adult rabbits die within 3 days of RHDV infection as a result of fulminant hepatitis, showing no symptoms of the disease until a few hours before death. Interestingly, young rabbits (less than 4 weeks-old) are resistant to Rabbit Haemorrhagic Disease (RHD), developing only a sub-clinical disease to the viral infection [3-6]. A central issue in the pathogenesis of RHD is to understand this age-related resistance to a viral infection that is fatal in adult animals. Pertinent to this issue, Ruvoën-Clouet et al. [7] reported that RHDV is capable of binding to histo-blood group antigens (HBGA) that are expressed on the mucosa of the upper respiratory and digestive tracts of adult rabbits, and they have postulated that the density of these attachment factors on mucosal cells is essential for adult rabbits to be susceptible to RHDV infection. In agreement with their view, they found only a weak binding of virus particles to the same mucosal tissues in young rabbits, thus indicating that low expression of HBGA could explain the resistance of young animals to RHD. Nevertheless, and despite this evidence, they recently reported that low expression of these facilitating factors of the infection, at the epithelial level, only confers partial protection against RHDV infection [3,8]. They also showed that hepatocytes, the main target of RHDV replication, do not express HBGA [7,8], which led them to suggest the existence of additional hepatic cellular receptor(s) for the virus [3]. Additionally, we demonstrated that young rabbits infected with RHDV by the intramuscular route develop the exact same mild liver disease that we had observed in young rabbits infected with RHDV by natural, oral and nasal routes [4,9-12]. This made us consider that resistance of young rabbits to RHD may depend on additional putative factors. A difference in innate immunity is one of these possible factors, since previous data have shown that young and adult rabbits develop different immune responses after RHDV infection [4-6,13-16]. Thus, we decided to study whether altering the immune physiology of young rabbits by methylprednisolone acetate (MPA)-induced immunosuppression would interfere with the resistance of young rabbits to RHDV infection.

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