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Magnitude and kinetics of multifunctional CD4$^+$ and CD8β$^+$ T cells in pigs infected with swine influenza A virus

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Abstract

Although swine are natural hosts for influenza A viruses, the porcine T-cell response to swine influenza A virus (FLUAVsw) infection has been poorly characterized so far. We have studied Ki-67 expression and FLUAVsw-specific production of IFN-γ, TNF-α and IL-2 in CD4$^+$ and CD8β$^+$ T cells isolated from piglets that had been intratracheally infected with a H1N2 FLUAVsw isolate. IFN-γ$^+$TNF-α$^+$IL-2$^+$ multifunctional CD4$^+$ T cells were present in the blood of all infected animals at one or two weeks after primary infection and their frequency increased in four out of six animals after homologous secondary infection. These cells produced higher amounts of IFN-γ, TNF-α and IL-2 than did CD4$^+$ T cells that only produced a single cytokine. The vast majority of cytokine-producing CD4$^+$ T cells expressed CD8α, a marker associated with activation and memory formation in porcine CD4$^+$ T cells. Analysis of CD27 expression suggested that FLUAVsw-specific CD4$^+$ T cells included both central memory and effector memory populations. Three out of six animals showed a strong increase of Ki-67$^+$perforin$^+$ CD8β$^+$ T cells in blood one week post infection. Blood-derived FLUAVsw-specific CD8β$^+$ T cells could be identified after an in vitro expansion phase and were multifunctional in terms of CD107a expression and co-production of IFN-γ and TNF-α. These data show that multifunctional T cells are generated in response to FLUAVsw infection of pigs, supporting the idea that T cells contribute to the efficient control of infection.

Introduction

Pigs are natural hosts for influenza A viruses and infections of humans with swine influenza A viruses (FLUAVsw) have been reported [1]. Moreover, the pig is considered as a "mixing vessel" i.e. a species where reassortments between avian and mammalian influenza virus strains can occur which may lead to the emergence of novel pandemic strains in humans. For example, in the 2009 pandemic H1N1 virus, genes closely related to swine North American and Eurasian H1N1 viruses were identified [2]. The 2009 pandemic H1N1 virus was frequently transmitted from farmers to pigs during the last years, thereby reflecting the zoonotic potential of this virus. As a consequence, this transmission established a new lineage of pandemic viruses (pandemic H1N2) in pigs via reassortment with circulating swine influenza viruses [3].

These observations, but also economic and animal welfare issues of FLUAVsw infections in pig production units, justify investigations on pig-FLUAVsw host-pathogen interactions. Of note, FLUAVsw infections are usually rapidly controlled by the porcine immune system and an elimination of replicating virus from the respiratory tract within one week has been reported [4]. Neutralizing antibodies appear in serum within seven days post inoculation [4]. It is assumed that these antibodies play a major role in control of infection, although a production of IgA antibodies by B cells in the nasal mucosa has also been reported [5].

The rapid control of FLUAVsw infections suggests that also cell-mediated immune responses contribute to viral

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