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Immunization of mice with a novel recombinant molecular chaperon confers protection against Brucella melitensis infection

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abstract

Brucella spp. are zoonotic Gram-negative intracellular pathogens with the ability to survive and replicate in phagocytes. It has been shown that bacterial proteins expressed abundantly in this niche are stress-related proteins capable of triggering effective immune responses. BMEI1549 is a molecular chaperone designated DnaK that is expressed under stress conditions and helps to prevent formation of protein aggregates. In order to study the potential of DnaK as a prospective Brucella subunit vaccine, immunogenicity and protective efficacy of recombinant DnaK from Brucella melitensis was evaluated in BALB/c mice. The dnak gene was cloned, expressed in Escherichia coli, and the resulting recombinant protein used as subunit vaccine. DnaK-immunized mice showed a strong lymphocyte proliferative response to in vitro antigen stimulation. Although comparable levels of antigen-specific IgG2a and IgG1 were observed in immunized mice, high amounts of IFN- , IL-12 and IL-6, no detectable level of IL-4 and very low levels of IL-10 and IL-5 were produced by splenocytes of vaccinated mice suggesting induction of a Th1 dominant immune response by DnaK. Compared to control animals, mice vaccinated with DnaK exhibited a significant degree of protection against subsequent Brucella infection ($p < 0.001$), albeit this protection was less than the protection conferred by Rev.1 ($p < 0.05$). A further increase in protection was observed, when DnaK was combined with recombinant Omp31. Notably, this combination, as opposed to each component alone, induced statistically similar level of protection as induced by Rev.1 suggesting that DnaK could be viewed as a promising candidate for the development of a subunit vaccine against brucellosis.

1. Introduction

Brucella melitensis is a zoonotic Gram-negative pathogen that is an important etiological agent causing abortion and infertil- ity in domestic animals, and undulant fever, migratory arthralgia, myalgia and osteomyelitis in humans [1,2]. Because of the severe economic and medical burden of brucellosis, vaccination of all vul- nerable hosts and culling of infected animals is the only way of controlling the disease [3]. The live attenuated B. melitensis Rev.1 strain is the most broadly used vaccine in control programs against brucellosis in the livestock [4]. It has been shown that Rev.1 can be useful for eradicating this disease [5]. Thus, it is considered in widespread vaccination programs in many countries [6]. Nev- ertheless, availability of such vaccines as Rev.1 does not obviate the need for development of new vaccines due to some problems associated with application of this vaccine, included among them are eliciting long lasting immune responses against the O polysac- charide making it difficult to differentiate vaccinated animals from those naturally infected, induction of abortion when administered during pregnancy, pathogenicity for humans and resistance to streptomycin [7]. These problems have stimulated scientists to find alternative ways to protect the livestock from Brucella infection.

In order to increase safety, subunit vaccines have been developed but these depend on the identification of antigens able to confer protection against brucellosis. Numerous protein antigens

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