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Analogues of muramyl dipeptide (MDP) and tuftsin limit infection and inflammation in murine model of sepsis

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ABSTRACT

Pharmacological manipulation of the balance between pro- and anti-inflammatory mediators emerges as a key aspect of a successful treatment of sepsis. A murine model of septic shock was developed and chosen conjugates (1a, 1b, 8a, 8c) and analogs (T2) of muramyl dipeptide and tuftsin were tested in this model as prospective anti-bacterial drugs or adjuvants. The phagocytic activity of monocytes/macrophages was determined (flow cytometry, bacterial clearance from vital organs). To evaluate cytokines levels (TNFα, IFNγ, IL6, IL10) we used real-time PCR. The most promising immunomodulatory properties were displayed by the analogue T2 and two conjugates: 8a, 8c.

1. Introduction

Bacterial infections still consist important medical problem, notably in immunocompromised individuals [1]. The host response to invading microorganisms is complex and many factors need to be orchestrated in order to prevent from the development of severe complications of infection, such as sepsis and septic shock. Hence, new therapeutic targets are necessary for better control of infections and faster recovery [1,2].

Pharmacological manipulation of the balance between pro- and anti-inflammatory mediators emerges as a key aspect of a successful treatment of severe sepsis [3]. Efficient driving of this balance can be achieved with adjuvants that modulate immune response and are capable of reinforcement of standard treatment. Muramyl dipeptide (MDP) and tuftsin are naturally occurring molecules with known immunomodulatory activity. These are peptidoglycan present in bacterial wall and phagocytosis stimulating tetrapeptide (Thr-Lys-Pro-Arg) present in the blood of mammals, respectively [4–6]. The compounds affect mainly innate immunity and stimulate monocytes and dendritic cells [6–8]. Conjugates of both MDP and tuftsin have been reported in our earlier works in vitro as more efficient and durable than native agents separately [8–10]. The most propitious compounds were then chosen for further in vivo studies. In this study we assumed that targeting synthesis of pro- and anti-inflammatory agents secreted by monocytes might be a crucial point in the regulation of the severity of sepsis.

A murine model of septic shock was developed in our lab to mimic severe sepsis observed in the clinic and then the chosen analogues were tested in this model for their usefulness as prospective anti-bacterial drugs or adjuvants. This study showed that three out of nine, analogues of MDP and tuftsin, that is conjugates 8a, 8c and one analogue T2, revealed promising activity in vivo.

2. Materials and methods

2.1. Animals

Male BALB/c mice, age 14–18 weeks, were used in all experiments (supplied by the Medical Research Center, Polish Academy of Science, Warsaw, Poland). All procedures were performed in accordance to the guidelines of the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the Local Ethical Committee of Animal Care and Use in the Medical University of Gdansk.

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