



The immunosuppression mechanism of hypodermin A on complement



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ABSTRACT

Hypodermin A (HA), a serine protease secreted by first-instar larvae of *Hypoderma lineatum* (Diptera: Oestridae) is associated with inflammatory and the specific immune responses in cattle hosts. In the present study, the cDNA sequence of HA was synthesized, and found to have fifteen amino acids which differed from the sequence available in GenBank. We then examined the association between recombinant HA and guinea-pig complement component 3 (C3) through a co-immunoprecipitation assay. Cos7 cells stably expressing HA were generated, and were found to be more resistant to lysis by guinea-pig C3 than the controls. HA was also able to degrade the C6 and C5b-9 of guinea-pig C3. The presumed DNA binding site of HA with guinea-pig C3 was detected by an electrophoretic mobility shift assay (EMSA). In contrast, after stable transfection, mHA was unable to reduce the amount of C3 or to inhibit its cytotoxicity, while HA could degrade guinea-pig C3 and inhibit the complement pathway. The findings suggest that recombinant HA could serve as an immunosuppressive agent against organ rejection after xenotransplantation.

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1. Introduction

Organ transplantation has become the treatment of choice for many end-stage organ diseases. However, the unavailability of sufficient organs to meet the existing demand for transplantation has resulted in major organ shortage crises. Although heterologous grafts have been widely viewed as alternatives, they unfortunately give rise to another more troublesome problem – transplant rejection. One of the methods used to relieve such a negative response is the application of immunomodulatory agents from parasites, such as *Hypoderma lineatum*. This insect's larvae develop after passing through their hosts' deep connective tissue, a process which involves modulation and evasion of the host's immune system is involved [1]. More specifically, these larvae usually secrete substances which act to weaken host defenses [2,3].

Hypodermin A (HA), secreted by first instar larvae, is able to escape the host immune responses and suppress lymphocyte proliferation [4],

and suppress bovine interleukin 2 (IL-2) production via the prostaglandin pathway [5]. HA can also cleave the complement component C3 from bovine serum, block the complement pathway and reduce inflammation [6–8]. The rejection of heterogenic transplantation is attributable to the activation of the host complement system where C3 assumes an important role [9]. HA can inhibit C3-mediated cytotoxicity and cleave the C3 in rat and human. As a result, HA shows enormous potential to slow down the rejection associated with xenotransplantation [10].

To further investigate the role of HA in modulating host immune responses, a cos7 cell model with stable expression of recombinant HA was established in the current study. The recombinant HA exhibited biological properties similar to those of the native form. Possible mechanisms of interaction between HA and C3 were discussed. All the findings will provide increased theoretical support for allotransplantation research.

2. Materials and methods

2.1. Animals

The first-instar larvae of *H. lineatum* were collected from the oesophagi of slaughtered poephagus grunniens. The larvae were

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