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Review

A review of CpGs and their relevance to aquaculture

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Abstract

CpG oligodeoxynucleotides (ODN) have been described as functioning as natural adjuvants because they promote professional antigen presenting cell (APC) function and co-stimulate lymphocytes. The majority of studies into the immune effects of CpG ODN to date have been carried out on mammals where they are proving very successful at stimulating innate and adaptive immune responses in a variety of species as well as protecting them from bacterial, viral and protozoan pathogens. Fish also possess the ability to raise both innate and adaptive immune responses to invading pathogens and interest in the effect of CpG ODN on the piscine immune system is growing. Various studies have now been carried out to elicit the effects of CpG ODN on diverse fish species showing that 31 different B-class CpG ODN exert various immune responses both in vivo and in vitro in salmonids, cyprinids and pleuronectiformes. These responses include activation of macrophages, proliferation of leucocytes and stimulation of cytokine expression. CpG ODN have also been shown to be protective against bacterial and viral challenge as well as against pathogenic amoebae. As would be expected these effects are all dependent on not only the ODN sequence and length but on the concentration and the species in which it is being used. This review provides the first comprehensive overview of all CpG ODN tested in fish to date and brings together all the work carried out in this field.

Keywords: CpG; Aquaculture; Adjuvant

Contents

Abbreviations: DC, dendritic cell; FCA, Freund's complete adjuvant; FIA, Freund's incomplete adjuvant; IHNV, Infectious hematopoietic necrosis virus; IPNV, Infectious pancreatic necrosis virus; MPL, monophosphoryl lipid A; NCC, Non-specific cytotoxic cells; ODN, oligodeoxynucleotides; PAMPs, pathogen associated molecular patterns; PO, phosphodiester; PRRs, pattern recognition receptors; PS, phosphorothioate; TLRs, toll like receptors

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1. Introduction

As we move into the new millennium increasing populations and a rise in living standards and disposable incomes are fuelling an ever increasing consumer demand for fish and shellfish products. However, due to globally dwindling yields from many traditional marine and inland capture fisheries (Watson and Pauly, 2001) it is falling to the aquaculture industry to meet the shortfall in supply. As a result there has been a rapid expansion of this sector, which grew at an average annual rate of almost 10% between 1984 and 1996 compared with 3% for livestock meat and only 1.6% for capture fisheries production (Fishery Information, Data and Statistics Service (FIDI) http://www.fao.org/DOCREP/FIELD/006/AD742E/AD742E00.HTM).

Indeed, in 1996 over a quarter of total world supply of fish and shellfish was derived from aquaculture and with the increasing calls to reduce fishing of many marine stocks this trend looks set to continue.

In spite of this, factors such as infectious diseases continue to remain an impediment to the development, productivity and profitability of fish farms. A successful, commercial fish farm depends heavily on a commitment to animal health. Many things, including import and export of stock, species being farmed, location and management techniques impact greatly on the health of the fish. Unfortunately, the long-term use of antibiotics to treat disease outbreaks is known to induce resistance in both pathogenic and non-pathogenic micro-organisms, causing a threat to both the environment and animal and human safety. Thus the establishment of a comprehensive, cost effective programme of vaccination or prophylactic treatment is essential in any farming environment. However fish are a low value species and cost effective vaccines for many piscine diseases have not yet been produced.

2. Current vaccine technology in aquaculture

While most of the vaccines in current use are targeted against bacterial pathogens there are still a number of commercially important diseases of bacterial, viral and parasitic origin for which there is no prophylactic treatment (Gudding et al., 1999; Heppell and Davis, 2000). Until recently, conventional killed or modified pathogens were the only vaccines licensed for commercial use in farmed animals in many European countries. However, the introduction of commercially licensed subunit vaccines in the early 1990s for use in food animals such as cattle and pigs signalled a new era in vaccine technology (van Drunen Littel-van den Hurk et al., 2000). This led to the production of a recombinant fish vaccine for protection against infectious pancreatic necrosis virus (IPNV) (Frost and Ness, 1997). Limited vaccines against other viral fish diseases are commercially available, including a newly licensed DNA vaccine against infectious hematopoietic necrosis virus (IHNV) (Novartis Aquahealth), but a vaccine against the rhabdovirus, viral haemorrhagic septicaemia virus (VHSV), which causes significant economic losses in farmed rainbow trout (*Oncorhynchus mykiss*) across Europe, has yet to be successfully produced beyond the experimental stage (Corbiel et al., 2000b; Lorenzen et al., 2000).

Traditional veterinary vaccines often contain many of the features of the real pathogen such as bacterial DNA or LPS which function as adjuvants and can frequently be sufficiently immunogenic to induce protective immune responses. However, as the antigens become progressively more purified, making them less antigenic, as in these ‘new generation’ vaccines – particularly those based on recombinant proteins or DNA, they also become less immunogenic (Singh and O’Hagan, 2002). This has necessitated the development of new and improved vaccine adjuvants.