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Invited Review

Anisakis – A food-borne parasite that triggers allergic host defences

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ABSTRACT

Anisakis is a parasitic nematode which infects fish and marine invertebrates, including crustaceans and molluscs. Ingestion of contaminated seafood can cause acute gastrointestinal diseases. Infection can be accompanied by severe allergic reactions such as urticaria, angioedema and anaphylaxis. Diagnosis of allergy due to *Anisakis* currently relies on the detection of serum IgE antibodies to allergenic proteins and a history of reactions upon exposure to fish. *Anisakis* proteins demonstrate considerable immunological cross-reactivity to proteins of related nematodes and other invertebrates such as crustaceans and house dust-mites. In contrast, very limited molecular associations with other parasite groups are observed, including trematodes and cestodes. This review outlines current knowledge on *Anisakis* as a food-borne parasite, with special focus on the underlying immunological mechanisms resulting in allergic host defence responses.

1. Introduction

Anisakis species are marine roundworms (nematodes) which use marine mammals such as dolphins and whales as primary hosts. The L3 of *Anisakis* infects fish and other seafood such as squid, and consequently humans may become accidental hosts for *Anisakis* if they consume raw or undercooked fish (Sakanari and McKerrow, 1989). Infection is known as anisakiasis (or anisakidosis) and is often associated with acute gastrointestinal symptoms such as abdominal pain, diarrhoea, nausea and vomiting. However patients range from being asymptomatic to requiring emergency room care. In addition, IgE mediated allergic reactions to a range of allergenic proteins are often reported. Some of these allergens, tropomyosin and paramyosin, demonstrate strong molecular and immunological cross-reactivity to other invertebrates, including crustaceans and mites, but are only distantly related to trematodes and cestodes. Since 1960 when anisakiasis was first described, thousands of cases have been reported from Japan and hundreds from Europe as well as from other parts of the world (Audicana et al., 2002).

2. Biology and life cycle

Anisakis spp. belong to the subfamily Anisakinae, family Anisakidae, superfamily Ascaridoidea, suborder Ascaridina, order Ascarida (Smith and Wootten, 1978). Phylogenetic studies indicate that the human parasite to which *Anisakis* is most closely related is *Ascaris* (Blaxter et al., 1998; Nielsen, 1998). As a genus, *Anisakis* is found world-wide, but *Anisakis* spp. are differentially distributed geographically and utilise different host species (Mattiucci et al., 1997; Paggi et al., 2001; Mattiucci and Nascetti, 2006; Jabbar et al., 2013). Species recognised include the three sibling species of the *Anisakis simplex* complex (*A. simplex sensu stricto*, *A. simplex* C and *Anisakis pegreffii*), as well as the morphologically different *Anisakis typica*, *Anisakis ziphidarum*, *Anisakis schupakovi*, *Anisakis physeteris* and *Anisakis brevispiculata* (Paggi et al., 1985, 2001; Nascetti et al., 1986; Mattiucci et al., 1997, 2001; D'Amelio et al., 2000). With the advent of molecular approaches, it is now possible to identify anisakid nematodes to the species level and to reveal cryptic species (Mattiucci and Nascetti, 2006, 2008). A number of studies have demonstrated that the first and second internal transcribed spacers (ITS-1 and ITS-2, respectively) of nuclear ribosomal DNA (rDNA) provide suitable genetic markers for the identification of anisakid species, irrespective of their developmental stage

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(Zhu et al., 1998, 2007; Zhang et al., 2007; Shamsi et al., 2011a,b; Jabbar et al., 2012, 2013) and PCR-coupled mutation scanning of the ITS-1 and/or ITS-2, combined with targeted sequencing (Gasser et al., 2006) and phylogenetic analysis (Jabbar et al., 2012, 2013) provides a powerful approach for exploring the genetic composition of anisakid populations and for investigating their biology. The other genera in the subfamily Anisakinae, collectively known as the anisakids, are *Pseudoterranova*, *Contracaecum* and *Hysterothylacium*.

All of these nematodes appear to have similar life-cycles, although their host species vary (Ishikura et al., 1993; Mattiucci et al., 1997; Audicana et al., 2002). The primary/definitive hosts of anisakids are marine mammals such as whales, dolphins, seals and sea lions, as well as aquatic birds and turtles (Fig. 1). *Anisakis* spp. utilise cetaceans such as dolphins and whales as primary hosts. Eggs are passed into the sea via the faeces. The first moult (L1 to L2 takes place inside the egg, releasing free-swimming L2s that are ingested by tiny crustaceans such as krill (e.g. *Euphausia*, *Tysanoessa*), which are the first intermediate hosts (Smith and Wootten, 1978; Audicana et al., 2002). The crustaceans in turn are eaten by second intermediate hosts, which are fish, larger crustaceans or cephalopods. Inside these hosts, the larvae moult into L3s and become encapsulated on the surfaces of organs or muscles. Larger fish may become infected by eating smaller fish, leading to an accumulation of larvae with the age of the fish. All L3-infected seafood including fish, crustaceans and mollucs, can cause anisakiasis when ingested by humans. Humans are an "accidental host" in which the larvae cannot complete their life-cycle; other accidental hosts include bears, otters and cats (Davey, 1971; Sohn and Chai, 2005; Torres et al., 2004). In the natural cycle, the L3s in fish are ingested by cetaceans and moult into L4s and then adults. They cluster inside the stomachs of the cetaceans, where the female adult worms are fertilised and lay eggs, completing the cycle. Occasionally, anisakids moult into L4s in humans, but do not progress into adults. *Pseudoterranova* spp. are more likely to moult into L4s than *Anisakis* spp. In a rare case, an adult male worm of *Pseudoterranova* was found in a patient and is regarded as an exception (Kliks, 1983; Ishikura, 1989).

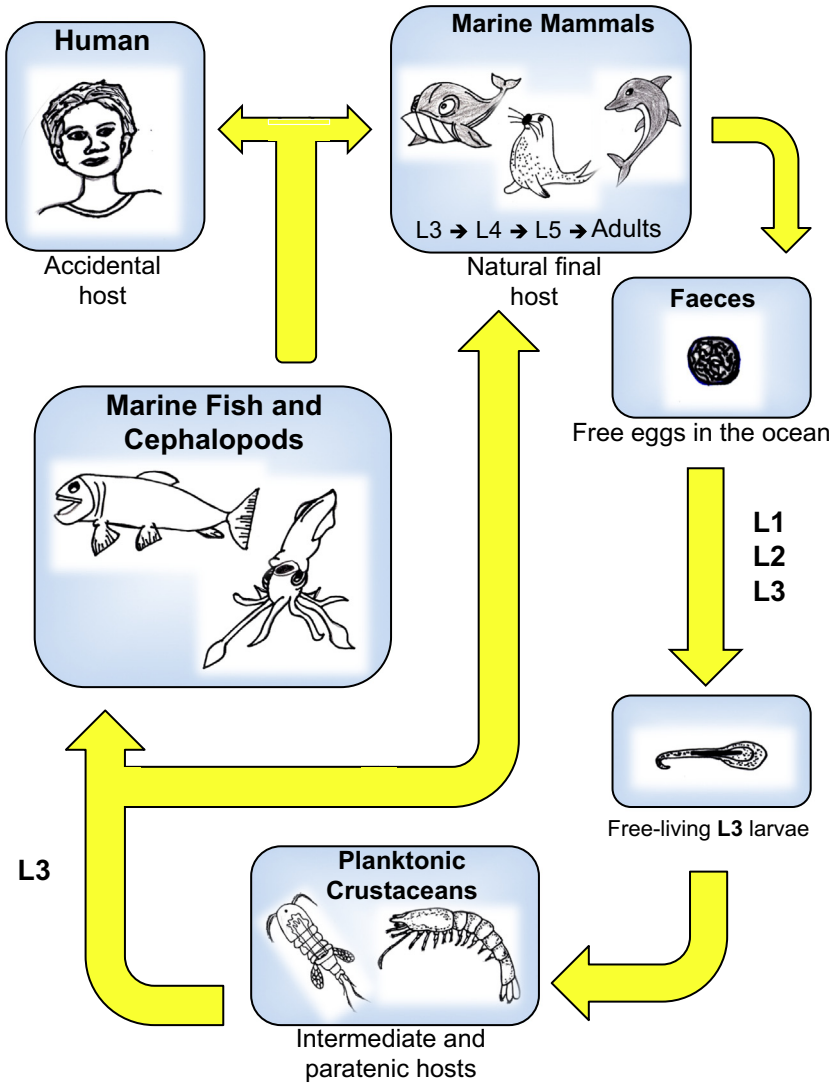

Fig. 1. Life cycle of *Anisakis simplex* including accidental human hosts. Adult parasites live in the stomach of marine mammals and unembryonated eggs are expelled with the faeces. These eggs develop and hatch, releasing free-living *A. simplex* L3s. These L3s are ingested by krill (euphausiid) and copepods, which form the intermediate hosts. Marine fish and cephalopods, which are paratenic hosts, contribute to the dissemination of this parasite by ingesting crustaceans, fish and cephalopods infected with L3s. The infective L3s are mostly embedded in the viscera and muscle and transferred to the final hosts (marine mammals) by ingestion of infected fish, cephalopods or krill. The L3 develops to the adult in the final host, closing the life cycle of this parasite by producing and releasing eggs. Ingestion of raw fish or cephalopods infected with L3s by humans, who are accidental hosts since the larvae do not develop further, can generate adverse reactions through activation of various host-defence responses.