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The teleost head kidney: Integrating thyroid and immune signalling

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ABSTRACT

The head kidney, analogous to the mammalian adrenal gland, is an organ unique for teleost fish. It comprises cytokine-producing lymphoid cells from the immune system and endocrine cells secreting cortisol, catecholamines, and thyroid hormones. The intimate organization of the immune system and endocrine system in one single organ makes bidirectional signalling between these possible. In this review we explore putative interactions between the thyroid and immune system in the head kidney. We give a short overview of the thyroid system, and consider the evidence for the presence of thyroid follicles in the head kidney as a normal, healthy trait in fishes. From mammalian studies we gather data on the effects of three important pro-inflammatory cytokines (TNFα, IL-1β, IL-6) on the thyroid system. A general picture that emerges is that pro-inflammatory cytokines inhibit the activity of the thyroid system at different targets. Extrapolating from these studies, we suggest that the interaction of the thyroid system by paracrine actions of cytokines in the head kidney is involved in fine-tuning the availability and redistribution of energy substrates during acclimation processes such as an immune response or stress response.

1. Introduction

The thyroid system is an evolutionary well-conserved endocrine system and is present in all vertebrate species investigated thus far. Thyroid hormones, or iodothyronines, are the main effector compounds. Thyroid hormones have pervasive actions on important physiological processes, including basal metabolic rate, growth and development. Proper functioning of the immune system is highly dependent on the adequate regulation of metabolism. It is difficult to conceive, therefore, that major regulatory systems such as the endocrine and immune system, and, for that matter, the nervous system as well, operate in isolation and unaware of each other's actions.

As we will argue below, the fish' immune and thyroid system are, anatomically at least, intimately connected. We here wish to explore putative interactions between the thyroid and immune system in the context of this unique aspect of teleost thyroid anatomy. From this we will attempt to derive new insight in the thyroid-immune interactions in fish.

2. The head kidney is a major lymphoid and endocrine organ

The head kidney, an organ analogous to the mammalian adrenal gland, is an important endocrine and haematopoietic-lymphoid organ in teleostean or "true bony" fish (reviewed by Gallo and Civinini (2003), Uribe et al. (2011)). The head kidney lacks the clear structure of its mammalian counterpart as a zonal cortex and medulla cannot be discerned. Instead, cortisol-producing interrenal cells and catecholamine-producing chromaffin cells are embedded in and surrounded by haematopoietic antibody- and cytokine-producing tissue.

Thyroid hormones are synthetized in thyroid follicles, the functional unit of the thyroid gland in vertebrates. Follicles consist of a monolayer of thyrocytes, enclosing an extracellular lumen filled with a colloid matrix. In many vertebrate classes the thyroid gland is an encapsulated and bilobed gland, located in the anterior neck region, ventral to the larynx and pharynx. Fishes have a different thyroid anatomy, however, as they lack a compact thyroid gland. Instead, individual thyroid follicles appear in different anatomical locations in the fish' body, of which the head kidney is a preferential organ (see Section 4).

In the context of thyroid – immune system interactions, the presence of thyroid follicles in the fish' head kidney is interesting.

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This anatomical location would, in principle, greatly facilitate a (paracrine) interaction between the immune system and the thyroid system. Indeed, a similar notion for other endocrines has already been suggested by others (Engelsma et al., 2002; Verburg-van Kemenade et al., 2009; Weyts et al., 1999).

The human thyroid gland is particularly susceptible to autoimmune disease. Graves' disease and Hashimoto's thyroiditis are two well-characterized pathologies (Saranac et al., 2011; Tomer, 2014) affecting more than 400/100,000 females per year worldwide, an incidence rate 4 to 10 times larger than that for males (McGrogan et al., 2008). Rather speculatively, the teleost head kidney can perhaps be considered a natural model for a lymphocyte-infiltrated thyroid gland in patients with Hashimoto's disease. New insights into human thyroid autoimmune disease can possibly be derived from a consideration of the putative interactions between thyroid and immune system in fishes.

3. A short introduction to comparative thyroidology

Thyroxine (3,5,3′,5′-tetraiodo-L-thyronine, or T4) is the main secretion product of the thyroid gland and can be considered to be a prohormone with little biological activity of its own. The enzymatic removal of an iodine atom from thyroxine's molecular structure yields the biologically active 3,5,3′-triiodo-L-thyronine (T3). Most biological actions of thyroid hormone can be ascribed to the latter. Thyroid hormones have pervasive actions as they affect basal metabolic rate, growth, and major developmental processes, most notably metamorphosis in fishes and amphibians (Eales, 2006; Power et al., 2001).

The secretory activity of the thyroid gland is regulated centrally by a hypothalamo-pituitary axis. Typical for the thyroid system is the involvement of peripheral processes and mechanisms that greatly determine the thyroid status of an animal. Different components of the thyroid system are potential targets for thyroid-immune interactions, and a very short overview of general thyroid physiology is warranted.

3.1. Thyroid hormone biosynthesis

Thyroid hormones, or iodothyronines by their chemical group name, are derivatives of the amino acid tyrosine containing one or two iodine substituents. Biosynthesis starts with the uptake of plasma-borne iodide by the thyroid gland via a sodium-iodide symporter (NIS) located in the basolateral membrane of the thyrocyte (Dai et al., 1996). Iodide moves transcellularly to the apical membrane of the thyrocyte, where it is secreted into the follicular lumen by the SLC26A4 pendrin ion transporter in mammals (Bizhanova and Kopp, 2009; Royaux et al., 2000). Although zebrafish (*Danio rerio*) express pendrin in their branchial ionocytes (Bayaa et al., 2009), the apical iodide transporter in teleost thyrocytes in general has not yet been identified. Extracellularly, at the interface of the apical membrane and the colloid, iodide is oxidized by thyroid peroxidase (TPO) to the reactive iodonium ion, H_2I^+. This reaction requires hydrogen peroxide, H_2O_2, supplied by thyroid oxidase type 2, also known as dual oxidase type 2 (Moreno et al., 2002; Ohye and Sugawara, 2010).

Thyroid hormone synthesis (reviewed by Miot et al., 2015) takes place on thyroglobulin (TG), a 660 kDa homodimeric protein that is synthesized by the thyrocyte and secreted via exocytosis into the lumen of the thyroid follicle. TG is the main protein component of the follicle's colloid. Selected tyrosines on the TG molecule are iodinated by iodonium. TPO catalyses the chemical coupling of two iodinated tyrosines to yield T4 and, to a lesser extent, T3 (de Vijlder and den Hartog, 1998). Upon stimulation of the thyroid gland by TSH, the colloid is partly resorbed by endocytosis, TG is degraded in lysosomes, T4 and T3 are cleaved by proteinase action, and the hormones are released into the bloodstream.

Circulating thyroid hormones are bound to carrier proteins: transthyretin (TTR), thyroxine-binding globulin (TBG) and albumin (Richardson et al., 1994, 2005). As a consequence, free thyroid hormone concentrations in fish plasma are generally less than 0.5% of the total concentration (Eales and Shostak, 1985), a value comparable to that of mammals.

3.2. Regulation of the thyroid axis

The mammalian hypothalamus-pituitary-thyroid (HPT) axis is often described as a classical endocrine example of negative feedback regulation. According to this view, hypothalamic thyrotropin stimulating hormone (TRH) stimulates the pituitary pars distalis to secrete thyrotropin or thyroid-stimulating hormone (TSH), which in turn stimulates the thyroid gland to produce and secrete thyroid hormone. In particular T4 negatively feeds back on the release of hypothalamic TRH and pituitary TSH.

In fishes the central regulation of the thyroid gland definitely differs between species. Teleosts lack a median eminence with a capillary portal system that connects the hypothalamus with the pituitary pars distalis. Instead, hypothalamic neurons project directly on or near cells in the pars distalis that secrete trophic factors such as TSH. This might explain that, besides TRH, other hypothalamic factors such as corticotropin releasing hormone (CRH) and dopamine, and likely more, are involved in the regulation of the thyroid axis (reviewed by Bernier et al., 2009).

3.3. Extrathyroidal thyroid hormone metabolism

Specific membrane transporters regulate access of T4 and T3 to their intracellularly located targets, i.e. iodothyronine deiodinases and intracellular receptors. Thyroid hormone membrane transporters are therefore key for undisturbed thyroid hormone action (Heuer and Visser, 2013; van der Deure et al., 2010).

The enzymatic conversion by 5′-deiodination of T4 to T3 can be regarded as an activation pathway of T4. Further deiodination reactions at other C-positions of the iodothyronine molecule can subsequently convert T3 to metabolites with no or little biological activity, and thus serve to terminate a hormone signal. Deiodination reactions are catalysed by a family of deiodinases, each with different substrate affinities, cosubstrate requirements and type of deiodination reaction catalysed (Gereben et al., 2008; Köhrle, 1999). Fish deiodinases largely resemble their mammalian counterparts (Mol et al., 1998; Orozco et al., 2012), but with some subtle differences in biochemistry (Klaren et al., 2005, 2012; Mol et al., 1997; Orozco and Valverde-R, 2005).

3.4. Thyroid hormone receptors

Thyroid hormone receptors (TRs) are members of a superfamily of ligand-dependent zinc-finger transcription factors. TRs are encoded by two genes, α and β, and alternative splicing produces at least three receptor isoforms for every gene product (Brent, 2012; Ortiga-Carvalho et al., 2014). Virtually every body cell, including cells of the immune system (Luo et al., 1989; Villa-Verde et al., 1992) expresses one or more TRs, explaining the pervasive effects of thyroid hormone. Multiple transcripts of TRα and TRβ genes have also been detected in fish (reviewed by Heijlen et al., 2013).

All TRs have a DNA-binding domain that bind to a thyroid hormone response element in or near the promoter region of their target genes (Yen, 2001). The genomic action of T3 is via the regulation of gene expression, and explains most biological effects of thyroid hormone. Still, important non-genomic effects of the

"classical" prohormone T4 and its metabolites have been described (Orozco et al., 2014; Scanlan, 2009; Senese et al., 2014).

3.5. Invertebrate thyroid physiology

The generalized description of the thyroid endocrine system given above roughly applies to all vertebrate classes and even beyond. From a comparative point of view it is interesting to note that thyroid hormone-related activity has also been described in organisms lacking an anatomically well-defined thyroid gland. Thyroid hormone synthesis has been demonstrated in the endostyle, a pharyngeal structure present in adult protochordate urochordates (*e.g.* sea squirts) and cephalochordates (*e.g.* lancelets). In other invertebrate phyla (*e.g.* echinoderms, arthropods, molluscs, cnidarians, poriferans) thyroid hormones are present, or biological effects of exogenously administered thyroid hormones are known (Eales, 1997). Even bacteria (*Escherichia coli*) and plants have been shown to metabolize exogenous thyroid hormones and to endogenously synthesize thyroid hormones, respectively. These observations emphasize the significance of thyroid hormones as important signalling molecules within an evolutionary context (Heyland and Moroz, 2005).

4. Thyroid anatomy and location in teleostean fish

As mentioned earlier, the thyroid gland in teleost fish is not a compact gland and thyroid follicles are typically scattered within the subpharyngeal area and other tissues. In an extensive literature and experimental study, Chanet and Meunier (2014) compared the thyroid gland of 215 teleost fish species and identified 4 different thyroid tissue organizations within the Teleostei infraclass.

The most common pattern is indeed the organization where thyroid follicles are diffusely scattered in the branchial region surrounding the ventral aorta. A second pattern is where thyroid follicles are organized in several lobes gathered around the ventral aorta. A third thyroid pattern appears to be restricted to species of the Lophiiformes and Tetraodontiformes families. Here, a rather compact gland is included in a blood sinus located dorsal to the ventral aorta. The fourth thyroid pattern includes the presence of heterotopic thyroid follicles in extra-pharyngeal tissues, next to the presence of subpharyngeal thyroid follicles. Heterotopic thyroid follicles have been observed in tissues such as the heart, spleen, liver, oesophagus, brain and choroid rete mirabile. However, the principal locations for these heterotopic thyroid follicles are the head kidney (pronephros) and trunk kidney (opistonephros) (Baker, 1959).

We have performed an extensive literature search on studies that describe heterotopic thyroid follicles in fish and were able to construct a complete list of fish species with renal heterotopic thyroid tissue, excluding species with hyperplastic heterotopic thyroid follicles or heterotopic thyroid follicles in other tissues (Table 1). Renal thyroid heterotopia have been described in representatives of the order of anchovies and herrings (Clupeiformes, 1 species), minnows and suckers (Cypriniformes, 16 species), catfish (Siluriformes, 3 species), gobies and sleepers (Gobiiformes, 1 species), swamp eels (Synbrachiformes, 2 species), gouramis (Anabantiformes, 1 species), jacks and relatives (Garangiformes, 1 species), rainbow fish and silversides (Atheriniformes, 1 species) and killifish (Cypridontiformes, 3 species).

Remarkable is the high incidence of renal heterotopic thyroid follicles in the order of the Cypriniformes (16 out of 29 species in total), suggesting it may be induced by a shared cyprinid trait, although not all cyprinid species (*e.g.* zebrafish, personal unpublished observation) display thyroid heterotopia. A phylogenetic analysis of the presence of renal thyroid heterotopia does not provide a clear explanation for its occurrence; families with species that exhibit renal thyroid heterotopia are widely distributed and not confined to a specific clade (Fig. 1). The distribution of renal thyroid follicles may be the result of convergence and may have appeared twice, first in a common ancestor within the supercohort Clupeocephala, and then in a common ancestor within the subdivision of Percomorphaceae. However, thyroid heterotopia has not been investigated in sufficient species to support this hypothesis. More likely the distribution of renal heterotopic thyroid follicles is the result of independent events within Teleost families (Chanet and Meunier, 2014). Clearly phylogenetic analysis alone cannot explain the occurrence of heterotopic thyroid follicles in renal tissues, and answers may have to be found within the context of their physiological relevance in these renal tissues.

5. Renal ectopic thyroid follicles: physiology or pathology?

It remains unclear why thyroid follicles are preferentially present in renal tissues in fish, while at the same time apparently normal thyroid tissue is present in the sub-pharyngeal area. A plausible notion is that these heterotopic thyroid follicles in fish are the result of pathophysiological processes. Indeed, thyroid heterotopia in fish has previously been suggested to result from thyroid cancer metastasis, hypothyroidism or developmental defects.

5.1. Thyroid carcinoma are metastases?

Because of their seemingly misplaced localization, renal heterotopic thyroid follicles have often been interpreted to be the result of metastasis of subpharyngeal thyroid cancers (Berg et al., 1953; Blasiola et al., 1981; Nigrelli, 1952). Indeed, thyroid hyperplasia and neoplasia have been described in teleostean fishes (Fournie et al., 2005; Leatherland and Down, 2001). However, renal heterotopic thyroid follicles (and their subpharyngeal counterparts) do not follow the histological diagnostic criteria for thyroid hyperplasia, adenoma or carcinoma as proposed by Fournie et al. (2005), indicating that renal thyroid follicles in fish are the result of physiological processes.

5.2. A compensatory mechanism for iodine deficiency?

In a series of landmark studies on thyroid heterotopia in fish, K. France Baker (1958a,b, 1959) suggested that thyroid heterotopia is a compensatory mechanism to cope with iodine deficiency, as the administration of a 1000-fold surplus of iodine to the water resulted in the developmental arrest of heterotopic thyroid follicles in platyfish. However, since the availability of iodine in a water body is virtually infinite and fish are highly efficient in the uptake of iodine from water (Geven et al., 2007; Moren et al., 2008), it is questionable whether fish can actually experience "environmental" hypothyroidism in the ambient water of their natural habitat. Moreover, if hypothyroidism could indeed be experienced, a goitrous thyroid within the pharyngeal region is more likely to occur than translocation of thyroid tissue to other organs, as has been observed in fish exposed to xenobiotic disruptors (Moccia et al., 1977, 1981). Taken together, one could argue whether the emergence of heterotopic thyroid follicles in renal tissues is a *bona fide* compensatory mechanism for iodine deficiency within a physiological context.

5.3. Thyroid heterotopia is the result of developmental defects?

Heterotopic thyroid follicles in the renal tissues of fish have also been suggested to be the result of defects during thyroid development. The development of the thyroid gland in fish largely

Table 1
Fish species described in the literature with heterotopic thyroid follicles in renal tissues.

Order	Family	Species	References
Clupeiformes	Engraulidae	Gangetic hairfin anchovy (*Setipinna phasa*)	(Sathyanesan and Chary, 1962)
Cypriniformes	Cyprinidae	Common carp (*Cyprinus carpio*)	(Chavin, 1966; Geven et al., 2007; Lysak, 1964; Qureshi and Sultan, 1976; Sugiyama and Sato, 1960)
		Goldfish (*Carassius auratus*)	(Chavin, 1956a, b; Chavin and Bouwman, 1965; Peter, 1970; Qureshi et al., 1978)
		Crucian carp (*Carassius carassius*)	(Frisén and Frisén, 1967)
		Silver carp (*Hypophthalmichthys molitrix*)	(Kruger, 1991)
		Ide (*Leuciscus idus*)	(Kruger, 1991)
		Pool barb (*Puntius sophore*)	(Agrawala and Dixit, 1979; Sathyanesan, 1963; Srivastava and Sathyanesan, 1971b)
		Iraq blind barb (*Typhlogarra widdowsoni*)	(Olivereau, 1960)
		Mahseer (*Tor tor*)	(Qureshi and Sultan, 1976)
		Mrigal (*Cirrhinus cirrhosus*)	(Joshi and Sathyanesan, 1976)
		Garra (*Garra lamta*)	(Pandey, 1964; Qureshi et al., 1978)
		Catla (*Catla catla*)	(Ahuja and Chandy, 1962)
		Rosy barb (*Puntius conchonius*)	(Sathyanesan, 1963; Sathyanesan and Prasad, 1962)
		Rohu (*Labeo rohita*)	(Kulkarni and Sathyanesan, 1978)
		Cherry barb (*Puntius titteya*)	(Baker, 1959; Sathyanesan, 1963)
		Ticto barb (*Puntius ticto*)	(Bose and Firoz Ahmad, 1977)
	Cobitidae	Pond loach (*Misgurnus anguillicaudatus*)	(Sugiyama and Sato, 1960)
Siluriformes	Clarridae	Walking catfish (*Clarias batrachus*)	(Bhattacharya et al., 1976b; Sharma and Kumar, 1982)
	Bagridae	Striped dwarf catfish (*Mystus vittatus*)	(Bose and Firoz Ahmad, 1978; Gurumani, 1971)
	Heteropneustidae	Stinging catfish (*Heteropneustes fossilis*)	(Qureshi, 1975; Qureshi and Qureshi, 1974)
Gobiiformes	Gobiidae	Tank goby (*Glossogobius giuris*)	(Qureshi et al., 1978)
Synbrachiformes	Synbranchidae	Cuchia (*Monopterus cuchia*)	(Srivastava and Sathyanesan, 1967, 1971a)
		Asian swamp eel (*Monopterus albus*)	(Wai-Sum and Chan, 1974)
Anabantiformes	Channidae	Spotted snakehead (*Channa punctatus*)	(Bhattacharya et al., 1976a)
Carangiformes	Polynemidae	Sixfinger threadfin (*Polydactylus sexfilis*)	(Qureshi et al., 1978)
Atheriniformes	Atherinopsidae	Inland silverside (*Menidia beryllina*)	(Fournie et al., 2005)
Cyprinodontiformes	Poeciliidae	Southern platyfish (*Xiphophorus maculates*)	(Baker, 1958a, b; Baker et al., 1955)
		Montezuma swordtail (*Xiphophorus montezuma*)	(Baker, 1959)
	Nothobranchiidae	Redtail notho (*Nothobranchius guentheri*)	(Markofsky and Milstoc, 1979)

resembles that in mammals (De Felice and Di Lauro, 2004) Briefly, endodermal cells from the thyroid anlage, situated in the midline of the embryonic pharyngeal floor, are determined to develop into thyroid cells. After proliferation of the thyroid anlage, primordial cells migrate to their ultimate anatomical location, *viz*. the ventral neck region in mammals and the subpharyngeal region in teleostean fish, where they differentiate and organize into functional thyroid follicles. In fish, the thyroid follicles then multiply and migrate caudally along the anterior-posterior axis of the ventral aorta (Alt et al., 2006a; Elsalini et al., 2003; Wendl et al., 2002).

In humans, ectopic thyroid tissue is a rare clinical observation (1–3 cases per 100,000 persons) and is indeed regarded the result of a defective thyroid gland development (Guerra et al., 2014). Human ectopic thyroid follicles are mainly restricted to the lingual area and other head and neck regions along the developmental pathway of the thyroid gland and in only very rare cases observed in other distant tissues, only 10 cases of ectopic thyroid tissue in adrenal glands have been described in literature (Tada et al., 2016). Since renal heterotopic thyroid follicles in fish are not incidentally, but consistently observed within a fish species, it appears unlikely that renal thyroid tissue results from a mere passive developmental defect, but that an active process is guiding thyroid tissue to these tissues.

5.4. Active migration of thyroid tissue guided by vasculature

Baker (1958a,b) already suggested that thyroid cells or follicles may migrate via the walls of blood vessels to their ultimate destination because of the strong association *in situ* of the subpharyngeal thyroid follicles with the ventral aorta and branchial arteries in fish. Indeed, in a zebrafish mutant with an impaired pharyngeal vascular architecture, thyroid follicles did not develop along the anterior-posterior axis of the ventral aorta, but extended more laterally. Grafting of ectopic endothelial cells in zebrafish during late blastula stage affected thyroid localization: the thyroid follicles projected towards nearby located grafted endothelial cells (Alt et al., 2006b). It appears that the pharyngeal vascular system provides chemotactic cues that guide the organization of thyroid tissue along the ventral aorta. A specific expression pattern of these signals along the inferior jugular vein, sinus venosus, Cuverian duct and the cardinal veins (homologous to the mammalian venae cavae) may facilitate the specific migration of thyroid tissue towards the renal tissues. Though this may provide a mechanism by which the thyroid follicles migrate to the renal tissues, it does not explain the reason why these thyroid follicles are present in the head kidney or kidney.

5.5. Heterotopic thyroid follicles are physiologically relevant

Clearly renal heterotopic thyroid follicles are not the result of a pathophysiological process but are physiological relevant thyroid tissues involved in the regulation of systemic thyroid hormones levels. Indeed, renal thyroid follicles in fish are active endocrine tissues as they accumulate iodine and synthesize T4, which can be modulated by TSH and thyrostatics (Bhattacharya et al., 1976a; Chavin and Bouwman, 1965). Its contribution to the total thyroid activity in fish appears variable, renal thyroid tissue has been reported to be less active than (Bhattacharya et al., 1976a), of equal activity to (Frisén and Frisén, 1967) or more active than (Chavin and Bouwman, 1965; Peter, 1970; Srivastava and Sathyanesan, 1971b) the subpharyngeal thyroid tissue.

The most extreme example of functional renal thyroid tissue

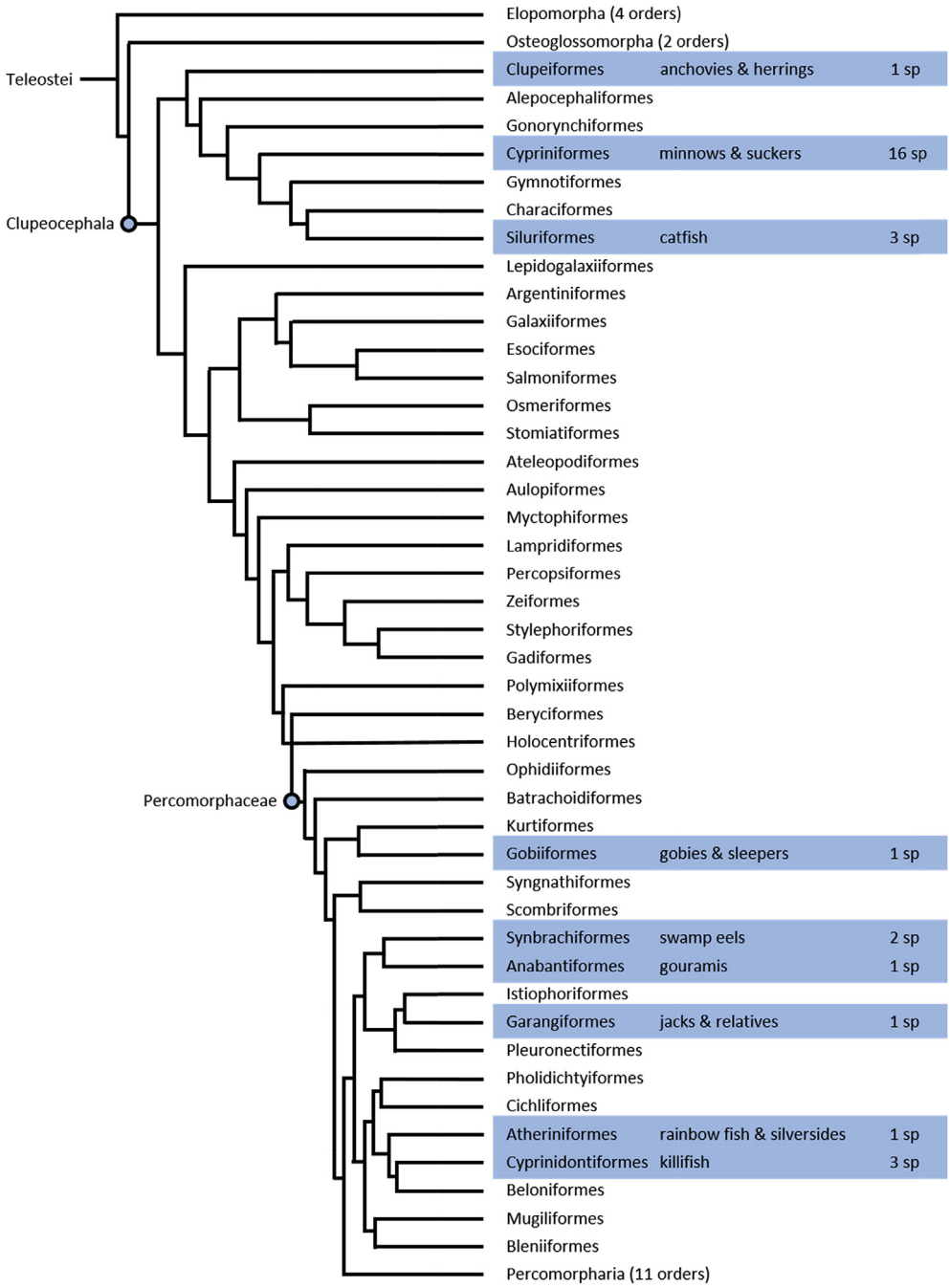

Fig. 1. Phylogenetic tree of teleost orders showing the distribution of renal thyroid heterotopia within the Teleostei infraclass. Number of fish species reported to exhibit renal thyroid heterotopia per order are shown in blue boxes. Adapted from Betancur-R et al. (2013). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was observed in common carp (*Cyprinus carpio*). In a comparative study it was found that the complete functional thyroid is located in the renal tissues of carp while in Mozambique tilapia (*Oreochromis mossambicus*) the functional thyroid is located in the sub-pharyngeal area (Geven et al., 2007). Although thyroid follicles were present in the sub-pharyngeal area of common carp and appear histologically normal (Fig. 2), these follicles did not accumulate iodine, did not synthesize thyroid hormones, and were not responsive to TSH stimulation *in vitro*. In contrast, thyroid follicles in head kidney and kidney accumulated iodine and synthesized thyroid hormones which were released upon TSH stimulation, and can therefore considered to be responsible for the complete thyroid hormone output in this species. These results may prompt us to reconsider the term “heterotopic”, and to designate renal thyroid tissue in fish as “orthotopic” (meaning: “in the normal or usual place in the body.”)

Renal thyroid follicles are clearly a normal anatomical, physiological relevant feature, that either works in concert with the sub-pharyngeal thyroid follicles, or is complete responsible for maintaining a healthy thyroid status in the animal.

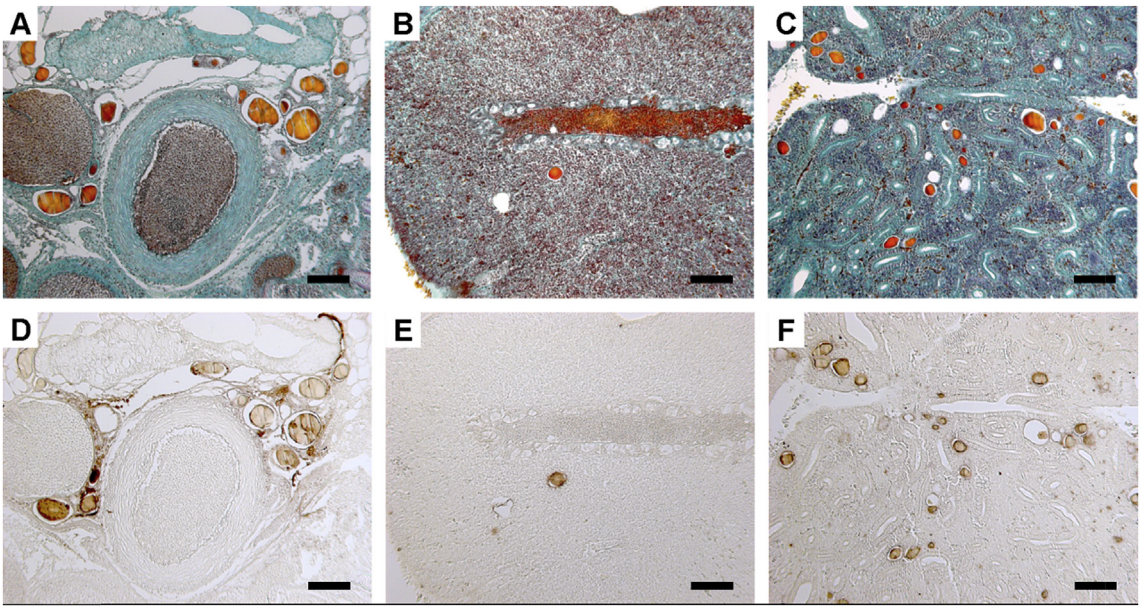

Fig. 2. Histochemistry using Crossmon's modified Mallory's trichrome stain (A, B, C) and thyroxine immunohistochemistry (D, E, F) of 7-μm thick serial sections of carp subpharyngeal area and ventral aorta (A, D), head kidney (B, E) and trunk kidney (C, F). The colloid in the thyroid follicles stains bright orange after trichrome staining (upper panels) and coincides with thyroxine immunoreactivity (lower panels). Scale bars indicate 200 μm. From Geven et al. (2007).

6. Thyroid – immune system communication

The location of thyroid follicles adjacent to cytokine-producing haematopoietic tissue in fish hints to a paracrine interaction between the immune and thyroid system. Indeed, the effects, genomic and non-genomic, of T4 and T3 on the mammalian immune system are well-established (De Vito et al., 2012; De Vito et al., 2011; Grymuła et al., 2007; Hodkinson et al., 2009). Reciprocally, the immune system is considered to be an important regulator of thyroid hormone activity (Klein, 2006).

In humans the thyroid gland in particular appears to be particularly susceptible to immunological disorders. Patients with Graves' autoimmune disease suffer from hyperthyroidism, caused by immunoglobulins that inappropriately stimulate the TSH receptor on thyroctes (Ajjan and Weetman, 2003; Rapoport et al., 1998). Hashimoto's thyroiditis is an autoimmune disorder caused by antibodies that target different components of the thyroid system, *e.g.* thyroid peroxidase, thyroglobulin, and the TSH receptor, resulting in hypothyroidism (Chistiakov, 2005; Ganesh et al., 2011). Patients with an autoimmune thyroid disease, and those with non-autoimmune thyroid disorders as well, show different expression profiles of cytokines (de Vries et al., 2015; Heuer et al., 1996; Mikos et al., 2014).

There are very few data on thyroid-immune system interactions in fishes. As does virtually every vertebrate somatic cell, immune cells of rainbow trout (*Oncorhynchus mykiss*) express both thyroid hormone receptor genes, TRα and TRβ (Quesada-García et al., 2014). The regulatory role of thyroid hormones in the development of immune system, in particular the thymus and thymopoiesis, has already been mentioned. Further evidence for thyroid-immune system interactions mainly has to be derived from studies in mammals. Hypothyroid mice are more susceptible to infections (Dorshkind and Horseman, 2000), and this pathology can be correlated with the presence of thyroid hormone receptors on thymocytes and spleen mature lymphocytes (Luo et al., 1989; Villa-Verde et al., 1992) and the TSH receptor in lymphocytes and its precursors (Pekonen and Weintraub, 1978; Wang et al., 2003). Early indications for thyroid-immune system interactions in fish came from hypothyroid killifish (*Fundulus heteroclitus*) that showed a reduced count of circulating leukocytes (Slicher, 1961), an effect that was restored by administration of TSH or T4 in guppy (*Poecilia latipinna*) (Ball and Hawkins, 1976).

As mentioned before, the preferential location of thyroid follicles in the head kidney of teleosts hints at a paracrine mode of communication between myeloid and lymphoid cells of the head kidney, and the thyrocytes. Activated macrophages from the teleost's innate immune system secrete pro-inflammatory cytokines: tumour necrosis factor α (TNFα) and the interleukins IL-1β and IL-6. These cytokines in turn induce inflammation, neutrophil activation, and the release of a series of chemokines (reviewed by Verburg-van Kemenade et al., 2009). TNFα, IL-1β and IL-6 thus appear to be prime candidates to fulfil a role as a local conveyor of information from the immune system to the thyroid system. We will consider evidence for this proposition from (mammalian) literature, and make an attempt to formulate a hypothesis on the physiological relevance of the presence of thyroid follicles in an important lymphoid and myeloid organ in teleosts, a highly diverse vertebrate infraclass that arose ca. 450 My ago and comprises an estimated 28,500 extant species (http://www.fishbase.org/home.htm, ver. 10/2015).

6.1. TNFα

The cytokine TNFα may encounter many targets in the thyroid system. At a central level, TNFα inhibits the basal release of a number of hormones from cultured rat pituitary cells, among which TSH (Harel et al., 1995). In cultured human thyrocytes, TNFα inhibits iodine organification, *i.e.* the incorporation of iodine in the thyroid hormone precursor TG (Sato et al., 1990). Indeed, TNFα targets multiple steps in thyroid hormonogenesis: it inhibits TG synthesis and secretion in thyrocytes from human patients (Poth et al., 1991; Rasmussen et al., 1994), it inhibits TSH-induced hydrogen peroxide production (which is necessary for the oxidation of iodide to iodonium) in rat FRTL-5 thyrocytes (Kimura et al.,

1997), and it also inhibits basal and TSH-induced expression of the NIS iodide transporter in FRTL-5 cells (Ajjan et al., 1998; Pekary et al., 1998). These actions will all lead to a defective organification of iodide and thyroid hormone production.

TNFα not only inhibits thyroid hormone production, it also inhibits the activating 5′-deiodination pathway in human and FRTL-5 thyrocytes (Hashimoto et al., 1995; Molnár et al., 2002; Ongphiphadhanakul et al., 1994; Pekary et al., 1994) and the HepG2 hepatocarcinoma cell line (Jakobs et al., 2002). However, in other cell types (Φ_1 rat liver carcinoma cells, primary cultures of rat anterior pituitary) TNFα and other pro-inflammatory cytokines do not inhibit but stimulate 5′-deiodination (Baur et al., 2000; Davies et al., 1997).

Perhaps contradictory to its inhibitory effects on the thyroid system, plasma levels of TNFα and its soluble receptor are high in Graves' disease (Pichler et al., 2003; Wakelkamp et al., 2000). This can indicate an autonomous source and paracrine action of the cytokine.

6.2. IL-1β

At a central level, IL-1β inhibits the basal release of TSH but not that of the related luteinizing hormone (LH) and follicle stimulating hormone (FSH) from cultured rat pituitary (Wassen et al., 1996). Its action therefore seems to be more specific than that of TNFα. As is the case for TNFα, IL-1β has multiple targets in the hypothalamus-pituitary-thyroid axis. Infusion of IL-1β in the liquor cerebrospinalis reduces the content of pro-TRH in the hypothalamic nucleus paraventricularis, and, consequently, decreases plasma T4 levels in rat (Kakucska et al., 1994).

IL-1β dose-dependently inhibits TSH-induced TG transcription and release in cultured human thyrocytes (Yamashita et al., 1989). In the rat thyroid FRTL-5 cell line IL-1β inhibits the expression and activity of NIS (Schumm-Draeger, 2001) and of iodothyronine deiodinase type-1, an enzyme that can catalyse a T4-activating pathway (Hashimoto et al., 1995; Pekary et al., 1994).

IL-1β's stimulatory or inhibitory effects have to be considered with some caution. At pharmacological levels IL-1β inhibits TG secretion in cultured human thyrocytes, but at physiological, 4 to 5 orders of magnitude lower levels it stimulates (Krogh Rasmussen et al., 1988; Rasmussen et al., 2000). This dose-dependent stimulation or inhibition cannot explain the different effects observed by Hashimoto et al. (1995) and Davies et al. (1997), however. They measured an inhibition and stimulation, respectively, of 5′-deiodination in two different hepatic cell lines using similar IL-1β concentration ranges of 0.1–10 ng/mL. Still, in paracrine signalling locally high doses of signalling molecules can be attained. The different effects of IL-1β, and those of other cytokines as well, could well be explained by this phenomenon.

In human HepG2 hepatoma cells, treatment with IL-1β decreased the expression of thyroid hormone receptor TRα1 *in vitro*, and a similar effect was seen in mice treated with lipopolysaccharide (LPS) *in vivo* (Kwakkel et al., 2007). This study plausibly connects an induced immune response with inflammatory cytokines and a shared thyroid hormone receptor target.

As stated in section 3.1 fish' heterotopic thyroid follicles are clearly no metastases. Still, it is interesting to mention that human thyroid carcinoma cells produce IL-1β (Tohyama et al., 1992), and that IL-1β inhibits proliferation of human papillary thyroid carcinomas (Kimura et al., 1992; Ohta et al., 1996), an effect that is opposite of that observed in healthy thyroid follicular cells in rats *in vivo* (Żerek-Mełeń et al., 1994). Also, it has been proposed to use promoter polymorphisms of the gene for IL-1β, but not for other pro-inflammatory cytokines, as a genetic marker for susceptibility for Graves' disease (Chen et al., 2005a, 2005b).

6.3. IL-6

Interleukin-6 suppresses plasma TSH levels in human *in vivo* (Stouthard et al., 1994; Torpy et al., 1998; Tsigos et al., 1997) and experimentally hypothyroid rats (Bartalena et al., 1994b). This effect seems to be independent of hypothalamic TRH release (Kennedy et al., 1995).

In mammalian thyrocytes, IL-6 exerts roughly the same repertoire of inhibitory effects as TNFα and IL-1β: inhibition of TPO gene expression (Tominaga et al., 1991), and inhibition of basal and TSH-induced 5′-deiodination (Hashimoto et al., 1995; Wajner et al., 2011). The production of TG in cultured human thyrocytes, however, was unaffected by IL-6 (Krogh Rasmussen et al., 1991).

The production of IL-6 by human thyrocytes and thyroid carcinomas is well established, as well as its stimulation by IL-1 (Diamant et al., 1991; Tohyama et al., 1992; Watson et al., 1995; Yoshida et al., 1994; Zheng et al., 1991). Interestingly, it has been proposed that the stimulating IL-1 originates from the thyrocytes (Krogh Rasmussen et al., 1993).

The inhibitory effects of IL-6 are reflected in the negative correlations between the plasma levels of the cytokine and circulating thyroid hormones in patients with thyroid disease (Bartalena et al., 1993, 1994a; Boelen et al., 1993; Çelik et al., 1995).

6.4. Observations in fishes

As mentioned earlier, literature on the interaction of the thyroid system with the immune system in fish is scarce. In a series of pilot studies we therefore investigated the putative interaction between the thyroid axis and the immune system in common carp. In particular, we measured the effects of T3 and T4 administration on the activity peripheral blood leukocytes (PBL) *in vitro*.

Exposure of PBL to 10 or 100 nM T4, but not T3, resulted in an upregulation of the expression of TNFα with a maximum effect size half of that induced by 10 μg/mL concanavalin A ($n = 1$). Moreover, leukocyte-enriched fractions derived from peripheral blood and head kidney displayed a 5′-deiodinase activity that was inhibited by dithiothreitol, DTT ($n = 1$). A DTT-sensitive 5′-deiodination activity was also measured in three leukocyte subpopulations (macrophages, lymphocytes, granulocytes) enriched from peripheral blood leukocytes, head kidney cells and trunk kidney cells ($n = 7$). These first scant observations point to a mechanism where T4 is taken up by PBL via a specific transporter, *e.g.* the SLC16A2 monocarboxylate transporter type 8 (Arjona et al., 2011), and subsequently deiodinated to the potently bioactive T3.

7. Pro-inflammatory cytokines in general inhibit thyroid function

The general picture that emerges from the results from studies in mammals is that pro-inflammatory cytokines inhibit thyroid function. de Vries et al. (2015) show some elegant schemes on how TNFα, IL-1β and IL-6 inhibit thyroid hormonogenesis in the thyroid gland and key deiodinase enzymes, confirming the general picture. Here we will assume that pro-inflammatory cytokines have similar actions in fishes.

So, thyroid follicles in the fish' head kidney, a major immune organ, are surrounded by cells producing and secreting thyroid-inhibiting cytokines. This aspect bears some resemblance to the symptoms seen in non-thyroidal illness (NTI). NTI is a syndrome that is characterized by low plasma levels of T3 but normal TSH levels that is observed in critically ill patients or during chronic

starvation (Van den Berghe, 2014). Cytokines have been considered to play a role in NTI's aetiology (de Vries et al., 2015). The low plasma T3 levels can putatively be interpreted as facilitating a lower basal metabolic rate, or an "energy saving mode" of the body.

Animals are in constant contact and exchange with their environment, and need to acclimate to changes and challenges therein. A variety of stressors; physicochemical, biological, immunological, and even social, can require and evoke an acclimation response. Stress responses and immune responses play key roles in the acclimation of animals to their changing environment. In fishes, responses to a stressor are mediated by cortisol, the "classical" stress hormone, by cytokines from the immune system, and also by the end products of the thyroid axis. In fact, it has been argued that a proper understanding of the regulation of an acclimation response requires the consideration of a regulatory "web" rather than parallel running hypothalamus-pituitary axes (Bernier et al., 2009; Geven et al., 2006, 2009). Basically, stress and immune responses are energy demanding and require the reallocation of energy substrates away from growth and reproduction towards pertinent and relevant processes (reviewed by Rauw, 2012; Wendelaar Bonga, 1997). The interaction of the interrenal thyroid system by paracrine actions of cytokines most likely is involved in fine-tuning the availability of energy substrates that are, by their nature, in limited supply.

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