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Editorial: Get inspired - Lessons learned from evolution of thyroid hormone signaling in developmental processes

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Thyroid hormones (TH) are essential for normal growth and development. In humans, the clinical presentation of patients suffering from untreated congenital hypothyroidism persuasively illustrates the consequences of impaired TH supply for brain development, cognitive and motor function, bone maturation and metabolism (Grüters and Krude, 2011). Despite agreement on the importance of TH in development, there are still significant gaps in our understanding of when, where, and how TH act to initiate and orchestrate specific developmental processes. One related problem is that classical rodent *in vivo* models or established mammalian *in vitro* cell culture systems can present considerable obstacles to tackle specific questions, therefore calling for complementary alternative models to decipher TH function during developmental processes. In turn, comparative approaches have shown that studying TH-dependent cell and tissue responses in evolutionary distant vertebrates and non-vertebrate species can provide new clues to enhance our understanding of the biological role of TH and non-classical TH derivatives. As it becomes increasingly clear that TH influence the differentiation and functional maturation of diverse cell types by acting on early stem/progenitor cell populations, new experimental approaches are needed to study the actual targets of TH action during complex cellular developmental programs. In the light of these questions, we invited a number of colleagues to contribute to this Special Issue to provide readers with an updated overview on non-classical animal model systems in thyroid endocrinology, evolutionary aspects of TH signaling as well as on current developments in the field of TH signaling in stem and progenitor cell biology.

Comparative approaches in thyroid endocrinology have a long and fruitful history and experimental studies carried out with avian, amphibian and fish species contributed numerous seminal findings advancing our understanding of TH action. It is important to note that the regulatory function of TH during development is deeply rooted within vertebrate phylogeny and that there is significant conservation of the genes encoding key players of synthesis, distribution, cellular transport, metabolism and action of TH during vertebrate evolution (Darras et al., 2015; Grimaldi et al., 2013; Holzer and Laudet, 2013; Richardson, 2007). Moreover, it is frequently forgotten that in contrast to evolutionary and species differences found in peptide and proteohormones, the chemical structure of TH and hormonally active derivatives is essentially the same across vertebrates.

One of the 'top models' of developmental TH action is certainly the TH-dependent transformation of anuran tadpoles into frogs (metamorphosis). Indeed, anuran metamorphosis was the first animal model for the developmental actions of TH. The earliest demonstration of a causal link between thyroid function and amphibian metamorphosis dates back to 1912, when Gudernatsch reported that feeding mammalian thyroid tissue to *Rana temporaria* tadpoles causes a precocious induction and acceleration of metamorphosis (Gudernatsch, 1912). Notably, Gudernatsch's experiments showed that the thyroid contains components with a strong stimulatory function on metamorphosis a few years before the discovery of thyroxine in 1915 (Kendall, 1915). Soon thereafter, studies by Allen (1916, 1917) expanded this biological model by demonstrating that TH are in fact essential for metamorphosis when he noted that thyroidectomized tadpoles never develop into a frog - unless they are fed with thyroid preparations. Over the last few decades, work in genetically tractable frog species such as *Xenopus laevis* used the metamorphosis model in an impressive manner to delineate the molecular mechanisms how TH orchestrate the highly coordinated remodeling of tadpole tissues. In his review, Buchholz (2017) covers recent advances in our understanding how TH receptors (TRs) regulate TH responsiveness of tadpole tissues and how TH signaling influences timing of tissue transformations and cell fate decisions. By integrating recent findings made in knock-out *Xenopus* models, this paper concludes that in the various tissues studied, the predominant role of TRs is to regulate the timing of distinct developmental events rather than to act on cell fate decisions. The stimulating discussion by Buchholz raises important questions for future studies including whether such a model holds true for all tadpole tissues undergoing transformation during metamorphosis and to which extent this developmental timer model can be transferred to other TH-dependent developmental processes and other species.

Over the last decades, we also learned that TH-dependent metamorphosis is not limited to anuran amphibians but represents an ancestral feature that can be traced back to protochordates such as amphioxus (Laudet, 2011). Moreover, knowledge derived from

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analyzing TH regulation of anuran metamorphosis has been critical to generate a more holistic view on TH regulation of post-embryonic life stage transitions in vertebrates including processes such as perinatal development in humans, hatching in birds and larval-to-juvenile development in fish (Laudet, 2011). Similar to amphibians, larvae of various teleost fish species undergo a metamorphic transformation and the thyroid system positively regulates these developmental processes (McMenamin and Parichy, 2013). Yet, there are species where the relationship between thyroid system function and metamorphosis seems quite different to other vertebrates. The most prominent example are the lampreys, jawless fish (agnatha) phylogenetically located at the base of the vertebrate tree. In lamprey larvae, metamorphosis is not associated with a surge in TH levels but is rather initiated following a substantial decline in TH levels. In their review on lamprey metamorphosis, Manzon and Manzon (2017) summarize the current knowledge on TH signaling in this fascinating model system and compare key aspects of the endocrine control of lamprey metamorphosis with amphibian and teleost models. While many components of TH signaling in lamprey seem to represent an ancestral state relative to that found in jawed vertebrates (gnathostomes), the authors concluded that all major aspects of vertebrate TH-signaling are conserved in lamprey and that metamorphosis in lamprey indeed can be regarded a TH-driven process. What makes lamprey metamorphosis unique is that very high TH levels in premetamorphic larvae are important to promote initial larval growth and lipid accumulation in favor of differentiation. The provocative model put forward by the authors stimulates a plenty of new questions for future studies on lamprey metamorphosis.

Because of their phylogenetic position at the base of vertebrate evolution, lampreys also represent an exciting model to study the evolution of neuroendocrine control mechanisms of thyroid activity. Since a hypothalamic-pituitary system is only present in vertebrates, lamprey studies are essential to understand the origins of the neuroendocrine regulation of endocrine glands in vertebrates. In their review, Sower and Hausken (2017) point out that the lamprey system, as far as one can tell based on available data, represents a primitive but functional neuroendocrine regulatory circuit involving crosstalk signaling of gonadal and thyroidal axes. In contrast to gnathostomes, lampreys have only two glycoprotein hormones (one of which is thyrostimulin), lack a vertebrate-type thyroid-stimulating hormone (TSH), and the glycoprotein hormone receptor repertoire is also reduced as only two receptors are found in lampreys. One should stay tuned to see what future studies can reveal about the regulatory function of these glycoprotein hormones and their receptors for thyroid activity during lamprey metamorphosis.

Apart from evolutionary considerations, another beauty of the comparative approach lies in the fact that there are plentiful model systems available, each of them offering specific advantages to address certain problems in endocrinology. For this Special Issue, Zada et al. (2017) review the specific advantages of the zebrafish system for studies on the cellular transport mechanisms of TH. In contrast to the intrauterine development of mammalian embryo, the transparent zebrafish embryos and larvae develop externally and transgenic zebrafish expressing fluorescent reporters offer unique opportunities for monitoring the impact of disturbed TH transport on development in live animals. As a small and genetically tractable animal model, zebrafish allows the conduct of pharmaceutical screens and reverse genetic screens to identify new regulators of local TH actions and drugs for therapeutic strategies to tackle human thyroid diseases.

The review by Vancamp and Darras (2017) introduces the reader to the chick embryo as an excellent non-mammalian model for studies on the role of TH during early developmental processes. Chick embryos share with zebrafish the external development that prevents maternal compensatory mechanisms upon experimental manipulation of the thyroid status in the developing embryo. This can be an important advantage particularly when studying the role of TH transporters and deiodinases in local control of TH action during early brain development, a research field on which chick embryos proved a powerful system.

The metabolism of 3,3′,5-triiodothyronine (T3) and thyroxine (T4) generates several iodothyronine derivatives with often still poorly characterized biological activities in mammals. The review by Orozco et al. (2017) highlights the value of non-mammalian model organisms to uncover potent endocrine activities of naturally occurring iodothyronine derivatives such as 3,3',5-triiodothyroacetic acid (TRIAC) and 3,5-diiodothyronine (3,5-T2). TRIAC, for example, has recently been identified as the biologically active ligand of the TR in amphioxus larvae and might represent an ancestral TH in non-vertebrates (Paris et al., 2008). 3,5-T2 is a product of outer-ring deiodination of T3 and recent studies indicate that its role as a physiologically relevant TR ligand might be particularly prominent in teleost fish. This is because 3,5-T2 can function as a potent activator of a teleost-specific long TRβ1 variant that has not yet been detected in tetrapod TRβ sequences.

The contribution by McLean et al. (2017) deals with another layer of complexity in evolution of the thyroid system, namely the finely tuned regulation of the bioavailability of TH metabolites to their cellular target sites in various species. The highly hydrophobic nature of iodothyronines requires an efficient distribution system of TH in order to prevent their accumulation in cellular membranes. The authors compare the evolutionary rates of the various TH distributor proteins, including albumin, transthyretin and thyroxine-binding globulin, and emphasize that transthyretin is not only highly conserved across vertebrates but is also the only TH distributor proteins synthetized in the brain and secreted into the cerebrospinal fluid.

Two other papers take the comparative perspective on TH signaling even further by providing very inspiring analyses of the evolution of TH signaling in metazoans. The reviews by Holzer et al. (2017) and by Taylor and Heyland (2017) rightfully claim that improved mechanistic insights in iodothyronine signaling in invertebrates will be vital to understand the origins and the evolution of the complex thyroid system present in vertebrates. While there is ample evidence that classical TH like T4 and T3 can influence developmental processes in different invertebrate organisms, many key questions remain unanswered. What is the source of iodothyronines in invertebrate species lacking a thyroid-like tissue with known capacity to synthesize TH? What is the function of invertebrate TR orthologues that cannot be activated by classical TH and their derivatives? Are there other iodothyronine derivatives with yet unknown biological activities in invertebrates? Although the two papers discuss similar data sets and consequently ask related questions, the two groups address the aforementioned questions from different perspectives making the reading of both papers a very fruitful experience for any reader. Taylor and Heyland, for example, align their discussion of TH signaling in protostome and deuterostome invertebrates along the question whether ancestral ways of iodothyronine signaling might have been mediated mainly via non-genomic modes of action. Holzer et al., in turn, raise the interesting point that our view of T3 as the major biologically active iodothyronine might be biased by vertebrate studies whereas a variety of non-classical TH related compounds (i.e., TRIAC) can have significant biological activity in non-vertebrate animals.

One of the most exciting advances in the field of TH-regulated tissue differentiation and organ development is the demonstration that stem and progenitor cell populations are critical targets of TH signaling. Given the knowledge that TH have pleiotropic effects on