# Thyroid Hormone Signaling in Oligodendrocytes: from Extracellular Transport to Intracellular Signal

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**Abstract** Thyroid hormone plays an important role in central nervous system (CNS) development, including the myelination of variable axonal calibers. It is well-established that thyroid hormone is required for the terminal differentiation of oligodendrocyte precursor cells (OPCs) into myelinating oligodendrocytes by inducing rapid cell-cycle arrest and constant transcription of pro-differentiation genes. This is well supported by the hypomyelinating phenotypes exhibited by patients with congenital hypothyroidism, cretinism. During development, myelinating oligodendrocytes only appear after the formation of neural circuits, indicating that the timing of oligodendrocyte differentiation is important. Since fetal and post-natal serum thyroid hormone levels peak at the stage of active myelination, it is suspected that the timing of oligodendrocyte development is finely controlled by thyroid hormone. The essential machinery for thyroid hormone signaling such as deiodinase activity (utilized by cells to auto-regulate the level of thyroid hormone), and nuclear thyroid hormone receptors (for gene transcription) are expressed on oligodendrocytes. In this review, we discuss the known and potential thyroid hormone signaling pathways that may regulate oligodendrocyte development and CNS myelination. Moreover, we evaluate the potential of targeting thyroid hormone signaling for white matter injury or disease.

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## Introduction

Thyroid hormone (TH) regulates neural development, differentiation, and metabolism in mammals [1, 2]. The importance of TH in regulating brain development is manifested in humans under conditions of TH deficiency such as untreated congenital hypothyroidism, or profound maternal hypothyroxinemia due to iodine deficiency, clinically presenting as profound mental retardation and growth restriction [3]. THs including prohormone, thyroxine (T4), and relatively minimal circulating amounts of genomically active tri-iodothyronine (T3) are generated from the thyroid gland [1]. Serum TH-binding proteins (such as albumin, T4-binding globulin, and potentially transthyretin) bound to T4, along with free-T3 can be transported into the central nervous system (CNS) via transporters expressed on epithelial cells of the choroid plexus, endothelial cells of the blood–brain barrier (BBB) and astrocytic foot processes that are in contact with microvessels. This transport mainly occurs through the monocarboxylate transporter (MCT)8 and organic anion-transporting polypeptide 1c1 (OATP1C1) [4]. A low level of T3 in the brain can be compensated by intracellular deiodination of T4 to produce T3 by type 2 deiodinase (Dio2). On the other hand, in a case of cellular hyperthyroidism, type 3 deiodinase (Dio3) deiodinize THs into genomically inactive forms; T4 to reverse T3 and T3 to di-iodothyronine (T2) [1].

One of the well-studied effects of TH during CNS development is myelination, which is a highly organized process of axon ensheathment by oligodendrocytes to establish fast saltatory conduction via both, facilitation of electrical capacitance (myelin sheath) and molecular clustering of sodium channels at the node of Ranvier and potassium channels at the juxtaparanode (for review, see [5]). It is widely accepted that TH plays a crucial role in oligodendrocyte development and subsequently myelination. Adding T3 in vitro has been widely utilized to potentiate terminal differentiation of both rodent and human oligodendrocytes

through rapid cell-cycle arrest in a non-genomic manner and transcription of genes involved in their development upon binding to nuclear TH receptors in a genomic manner [6–9] (Fig. 1). Furthermore, recent data suggest that TH is also involved in regulating early specification of neural precursors to derive oligodendroglial lineage cells, indicating the involvement of TH throughout oligodendrogenesis along with time-dependent specification of oligodendrocyte developmental checkpoints. Importantly, TH is also suspected to be a key player in the context of white matter pathologies, affecting not only oligodendrogenesis in a cell-autonomous manner but also eliciting indirect effects to regulate the metabolism of oligodendrocytes via promoting angiogenesis under hypoxic conditions critical for the maintenance of viable oligodendrocytes [10, 11]. In this review, we discuss how TH regulates oligodendrocyte development and physiology from the extracellular transport to intracellular signaling from both a genomic and potentially non-genomic manner.

## Thyroid Hormone Signaling in Oligodendrocytes

(i)  Extracellular thyroid hormone transport

The cellular transport of THs has long been considered to be mediated by a simple diffusion process across membrane lipid bilayers because of their lipophilic properties. However, the recent discovery of a specific TH transporter, MCT8,

suggests that the cellular transport of THs is indeed a physiologically relevant process. So far, MCT8, MCT10, large neutral amino acid transporters (LATs), organic anion-transporting polypeptides (OATPs), and the Na$^+$/taurocholate co-transporting polypeptide (NTCP) protein families were identified to have the capacity to transport THs (for review, see [4]). However, it is MCT8 that has been suggested to be the most specific TH transporter [12], since the others also transport alternate physiological molecules such as amino acids and steroids [4]. In support of this, human mutations of SLC16A2 (encoding MCT8) exhibit severe X-linked inherited psychomotor retardation known as Allan-Herndon-Dudley syndrome (AHDS), which present clinically with increased serum T3 and either normal to reduced T4 levels in the circulation of affected patients [13, 14].

Although THs are trophic during oligodendrocyte development, the import/export of THs in these cells has not been defined. However, indirect evidence implicates MCT8 in oligodendrocyte plasma membrane transport since AHDS patients exhibit delayed myelination measured by longitudinal T2-weighted magnetic resonance imaging (MRI) [15–18]. To study the exact pathophysiological role of MCT8, the slc16a2 knockout mouse was generated [19]. However, despite the matching serum with those of AHDS patients, as well as the altered brain TH profiles (high T3 and low T4 in the circulation/low T3 and low T4 in the brain), no discernable neurological phenotypes were demonstrated in these mutant mice [19]. This species variation in the dependency of the
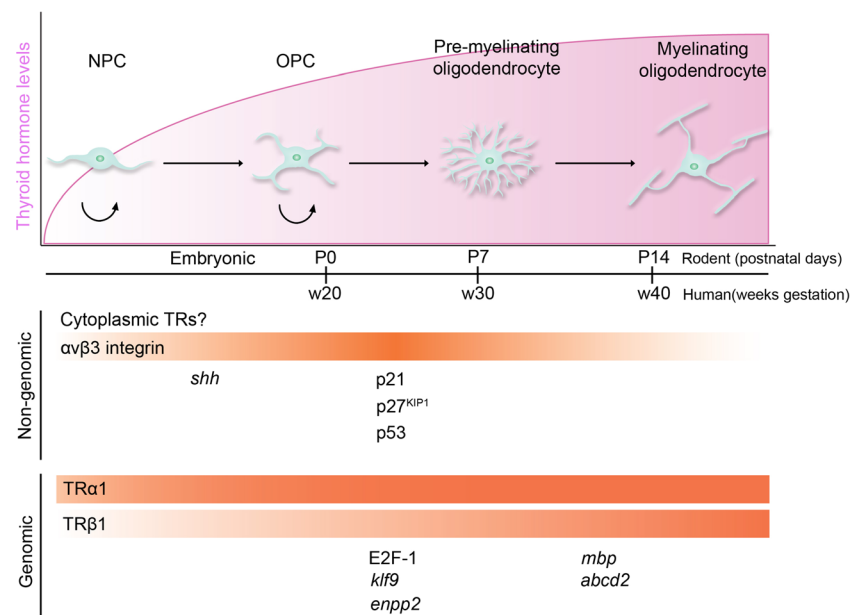


Fig. 1 Non-genomically and genomically regulated genes by thyroid hormone during oligodendrocyte development. The schematic shows elevation of brain thyroid hormone (TH) levels during oligodendrocyte differentiation. Developmental regulation of oligodendrocyte-associated genes by TH in a non-genomic and genomic expression pattern at different stages of lineage progression. Non-genomic TH signaling is thought to be mediated through putative cytoplasmic thyroid hormone receptor (TR), or αvβ3 integrin dimer, which is tightly regulated to be expressed in pre-myelinating oligodendrocytes. Genomic thyroid hormone signaling is mediated through nucleus TRα1 (expressed throughout oligodendrocyte development) and TRβ1 (increases in expression as oligodendrocytes differentiate)

*slc16a2* gene suggests that other transporters may indeed compensate for its loss in the knockout mice. Indeed, OATP1C1 enriched in the mouse choroid plexus but not in human [20, 21] was suggested to function in response to MCT8 deficiency facilitating the passage of T4 from the circulation into the brain. This hypothesis was confirmed once prominent neurological phenotypes, including hypomyelination, were detected in the *slc16a2/slco1c1* (the latter encodes OATP1C1) double knockout mice [22]. Interestingly, it has been shown that zebrafish lacking *slc16a2* exhibit similar neurological deficits that resemble the locomotor developmental abnormalities seen in AHDS patients [23]. Molecular analyses revealed significant reductions in myelin basic protein (*mbp*) and myelin protein zero (*mpz*; a critical gene for oligodendrocyte differentiation in zebrafish [24]) genes in this mutant, indicating that in humans and zebrafish, there exists no compensational expression of OATP1C1 in the brain oligodendrocyte development [23]. However, it is unclear whether the neurodevelopmental defects are caused by the dysregulation of MCT8-dependent TH transport at the BBB or at the CNS-specific cells. Therefore, it remains to be confirmed whether the cellular MCT8 of CNS-residing cells, including oligodendrocytes, is responsible for regulating their development. To address this question, a conditional deletion strategy must now be adopted to dissect out the direct role of MCT8 during oligodendrocyte development in vivo.

A recent study has identified that a reduction in the expression of MCT8 in the ventricular zone and sub-ventricular zone (SVZ) cells is observed in post-mortem brains from human fetuses with intra-uterine growth restriction (IUGR) [25]. IUGR is a condition of complicated growth potential most commonly due to the lack of energy supply from uteroplacental failure leading to congenital white matter pathology related to periventricular leukomalacia ultimately causing cerebral palsy (for review, see [26] and hypoxic condition and cytokines have been linked to dysregulation of TH signaling (see 'Thyroid Hormone as a Treatment for Demyelinating Disease'). This is not surprising as myelination and oligodendrocyte differentiation requires high metabolic support such as oxygen, glucose, and THs from the preformed vasculature (for review, see [27]). Furthermore, both guinea pig [28] and rat [29] models of IUGR were shown to exhibit delayed myelination as shown in children with prenatal brain injury [30]. One interpretation of these data could be that the reduction in MCT8 in the germinal zone-derived cells may be limiting the potential to derive appropriate numbers of oligodendroglial lineage cells, thereby stalling or delaying the development of these glial cells and by extension myelinogenesis under IUGR conditions. Moreover, we have recently identified MCT8 expression in oligodendroglial cells derived from human embryonic stem cells that plays an active role in their derivation [31], implicating an important role of MCT8 during oligodendrogenesis (Fig. 2). However, a more

sophisticated model of in vivo cell-specific conditional deletion of MCT8 is now required to differentiate the importance of MCT8 during oligodendrogenesis during development and disease. Such models may help identify the how MCT8 downregulation or ablation can modulate the maturation of oligodendrocytes and what effect the BBB plays in this process.

One of the most widely studied genes transcribed under hypoxic conditions is hypoxia-inducible factors (HIFs). Interestingly, a recent report has identified that the persistent stabilization of HIF1/2α in OPCs through Cre-mediated ablation of von Hippel Lindau (VHL; degrades HIF1/2α under normoxia) in Sox10+, Olig1+, or PLP+ oligodendroglia inhibits their differentiation through autocrine activation of Wnt7α/7β [11]. However, the same group also reported that the conditional ablation of HIF1/2α in the abovementioned oligodendroglial cells resulted in reduced angiogenesis, a consequence of reduced paracrine release of Wnt7α/7β (shown to be essential in CNS angiogenesis [32, 33]), leading to axonal injury in the corpus callosum [11].

As HIF1α was also shown to associate with Dio3 to reduce TH signaling, at least in SK-N-AS neuroblastomas under hypoxia [34], it is speculated that under hypoxia-associated developmental injury conditions (such as IUGR-mediated white matter disorders and neonatal brain injuries), reduced MCT8 expression and the active HIF1α in SVZ-derived neural precursors, may reduce TH signaling leading to oligodendrogliopathy and subsequently delayed myelination (Fig. 3). In fact, in humans, post-mortem brain sections of preterm infants show intra-ventricular hemorrhage (IVH) as sequelae associated with increased Dio3 and reduced Dio2 expression within the germinal zone [35].

Impaired TH signaling is also suspected in adult acquired diseases with demyelination such as multiple sclerosis (MS). Largely, MS can be sub-divided into two forms, acute (relapsing-remitting) and chronic (progressive). Remyelination upon demyelination can occur and is largely responsible for partial recovery of neurological deficits in relapsing-remitting MS whereas this largely fails in progressive MS [36]. In experimental autoimmune encephalomyelitis (EAE)-induced Dark Agouti rats by immunization with recombinant myelin oligodendrocyte glycoprotein, hypoxia was a definitive finding, measured from both in vivo oxygen-sensitive probe and the tissue expression of HIF1α within the inflamed spinal cords, which indeed correlated with neurological deficits [37]. This induction of HIF1α was further ratified through the findings of enlarged microvasculature within the inflamed spinal cords [37]. One plausible hypothesis is that neuroinflammation-driven hypoxia can mediate the induction of HIF1α in oligodendroglial cells, thereby inhibiting their differentiation in autocrine manner via persistent Wnt signaling and local hypothyroidism [11]. Furthermore, increasing evidence suggest for proinflammatory cytokine-driven hypothyroidism (see 'Thyroid
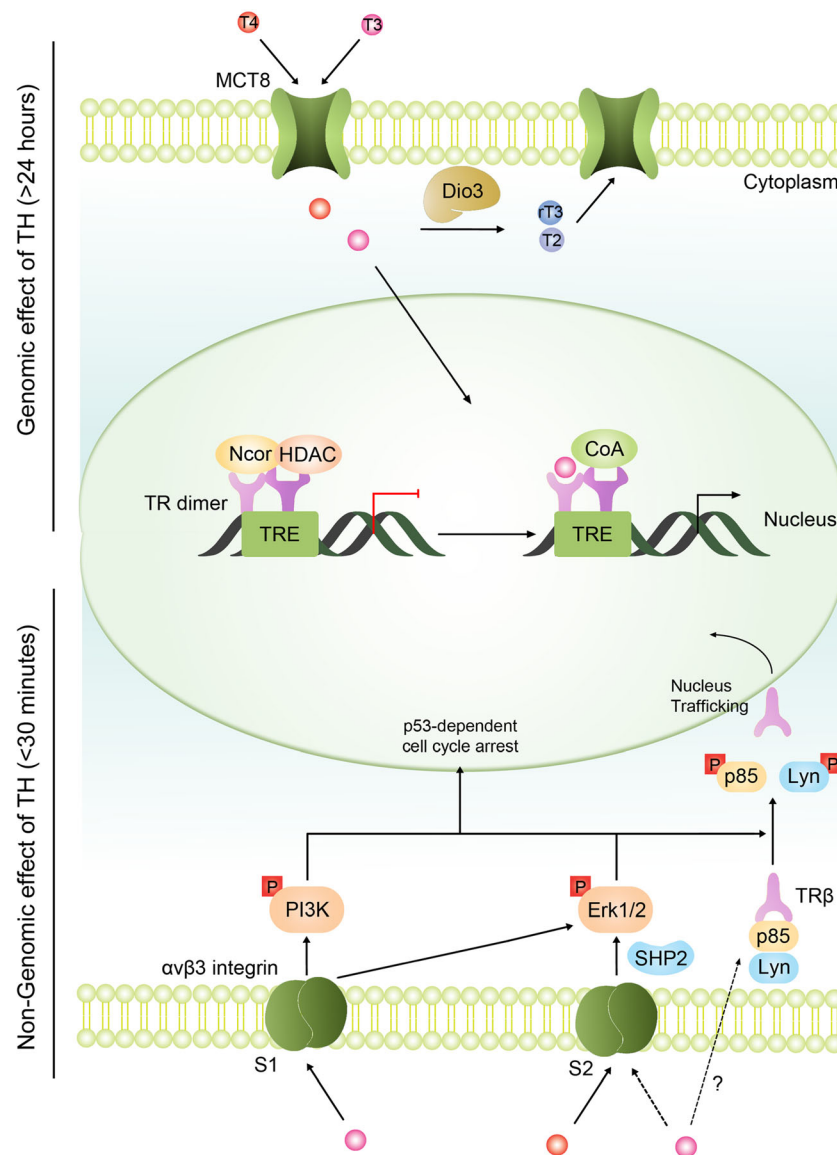
**Fig. 2** Non-genomic and genomic action of thyroid hormone in oligodendrocytes. Genomic effects of TH: oligodendroglial monocarboxylate transporter 8 (*MCT8*) may transport T4 and T3 into the cytoplasm where either can be deiodinized into genomically inactive rT3 and T2 or bind to the nuclear TR dimeric complex. Un-liganded TRs can recruit the nucleus co-repressor (*Ncor*) to repress transcription of genes within the TH response element (*TRE*). T3 binding of TRs can recruit co-activator (*CoA*) to regulate TRE-associated genes. Non-genomic effects of TH: THs may signal in a non-genomic manner either via binding to αvβ3 integrin dimeric receptor or cytoplasmic TRβ. Only T3 binds to the S1 site of αvβ3 integrin, and this can phosphorylate and activate phosphatidylinositol 3-kinase (*PI3K*) and extracellular signal-regulated kinase 1/2 (*Erk1/2*). Whereas T4 and to a lesser extent T3 binds to the S2 site of αvβ3 integrin and this can phosphorylate and activate Erk1/2 via Src-homology 2 domain containing tyrosine phosphatase (*SHP2*). Phosphorylated PI3K and Erk1/2 may potentiate the phosphorylation of p85 domain of PI3K and Lyn to dissociate cytoplasmic TRβ, which mediates nucleus trafficking of TRβ for genomic signaling. Activated PI3K and Erk1/2 can also induce p53-dependent cell-cycle arrest

Hormone as a Treatment for Demyelinating Disease'), indicating local CNS hypothyroidism driven by multiple factors (Fig. 3).

(ii)    Deiodination of thyroid hormone

Intracellular level of THs can be controlled by deiodinases (for review, see [38]). The amount of T3 transported into the CNS is relatively less than T4 during fetal development, and therefore, the majority of T3 in the CNS is generated by the activity of cellular Dio2 during fetal development [39]. In hypothyroidism, the activity of Dio2 increases to compensate reduced T3 availability in the brain [40]. On the other hand, in a hyperthyroidism state, the activity of Dio3 increases to convert excess T3 into T2 and prevent further generation of T3 from T4 [41]. Therefore, deiodination is crucial to maintain

**Fig. 3** Putative cellular hypothyroidism in oligodendrocytes during intra-uterine growth restriction (*IUGR*) or inflammation-mediated hypoxia. Under normoxic conditions, internalized T3 binds to nuclear TRs to transcribe pro-differentiation genes, thereby mediating oligodendrocyte differentiation. However, under hypoxic conditions such as IUGR and inflammation, persistent HIF1α transcription induces Dio3 and along with a reduced expression of MCT8, results in cellular hypothyroidism. Furthermore, pro-inflammatory cytokines such as TNF-α, IL-1β, and IFN-γ may contribute to dysregulation of thyroid hormone signaling. Un-liganded TRs may repress pro-differentiation genes thereby resulting in stalled oligodendrocyte maturation
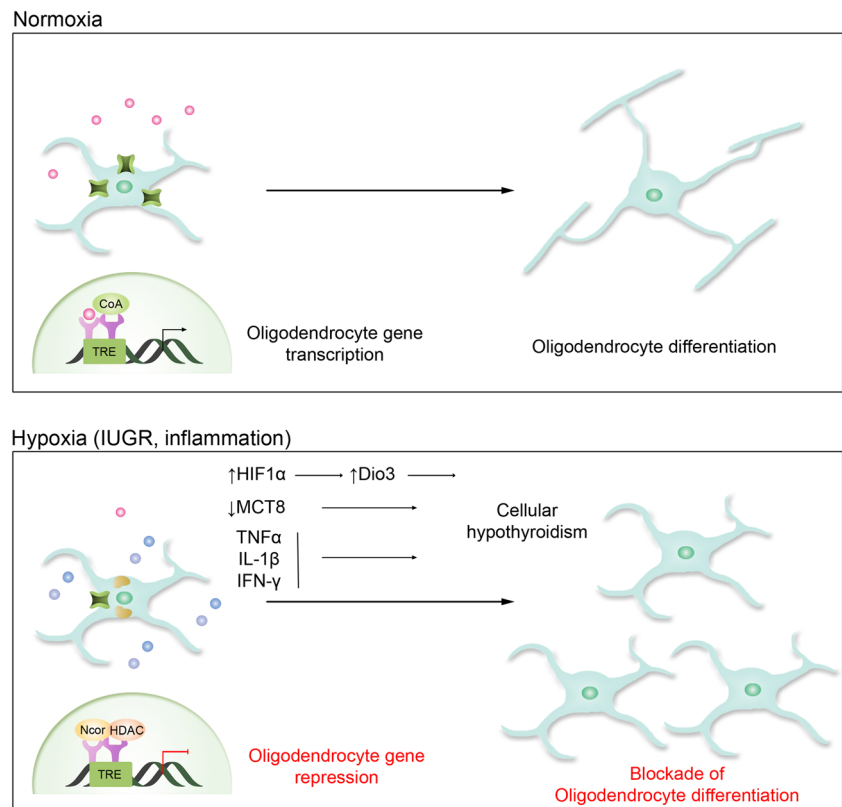


the level of T3. However, one should note that this theory is solely based on genomic effects of T3. It is largely unknown whether deiodinases are also involved in regulation of non-genomic effects of TH.

It has been assumed that Dio2 activity in glial cells including astrocytes or tanycytes is a major source of T3 for neurons or oligodendrocytes [42]. This hypothesis is supported by localized messenger RNA (mRNA) expression of *dio2* in astroglia and *dio3* in neurons [43–45]. Similarly, it is plausible to suggest that oligodendrocytes may receive T3 from astrocytic foot processes as localized expression of Dio3 but not Dio2 has been reported in Olig2-positive oligodendroglia in the human embryonic germinal matrix [35]. However, which transporter regulates the astrocyte-neuron or astrocyte-oligodendrocyte transfer of T3 remains undefined.

(iii)   Intracellular thyroid hormone signaling

**Role of Co-repressors**

The un-liganded TH receptors (TRs) may act as a repressor for T3-responsive genes [46]. In fact, the co-repressors for T3 signaling such as the nuclear receptor co-repressor (Ncor), and silencing mediator of retinoic acid and TH receptors (Smrt), are all essential regulators of embryonic brain development, exerting their effect by repressing genes that are

involved in neural lineage specification [47, 48]. As T3 signaling is important in oligodendrocyte development, it is suspected that in hypothyroidism, un-liganded TRs in oligodendrocytes may recruit Ncor to repress genes that are involved in oligodendrocyte differentiation. A recent microarray analysis revealed that in cortical embryonic neural stem cell (NSC) cultures from *ncor*$^{-/-}$ not *smrt*$^{-/-}$ mice, significant up-regulation of *mbp*, *plp* (encoding proteolipid protein), and *nkx2.2* were achieved without altering neuronal genes [49]. As Ncor was shown to enhance deacetylase activity of class I histone deacetylases (HDACs) including HDAC1, HDAC2, HDAC3, and HDAC8 [50], neural stem cells without *ncor* may have reduced the activity of class I HDAC. Indeed, small interfering RNA (siRNA)-mediated knockdown of *hdac2* but not *hdac3* in the presence of T3, increased mRNA levels of *mbp* and *plp* in rat cortical embryonic NSC cultures, the immortalized oligodendrocyte cell line, CG4, and cultures consisting of embryonic oligodendrocytes and neurons, Oli-Neu [49]. Interestingly, this increase in myelin genes by *hdac2* knockdown and T3 treatment was greater than T3 treatment alone and *hdac2* knockdown without T3 treatment did not show any up-regulation in these genes [49]. Further studies revealed that HDAC2 was enriched in the U2 enhancer region of an important oligodendroglial gene Sox10, by chromatin immunoprecipitation (ChiP) analysis [49]. This is somewhat in line with previous data which shows histone acetyltransferase activity is required for oligodendrocyte differentiation

[51]. Paradoxically, by using Cre-loxP conditional knockout mice of *hdac1* and *hdac2* in Olig1+ oligodendroglia, the activity of HDAC1/2 was shown to indirectly promote oligodendrocyte differentiation by competing with β-catenin for the transcription of T cell factor (TCF7L2/TCF4; oligodendrocyte-restricted transcription factor) [52]. Although these contradicting results require clear verification with regard to HDAC activity in oligodendrocytes, it seems that in the absence of T3, Ncor negatively regulates early oligodendrocyte differentiation from NSC via HDAC activity.

The co-repressors for T3 signaling not only regulate T3-target gene expression during embryonic development but also exert similar effects in adulthood as experimental induction of hypothyroidism in adult mice resulted in a reduction of mitotic cells and increased the number of cells in interphase G2, in the SVZ [53, 54]. A subsequent mechanistic study revealed that the T3-bound TRα1 expressed on type C DLX2+ transient amplifying cells directly represses Sox2, a gene involved in maintenance of neural stem cells, to promote neurogenesis [53]. However, whether TH signaling plays a similar role during adult OPC development as identified for adult NPCs remains unanswered.

## Nuclear Thyroid Hormone Receptors

The genomic effects of THs are mediated by nuclear TRs, which have high affinity for T3 binding. Liganded (T3-bound)-TRs can act as transcription factors by binding to specific TH response elements (TREs) to either activate or repress gene transcriptions. Without T3, un-liganded TRs in the nucleus can repress TH-responsive gene transcription by recruiting co-repressors. Therefore, this balance between co-activators (CoA) and co-repressors associated with TH signaling is dependent on the concentration of T3.

It is well documented that TRα and TRβ are expressed on oligodendrocytes, both in vitro and in vivo [55, 56] and play an important role in their differentiation by gene transcription upon binding to T3 [57, 58]. Early studies revealed that the TRα gene is expressed from early oligodendrocyte development (OPC); whereas, TRβ1 is expressed from later developmental stages of oligodendrocytes (pre-oligodendrocytes), for review, see [59] (Fig. 1). Importantly, during T3-induced oligodendrocyte differentiation, increased expression of TRβ1 not TRα1 in vitro occurs [60, 61]. In support of this, during post-natal rat brain development, the number of oligodendrocytes expressing TRβ1 increases from P0 to P40 when differentiation of oligodendrocytes and myelination occurs [62, 63]. On the other hand, OPCs lacking *thra1* (encodes TRα1) failed to differentiate upon TH treatment and *thra1*$^{-/-}$ mice showed reduced number of oligodendrocytes in optic nerves at post-natal days 7 and 14 [58]. These results indicate the importance of TRα1 in initial cell-cycle exit upon T3 binding and TRβ1

in driving their terminal differentiation and post-natal myelination.

The TRs are known to function as homodimers [1]. In the optic nerves of 6-month-old mice (a time where OPCs normally disappear from 4 weeks after birth) which lacked all TRβ isoforms showed BrdU+/NG2+ proliferating OPCs whereas these were not found in mice lacking all TRα isoforms [64]. Importantly, mice that were ablated for both TRα and TRβ isoforms exhibited more profound persistence of proliferating OPCs in the optic nerves [64], suggesting that both TRα and TRβ are required for T3-induced normal oligodendrocyte development. However, these knockout mice did not phenocopy the effect of hypothyroidism that can include hypomyelination, quite possibly because of dampened deleterious effects of un-liganded TRs as a physiological result of knocking out TRs. To overcome this, several TRα1 knock-in germline mutant mice were generated, such as TRα1$^{L400R}$, which targeted the conversion of the nuclear receptor to the transcription repressor. Indeed, the phenotype of these mutants was very similar to mice with hypothyroidism, including severe hypomyelination (for review, see [65]). In an attempt to reveal whether defects in oligodendrocyte lineage cells in these mutants are indirect or cell-autonomous, *cnp*-Cre (2′,3′-cyclic-nucleotide 3′-phosphodiesterase; thought to target mature oligodendrocytes) and tamoxifen-inducible *pdgfra*-Cre-ER$^{T2}$ (thought to target OPCs) lines were crossed with TRα1$^{L400R}$ floxed mice [66]. However, unexpectedly, these conditional mutant models did not target only oligodendrocytes but also other cell types in the cerebellum (*cnp*-Cre/loxP-TRα1$^{L400R}$: purkinje cells and oligodendrocytes; *pdgfra*-Cre/loxP-TRα1$^{L400R}$: granular neurons, purkinje cells, GABAergic inter-neurons, oligodendrocytes and astrocytes), confounding data interpretation [66]. However, what seems clear from these mutants was that TRα1 indirectly affects cerebellar oligodendrocyte development as these conditional transgenics, along with *sycp1* (synaptonemal complex protein 1, targets all cerebellar cells)-Cre/loxP-TRα1$^{L400R}$ and *ptf1a* (pancreas transcription factor 1a, targets purkinje cells and GABAergic inter-neurons)-Cre/loxP-TRα1$^{L400R}$ mice, exhibited increased numbers of Olig2+ oligodendroglia in the cerebellar white matter at P15 but not in P21, when compared with wild-type controls [66]. However, to reveal whether TRα1 is directly involved in oligodendrocyte development in a cell-autonomous manner, an oligodendrocyte-specific Cre line such as *sox10* (expressed throughout the whole oligodendrocyte lineage cells)-Cre may indeed be a more valuable model to uncover the importance of this TR's influence throughout the entire period of oligodendrogenesis. Furthermore, without conditional deletion of *thrb1* in oligodendroglial cells, the direct role of TRβ1 on oligodendrocyte development in vivo is not clear. At least, ChiP sequencing in p15 mouse cerebellum using TRβ antibody revealed oligodendrocyte-specific gene such as *mbp* and *mag* [67].

However, it remains to be determined whether these two different isoforms of TRs can regulate common or separate sets of genes during oligodendrocyte development. Although ChiP sequencing of TRα- and TRβ-bound gene promoters in oligodendrocytes may answer these questions, this approach is complicated by the sequence variety of TREs and known non-specificity of commercially available TR antibodies [68]. Strategies such as molecularly tagging TRs with fluorescent reporter such as green fluorescent protein (GFP) [68] or Flag may be useful to identify the TR target genes.

The TRs are known to form heterodimers with other nuclear receptor superfamilies, namely the vitamin D3 receptor [69], the peroxisome proliferator-activated receptor PPARδ [59], and the retinoid X receptor (RXR) [70]. All three of these co-receptors for TRs have been shown to be expressed in oligodendroglial cells [71–73]. Of these co-receptors to TRs, RXR is of significant interest as RXR-TR heterodimerization activity were shown to increase its binding to TRE and induce TR-medicated gene transcription [74]. Furthermore, RXR-TR heterodimer complex can be activated by T3 independently of RXR ligands and even showed synergistic transcriptional activity when both T3 and 9-cis-retinoic acid were applied [75]. RXR has been thought to be particularly important for oligodendrocyte development as RXR signaling was shown to modulate MBP transcript levels in a similar manner to THs [71]. In support of this, Huang et al., recently suggested that RXRγ signaling may play an important role in differentiation of oligodendrocytes and myelination, as siRNA-mediated rxrg (encodes RXRγ) knockdown or RXR-specific antagonists added to rat oligodendrocyte cultures prohibited the formation of the characteristic spider-web-like complex morphology of oligodendrocytes [76]. Moreover, administration of RXR-specific antagonists in co-cultures of dorsal root ganglion neurons with OPCs significantly inhibited myelination. However, the treatment of the RXR agonist, 9-cis-retinoic acids without T3 or T4 showed no changes in oligodendrocyte differentiation or myelination in vitro [76]. In their follow-up study using human embryonic stem cells as a model of oligodendrocyte differentiation, administration of the 9-cis-retinoic acids in the presence of T3 supplied in the differentiation medium significantly increased the yield of MBP+ pre-myelinating oligodendrocytes [77]. These results suggest that retinoic acids probably promote oligodendrocyte differentiation and myelination in concert with THs. It seems that RXR signaling is also important during remyelination (just like TH, see 'Thyroid Hormone as a Treatment for Demyelinating Disease') as intraperitoneal administration of 9-cis-retinoic acids upon lysolecithin-induced focal demyelination in the cerebellar peduncle significantly enhanced remyelination [76].

The TRβ agonist, GC-1 or RXR agonist, along with 9-cis-retinoic acids have all been shown to promote both human and rodent oligodendrocyte differentiation in vitro [76–78].

However, their effects in vivo during development are yet to be investigated robustly. Moreover, no in-depth investigation has been performed to clearly delineate the differences and under what circumstances TRβs homo- or hetero-dimerize with RXRs. Simultaneous induction of both TRβ and RXR during differentiation may be warranted to answer this question.

## Non-genomic Effects of Thyroid Hormones in Oligodendrocytes

There are rapid metabolic changes (within ~1 h) upon treatment of oligodendrocytes with THs that cannot be explained by genomic actions per se [6, 7]. These are called non-genomic effects of THs, which regulate cellular proliferation, development and metabolism via protein phosphorylation and kinase activation [1]. For non-genomic effects to occur, THs are required to bind either the membranous integrin αvβ3 dimeric receptor or cytoplasmic TRs [79, 80]. TH signaling through αvβ3 integrin phosphorylates and activates phosphatidylinositol 3-kinase (PI3K)/Akt and Erk1/2 [81]. The αvβ3 integrin has two binding sites for THs; only T3 binds to the S1 site to activate Src and subsequently PI3K, whereas T4 and to a lesser extent T3, binds to the S2 site, thereby activating Erk1/2. Both of these non-genomic actions of THs were shown to translocate TRs to the nucleus from the cytosol [81]. In the absence of THs, TRβ was shown to form a complex within the cytoplasm with the p85 subunit of PI3K and the Src family tyrosine kinase, Lyn [82]. Upon administration of either T3 or T4, dissociated TRβ from this complex and mediated its nuclear translocation through phosphorylation of PI3K or Erk1/2, respectively [82, 83] (Fig. 2). The activation of these two kinases in oligodendrocytes were well-recognized for their role in CNS myelination without altering the number of oligodendrocytes [84, 85]. Although the direct evidence is lacking for oligodendroglial cells, data exists for a potential role of TH in the regulation of non-genomic signaling.

It has been shown that αvβ3 integrin expression is tightly regulated during oligodendrocyte differentiation where its peak expression is at the transition stage (pre-oligodendrocyte) from O2-A progenitors to post-mitotic oligodendrocytes [86], indicating its role in rapid cell-cycle arrest. Furthermore, as genomic effect of THs during oligodendrocyte development is essential for their differentiation (see 'Regulation of OPC/NPC Differentiation by Thyroid Hormone: Genomic Effect of TH'), it is suspected that TH signaling through αvβ3 integrin in immature oligodendrocytes is an essential step for the accumulation of TRs, especially the β subunit isoform [60] in the nucleus (Fig. 2). Indeed, transfection of human full-length αvβ3 integrin in the CG-4 rat oligodendrocyte cell line showed a reduction of

MBP+ mature oligodendrocytes during their differentiation induced by both T4 and T3 [87]. As αvβ3 integrin is shown to physically interact with PDGFRα, a receptor for the major mitogen involved in oligodendrocyte proliferation, i.e., PDGF-AA [88], replacing this mitogen for THs may induce oligodendrocyte differentiation. In fact, this experimental replacement was previously shown to be important for the transition of proliferating OPCs into post-mitotic oligodendrocytes [89, 90] and widely used in culture experiments for both rodents and human oligodendrocyte differentiation (for review, see [91]). Moreover, T3 administration in primary rat OPCs increased phosphorylation of Erk1/2 and Akt within 30 min [92]. Importantly, an intracellular enzyme, Src-homology 2 domain containing tyrosine phosphatase (SHP2) was shown to be involved in this signal, as lentivirus-mediated knockdown of *ptpn11* (encodes SHP2) reduced the phosphorylation of Erk1/2 and reduced MBP+ cells under T3-induced differentiation conditions, whereas overexpression of SHP2 increased phosphorylation of Erk1/2 [92]. In addition, Cre-loxP-mediated deletion of SHP2 in Olig2+ oligodendroglial lineage cells in vivo resulted in reduced OPC generation in the embryonic telencephalon and subsequently reduced myelination in the corpus callosum [93]. The phosphorylation of Erk1/2 was reduced in the ventricular zone of these animals. Gain of function mutation of SHP2 in Olig2+ cells increased OPC numbers in the corpus callosum however, resulted in abnormal myelination measured by electron microscopy [93]. Molecular studies revealed an increase of phosphorylation of Erk1/2 in the ventricular zone but not Akt in these animals [93]. These results indicate that T3 binding to the S2 site of αvβ3 integrin and possibly through SHP2, activates the Erk1/2 pathway to translocate TRβ from the cytoplasm to the nucleus for T3-induced gene transcription. However, as major substrates for αvβ3 integrin are extracellular matrix proteins such as vitronectin and fibronectin, it is difficult to interpret the exact role of αvβ3 integrin-dependent TH signaling and more analytical experiments are warranted.

One of the events that are regulated by fast non-genomic actions of THs relates to the role played by TH to regulate the cell cycle. It has been shown that cyclin D kinase inhibitors (CdkI) that are involved in cell-cycle arrest such as p21 and p27 was found to be up-regulated within an hour post-T3 treatment in purified OPCs pre-treated with a protein synthesis inhibitor (to detect the immediate response) derived from P7 rat optic nerves [6]. Further studies revealed that the T3-induced up-regulation of CdkIs are p53-dependent as transduction of OPCs with retrovirus encoding a dominant-negative form of p53 resulted in a significantly reduced appearance of GalC+ mature oligodendrocytes even in the presence of T3 [7]. These results indicate that T3 can induce p53-dependent cell-cycle arrest in OPCs primarily through a non-genomic manner to promote their differentiation. However, it is yet to be determined whether this event is mediated by

integrins or cytoplasmic TRs. Pre-treating the OPCs with both a protein synthesis inhibitor such as cycloheximide and integrin αvβ3 antagonists such as tetraiodothyroacetic acid (tetrac) [94], or Arg-Gly-Asp (RGD) peptide [95], may reveal the mechanism of this non-genomic action further.

One of the strong morphogens that may regulate early oligodendrocyte specification is Sonic hedgehog (Shh), a developmentally regulated protein that plays a significant role in initial patterning and specification of both neurons and oligodendrocytes. In the developing forebrain, Shh is required for the maintenance of Nkx2.1+ medial ganglionic eminence progenitors for the production of both inter-neurons and oligodendrocytes. Similarly, Shh is important for the specification of the cells of the ventral neural tube to motor neurons and oligodendrocytes within the spinal cord, (for review, see [96]). TH-induced regulation of Shh-dependent signaling was proposed, since the *shh* gene expression was observed to be significantly reduced during the development of the rat cerebellum under hypothyroid conditions [97, 98]. At least in neuronal cell culture, acute treatment of T3 induced a rapid increase in histone acetylation within the *shh* gene promoter [98]. Intriguingly, at least in neuroblastoma and glioblastoma cultures, Shh signaling has been suggested to modulate thyroid hormone signaling by regulating the activity of Dio3 [99]. Therefore, although it requires validation, it seems that in early CNS development, T3 may rapidly induce *shh* transcription to promote oligodendrogenesis, then to prohibit precocious differentiation of these newly generated oligodendrocytes, via Shh-dependent induction of Dio3 to mediate local hypothyroidism.

## Regulation of OPC/NPC Proliferation by Thyroid Hormone

TH can also act on both young and adult NPCs to regulate their proliferation. Experimental models of hypothyroidism in adult rat induced by thyrotoxicant, propyl-thio-uracil (PTU) demonstrated that there is an increase in Ki-67+ and BrdU+ proliferating cells in the SVZ and olfactory bulb [100]. This result was correlated with reductions in mRNA levels of *pdgfra* and *mbp* in the optic nerve along with an observed reduction in MBP protein levels [100]. The same group also reported that upon T4 treatment following hypothyroidism, they observed a reduced proliferation of germinal cells within the SVZ and olfactory bulb [100]. Furthermore, ChiP assays upon acute T3 administration in both early embryonic and adult rat, indicated that there is an increase in histone acetylation at the *shh* promoter [101] in the forebrain of these animals acutely treated with T3 [98]. These data suggest a role for TH in the regulation of OPC proliferation within the germinal matrix.

In addition to the effects of TH regulating OPC proliferation, the TH can promote differentiation of these cells. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) studies showed that delayed myelination is a common feature of children with congenital hypothyroidism [102–104]. This hypothyroidism-related phenotype was shown to be reversed by T4 treatment [104]. This finding was then translated to oligodendrocyte culture where it can be used in vitro for OPCs to exit the cell cycle and differentiate [105]. One plausible explanation for T3 as an intrinsic timer for oligodendrocyte development would be that it may act to reduce mRNA and protein levels of E2F-1, which is a key transcription factor controlling G1 to S phase transition during T3-induced differentiation of OPCs [106]. Furthermore, the binding of T3 to its nuclear receptor can promote the myelination phenotype of oligodendroglial cells through its direct interaction with the promoter region of MBP [8]. Therefore, these results indicate that TH can exert cell-cycle exit in mitotic OPCs to control their differentiation in a timely manner.

## Regulation of OPC/NPC Differentiation by Thyroid Hormone: Genomic Effect of TH

As discussed above, TH can directly (cell-autonomous) or indirectly regulate oligodendrocyte differentiation. In the following section, we discuss the cell-autonomous regulation of oligodendrocyte differentiation by oligodendrocyte-specific gene/TRE complexes activated by T3-bound TRs (Figs. 1 and 2).

### Myelin Genes

As hypothyroidism leads to hypomyelination in the CNS, it is not surprising that T3 regulates myelin genes. In fact, gene expression studies have revealed that crucial myelin genes such as *mbp*, *plp*, myelin-associated glycoprotein (*mag*), and *cnp* were reduced in rodent brains upon thyrotoxicant-induced congenital hypothyroidism [107–109]. In early studies using electrophoretic mobility shift assays, in the presence of T3, both TRα and TRβ were found to bind specifically to the promoter region of the *mbp* gene within the TREs [8, 110]. Of interest, the subsequent study by the same group found that MBP-TRE complex preferentially binds to TRβ when compared with TRα [110]. As oligodendroglial expression of TRβ was found to be increased during their terminal differentiation (see 'Nuclear Thyroid Hormone Receptors'), TRβ not TRα seems to be involved in transcription of genes that are involved in maturation of oligodendrocytes.

### KLF9

Kruppel-like factor 9 (KLF9) has been implicated as an important member of the zinc finger family of transcription factors regulating the CNS development (for review, see [111]). Importantly, KLF9 is shown to be strongly induced upon T3 treatment under both in vitro and in vivo conditions [112, 113]. Furthermore, ChiP assays have revealed the presence of KLF9 within the TREs and the interaction with TRβ1 [114]. Therefore, it seems that T3-bound TRβ1 may potentiate transcription of KLF9 during CNS development. A recent microarray-based whole genome analysis revealed that KLF9 was strongly induced by T3 treatment in purified OPCs derived from P7 rat brains, indicating its role in oligodendrocyte differentiation [9]. In support of this, siRNA-based knockdown of *klf9* in OPCs repressed oligodendrocyte differentiation even in the presence of T3 [9]. However, despite its potential role in driving oligodendrocyte differentiation in vitro, developmental myelination was not altered in the corpus callosum, cortical white matter, and optic nerves of *klf9*^{−/−} mice. Whereas, delayed remyelination upon cuprizone-mediated demyelination was found in the same mutants [9]. As KLF9 is expressed ubiquitously in the CNS especially in neurons, as well as reported to play a crucial role in neurite outgrowth inhibition and axonal regeneration of both retinal ganglion cells and Purkinje cells [115, 116], oligodendrocyte-specific knock-out models are now required to clearly delineate the role of KLF9 in oligodendrocyte differentiation. However, from these data, it is plausible to suggest that during CNS development, T3 signaling may halt the overgrowth of axons upon establishment of neuritic synapses and thereby promote oligodendrocyte differentiation via the transcriptional activities of KLF9 within both cell types.

### Enpp2, Autotaxin

Ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), also known as autotaxin has been defined as one of the T3-induced transcriptional targets [99, 117, 118] in neural cells. During development, autotaxin has been shown to be expressed on cells that reside within the choroid plexus and also within parenchymal oligodendroglial cells. The oligodendroglial expression of autotaxin in particular, has been correlated with the period of active myelination (post-natal day 8 in rat) [119, 120], where serum T3 levels are at their peak [63]. Autotaxin is an extracellular factor, which has been shown to promote the adhesion and complex network formation of pre-myelinating oligodendrocytes [120, 121]. In purified OPCs derived from the P2 rat brain, upon T3 treatment, autotaxin was found to be up-

regulated, suggesting that *enpp2* may be a T3-responsive gene in oligodendrocytes [122]. However, whether T3 can induce the transcription of *enpp2* in oligodendrocytes during active myelination remains unanswered.

## Abcd2

The *abcd1* gene encodes for the adenosine triphosphate (ATP)-binding cassette transporter superfamily D member 1, also known as adrenoleukodystrophy protein (ALDP) [123]. ALDP is responsible for the import of very long chain fatty acids (VLCFA) into peroxisomes marked for degradation through β-oxidation [123]. The expression of this protein has been previously shown to be restricted to glial cells (oligodendrocytes, astrocytes, and microglia) [124]. The importance of this protein for lipid metabolism is emphasized by X-linked adrenoleukodystrophy (X-ALD) caused by the human loss-of-function mutation of *abcd1* [125]. X-ALD is a peroxisomal disorder characterized by inflammatory demyelination in cerebral white matter due to the accumulation of VLCFA [125]. Extracellular VLCFA administration in primary oligodendrocytes has verified its cytotoxic effects through the sustained elevation in intracellular [Ca2+] and potent oxidative stress mechanisms [126], suggesting a primary oligodendrocytopathy in X-ALD patients.

It has been shown that the ALDP-related protein (ALDRP; encoded by *abcd2*), a protein sharing 63 % sequence homology with ALDP, may be partially redundant leading to the hypothesis that lipid metabolism may be therapeutically normalized in X-ALD patients [127, 128]. Indeed, pharmacological induction of *abcd2* was shown to increase the rate of β-oxidation rate of VLCFA in X-ALD patients to homeostatic levels [127, 128] and importantly in oligodendrocytes derived from induced pluripotent stem cells (iPSCs) from X-ALD patients [129]. Interestingly, the *abcd2* promoter was found to contain a 4-base pair spacer (DR-4) motif of TRE that binds to the TRβ1 and RXRα heterodimer [130]. Further study revealed that T3 administration induced the expression of *abcd2* in the CG4 differentiated oligodendrocyte cell line and increased β-oxidation of VLCFA in X-ALD patient-derived fibroblasts [130]. On the other hand, un-liganded TRβ but not TRα suppressed the transcription of *abcd2* [131], implying that the regulation of *abcd2* is mediated through TRβ. In support of this, treatment of cells with the TRβ-specific agonists, GC-1 and CGS23425, showed marked increase in *abcd2* mRNA [132]. As expression levels of TRβ increase upon oligodendrocyte maturation [59] and β-oxidation of VLCFA is implicated in energy metabolism [133], TRβ-dependent transcription of *abcd2* is most likely required for the maintenance of myelinating oligodendrocytes. As T3 may compensate for the loss of *abcd1*, the severe phenotype exhibited in X-ALD patients suggests dysregulation of TH metabolism in oligodendrocytes. Furthermore, as conditional deletion of the peroxisomal targeting signal type-1 receptor (PEX5) in Cnp-expressing oligodendroglia (*cnp*-Cre/loxP-*pex5*) resulted in primary axonopathy preceding inflammatory demyelination [134], TH signaling in oligodendrocytes may be required for the maintenance of axons via axo-glia interactions.

## Thyroid Hormone as a Treatment for Demyelinating Disease

The pro-myelinating properties of thyroid hormone has led to its a promise as a physiological molecule capable of treating demyelinating diseases such as MS. Laura Calza's group has pioneered this research by administering either T4 or T3 subcutaneously into various experimental autoimmune encephalomyelitis (EAE) models [10, 135–137] and from these experiments has partially concluded that clinical EAE scores of neurological impairment are reduced after onset of disease. Molecular analyses of the post-mortem tissue from these experimental animals show increased immunoreactivity against MBP measured by either western immunoblot or immunohistochemistry. Similarly, subcutaneous [138], intraperitoneal [139], or intranasal [140] administration of T3 in a neurotoxicant, cuprizone-mediated demyelination model, all showed enhanced remyelination. In addition, co-administration of HDAC inhibitor, valproic acid, and T4 into dark agouti rat model of EAE increased myelin gene expressions in brain O4+ pre-oligodendrocytes during the remission stage of EAE [141]. Moreover, in other white matter injury model characterized by inflammation and demyelination such as intra-ventricular hemorrhage and hypoxic ischemia, T4 treatment increased myelination during early post-natal developments of rabbit and rat, respectively [35, 142]. Importantly, T4 treatment also showed increased number of O4+/O1+ mature oligodendrocytes in pre-term infants with IVH when compared with IVH alone control [35]. Although these results seem promising, it is difficult to conclude whether the exogenously administered THs are acting directly on the CNS oligodendroglia or indeed through the modulation of other cells that affect the course of these demyelination models, which may specifically include the innate and adaptive immune arms. Regarding this concern, treatment of T3 into MBP-specific T cell lines reduced IL-17+ T cells and adoptive transfer of these cells into naïve small rats but significantly reduced EAE symptoms [141]. Furthermore, even though THs may be beneficial in remyelination in the CNS, an excessive administration of THs may cause local hyperthyroidism in immune organs. Hyperthyroidism may functionally modulate immune cells, reflected in well-documented hyperthyroidism-mediated autoimmune thyrotoxicosis, Grave's disease. For example, the function of regulatory T cells (Tregs), essential for the regulation of a potential autoimmune response, has been shown to be

impaired in patients with Grave's disease (for review, see [143]). Furthermore, Tregs isolated from the peripheral mononuclear cells of patients with Grave's disease were found to be apoptotic [144], possibly through a T3-TRβ-dependent induction of precocious cell senescence [145]. Another important aspect to note is that although there is no direct evidence, pro-inflammatory cytokines released from peripheral immune cells that were shown to inhibit oligodendrocyte differentiation [146–149] such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-1β (IL-1β), and interferon-γ (IFN-γ) can induce local hypothyroidism as these cytokines secreted as a result of lipopolysaccharide-induced inflammation caused dysregulation of Dio2 [150], which may again cause modulation of T3 signaling. Recently, T4 treatment failed to rescue white matter injury including oligodendrocyte differentiation blockade induced by systemic administration of IL-1β [151], which may indicate for the dysregulation of thyroid hormone signaling by IL-1β. Therefore, to reduce side-effects from the peripheral immune arm, local rather than systemic administration of TH may be employed to promote remyelination. Alternatively, innovative nanoparticle-coated THs seem promising for better CNS-targeted drug delivery [152].

Another important point to note is that in a similar manner seen under in vivo hypoxic conditions such as IUGR, which can impair TH transport via a reduction in the expression of MCT8 [25], dysregulation of TH transport is also speculated to be a result of EAE-induced hypoxia [37], thereby further complicating any proposed TH treatment regime during EAE (Fig. 3). In light of this, future studies are required to uncover the implications imposed upon oligodendrocyte development and remyelination, as a consequence of dysregulation of the TH transporters during neuroinflammation. Robust neurobiological data may provide further insights on how treatments targeting the TH signaling cascades can limit inflammatory-mediated oligodendrocyte/myelin damage and further neurodegeneration.

## Conclusion

Development of mature, integrating cells within the CNS occurs via a tightly controlled sequence of regionally specific events. Only upon establishment of immature neuronal synaptogenesis, is the emergence of profound oligodendrocyte development. THs are fundamental to the regulation of the timing of oligodendrogenesis proposed through their putative effects upon mitosis and more specifically imposed following the nuclear translocation of TRs (non-genomic) and transcription of genes upon binding to nuclear localized TRs (genomic). Emerging evidence now identifies that dysregulation of TH signaling is a major hallmark of diseases with underlying hypoxia-associated developmental hypomyelination and inflammatory demyelination. Therefore, the design of novel

therapeutics to directly enhance TH signaling may indeed hold great potential to enhance developmental myelination or remyelination of denuded axons. However, as hyperthyroidism may lead to pronounced metabolic rates as documented during pathophysiological conditions, the induction of premature cell senescence may indeed be a contraindication of such treatments. Hence, a more cautious and considered design of therapeutic options is required to take advantage of the known TH signaling pathways that may be targeted for clinical use.

**Compliance with Ethical Standards**

**Conflict of Interest**   The authors declare that they have no conflicts of interest.

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