

REVIEW

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Effects of thyroid hormone on HSV-1 gene regulation: implications in the control of viral latency and reactivation

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Abstract

Thyroid hormone (TH) is involved in many biological functions such as animal development, cell differentiation, etc. Variation and/or disruption of plasma TH level often led to abnormalities and physiological disorders. TH exerts the effects through its nuclear receptors (TR). Literature showed that procedures resulted in TH alteration also linked to reactivation of several viruses including Herpes Simplex Virus Type -1 (HSV-1). Bioinformatic analyses revealed a number of putative TH responsive elements (TRE) located in the critical regulatory regions of HSV-1 genes such as thymidine kinase (TK), latency associated transcript (LAT), etc. Studies using neuronal cell lines have provided evidences demonstrating that liganded TR regulated viral gene expression via chromatin modification and controlled viral replication. The removal of TH reversed the inhibition and induced the viral replication previously blocked by TH. These results suggest that TH may have implication to participate in the control of reactivation during HSV-1 latency.

1. Thyroid Hormone Overview

Thyroid hormone (TH or T₃) contributes to numerous crucial physiological processes ranging from animal development, proliferation, differentiation, apoptosis, etc [1]. Aberration due to the lack of TH led to disorders such as the goiter (thyroid gland enlargement) and cretinism (a type of severe mental retardation) [2]. TH deficiency may result from the shortage of iodine (essential for TH biosynthesis), thyroidectomy, diseases, or inherited defects, etc. In humans, developmental defects because of TH deficiency can be treated by TH replacement at appropriate time frame [3].

2. Transcriptional regulation by TR

TH is vital for the normal functions of many organs and exert its ability through the nuclear receptor [1]. Two TR genes (TR α and TR β) were identified in vertebrates and both exhibit strong binding to their ligand TH [4-7]. They are members of nuclear hormone receptor super-family [8-10]. Although recent discovery suggested non-genomic action, TRs primarily produce their

activity by binding to TH response element (TRE) and regulating transcription in nucleus through the status of TH [11]. TRE is a short DNA sequence located within the promoter of a TH-response gene. The most common TRE sequence is a pair of direct repeats separated by four nucleotides (DR4), indicating that the correspondent receptors bound as a dimer [12]. This TRE is also described as positive TRE since transcription activated by TH requires the interaction of liganded TRs to the DR4-TRE within the promoter of TH-response genes, most likely as heterodimers with RXRs (9-cis retinoic acid X receptors). TR/RXR heterodimers display constitutive interaction to DR4-TRE in chromatin context regardless the status of TH [13]. In the absence of TH, they inhibit the gene expression and the inhibition can be reversed when TH is available for binding to the receptors [13]. TR controls gene expression by recruiting cofactors to the vicinity of promoters. The corepressors are preferentially recruited by unliganded TR while the coactivators are enriched at the promoter via liganded TR [13]. The characterization indicated that corepressors such as SMRT, N-CoR, etc establish complexes with histone deacetylases (HDACs) to facilitate hypoacetylation. This process eliminates those acetyl groups on histone tail, increases the positive charge of

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nucleosomes, and enhances the interaction between the histones and DNA backbone. As a result, it promotes the chromatin binding and condenses DNA structure, therefore preventing transcription [14]. On the contrary, many coactivators (e.g. SRC-1, CBP/p300) are histone acetyltransferases (HATs) and induce transcription by reversing the previous process [14].

3. Herpes Simplex viruses (HSV) and diseases

HSV is one of the most common causes of infectious disease in humans [15]. This virus contains two distinct types, HSV-1 and HSV-2. Their genomes demonstrate approximately 50% homology. Diseases caused by HSV-1 infection appear frequently [16]. It happens to children about 3 to 5 years old and lasts 5 to 12 days [17]. After the initial infection, the virus may establish latency in the trigeminal ganglia. Reactivation usually occurs over the anterior mucosa, lips or perioral area of face called cold sores or fever blisters [18]. About 10% of viral encephalitis resulted from herpes virus [19]. The factors leading to HSV encephalitis are unknown although a study suggested that latent virus reactivation in the trigeminal ganglia and prolonged lytic infection in the temporal-parietal area of the brain may play a role [20]. Other major clinical syndromes include cornea infection (herpes keratitis) [21], infection of finger and nail (herpetic whitlow) [22], herpes dermatitis [23], and genital HSV infection [24].

4. The genome of HSV-1 and gene expression

a. Genome

HSV-1 has a linear double-stranded DNA genome. The genome contains approximately 80-85 genes and is about 152 kbp long. The G+C content of HSV-1 genome is approximately 68% [25]. It includes two components, designated as L (long) and S (short). Both L and S contain unique sequences, designated as U_L and U_S , and each of them is bracketed by inverted repeats. The L and S of HSV-1 can invert with respect to one another, yielding four linear isomers. The isomers are defined as P (prototype), I_L (inversion of the L component), I_S (inversion of the S component), I_{SL} (inversion of S and L) [26].

b. Characterization of gene expression

Gene expression of HSV-1 is tightly regulated in a cascade fashion. The three temporal classes of genes are designated immediate-early (α), early (β) and late (γ) genes [27]. There are five α genes and their products are often named Infected Cell Protein (ICP), designated ICP0, ICP4, ICP22, ICP27, and ICP47. All of these proteins have regulatory functions except ICP47, which inhibits major histocompatibility complex class I antigen presentation [28,29]. The α genes are defined by the

presence of the sequence 5'-TAATGARATT-3' (the cis element for induction of α genes by VP16) upstream of the cap site [30]. VP16 interacts with cellular factors, including the protein Oct-1, a homeobox protein, to activate viral α gene transcription in trans [31]. The expression of β genes requires the expression of α genes [32].

5. HSV-1 latency, reactivation, and its regulation by TH

a. Latency and reactivation

HSV-1 establishes latent infections in peripheral nerve ganglia following primary infection in the cells of mucosal membranes or skin [33]. Latent infection is maintained lifelong in the human host. The virus may reactivate from time to time and infectious virus enters peripheral tissues by axonal transport causing recurrent disease or subclinical virus shedding [34]. Latent virus may be reactivated after local or systemic stimuli such as injury to tissues innervated by neurons harboring latent virus, or by emotional or physical stress [35,36]. During latency, the viral transcription is restricted to a region within the long terminal and internal repeats and the transcripts are designated as "LATs" (Latency Associated Transcripts) [37]. The molecular functions of LAT during latency and reactivation are elusive and the specific roles in gene regulation are not exactly understood. Some suggested that LATs produced anti-apoptotic effects [38]. In neuronal cells, LAT was shown to reduce viral gene expression and replication during productive infection [39]. *In vivo*, LAT mutant virus enhanced gene expression in sensory neurons during lytic and latent infection [40]. Additional report showed that LAT augments transcriptions of several lytic genes during the latent stage in rabbits [41]. Since they are the only major transcripts produced in significant amounts during latency, the LATs were suggested to play a role in establishing, maintaining, or reactivating latency [42].

During reactivation, LAT gene decreased and was shown to be associated with repressive histones [43]. Transcripts of ICP0, on the other hand, accumulated and the histones around its promoter became acetylated [43]. These results suggested the roles of LAT and ICP0 during the initial stage of reactivation. As for the viral gene expression profile in neurons during reactivation, it was suggested to follow the paradigm of α to β to γ cascade and viral DNA replication occurred after α synthesis, similar to the lytic cycle. However, other reports challenge this view by suggesting different sequence. For example, studies showed that TK-minus mutant exhibited greatly reduced α and β expression during reactivation [44,45]. These observations were further supported by the finding that TK, a β gene, was detected before α gene expression using explants reactivation model [46].

In addition, viral replication is required for efficient α and β expression in neuron during reactivation [47]. Together, these studies emphasized the importance of TK and viral DNA synthesis during reactivation. Since TK is required to provide dNTP for viral replication in resting cells such as neurons, it is likely that TK may play a critical role to stimulate viral DNA synthesis and α gene expression to promote reactivation.

b. Role of TH on HSV-1 reactivation

The impacts of TH on virus-mediated pathophysiology was discussed but not extensively studied. Low serum thyroxine and other hormone imbalance due to hypothalamic-hypopituitarism were associated with viral meningo-encephalitis and related complication [48]. Effects of TH on AIDS (Acquired Immuno-Deficiency Syndrome) and ARC (AIDS-Related Complex) were investigated and the results suggest that TH may affect disease development and progression [49]. At present, the molecular basis of the HSV-1 latency/reactivation is not extensively understood. In particular, it is not known why virtually the entire HSV genome is transcriptionally silent, with the exception of the LAT region. It is not entirely clear how the latent virus initiates gene expression/replication upon reactivation. Recent studies suggested that TH and TRs played roles on HSV gene silencing/activation and DNA replication during latency/reactivation [50,51]. There are reasons to hypothesize that the status of TH and its interaction with TRs modulate chromatin and exert functions in HSV-1 latency and reactivation. 1. TR is present in ganglia neurons [52,53]. 2. TH can affect different biological processes involved in the survival, differentiation, maturation of neurons [54]. 3. TH and nerve growth factor enhanced neurite outgrowth, and regulate the expression of dynein, a protein that is involved in axonal transport (important for virus movement), in ganlia neurons [55]. There is no direct, controlled clinical study regarding the effect of TH on HSV-1 reactivation although alteration of corticosteroid has been linked to HSV-1 reactivation [56,57]. A case study showed that a patient with myxedema coma under corticosteroid treatment developed herpes simplex encephalitis with

extremely low thyroxine level less than 5.2 nmol/L (normal range 12-30 nmol/L) [58]. In addition, literature indicated that many factors, such as stress, febrile diseases, trauma, surgery, radiotherapy, etc, triggering HSV-1 reactivation also altered thyroid hormone level (Table 1).

This table is intended to provide connection between variation of TH level and HSV-1 reactivation. For example, whole body hyperthermia was reported to reduce the level of serum TH by 50%, probably due to the suppression of thyroid stimulating hormone release, mono-deiodination alteration of T_4 from TH to reverse T_3 , and enhanced TH clearance [76]. Importantly, hyperthermia is regularly used by laboratories to trigger HSV-1 reactivation in the mouse latency model [72]. In addition, brain injury and trauma were reported to reduce TH levels [86] and also trigger viral reactivation (see Table 1). Therefore, TH is likely to participate in the regulation and maintenance of viral latency and reactivation. TH acts on almost every cell in the body including neurons. It is likely that TH contribute, at least in part, to the regulation of HSV-1 latency/reactivation.

c. Characterization of HSV-1 TKTRE

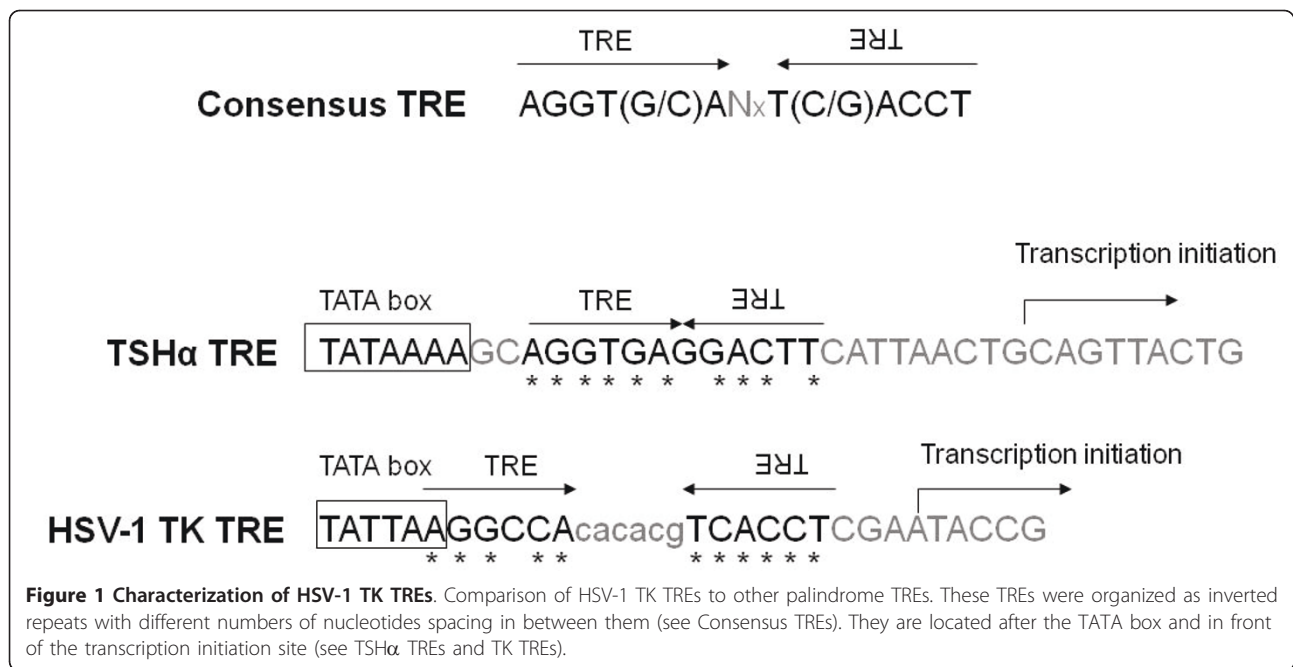
Early report revealed a pair of TRE located in the HSV-1 TK promoter and produced positive regulation [99]. Additional analyses indicated that these TK TREs are positioned between TATA box and the transcription initiation site arranged as "palindromes" with six nucleotides spacing each other (Figure 1). TREs in this format were also found in the promoters of $TSH\alpha$ and $TSH\beta$, both exhibit negative regulations by TH in hypothalamic-pituitary-thyroid (HPT) axis [100]. It has been suggested that this TK TREs exhibited negative regulation by TH and TR in neuronal environment [51,99].

i. TR negatively regulated HSV-1 TK transcription in neuronal cells

Analyses using mouse neuroblastoma cell lines N2a and N2aTR β showed that HSV-1 TK promoter activity was repressed by liganded TR and activated in the presence of TR without TH using transient transfection assays [51]. It appears that TR exerted negative regulation on

Table 1 Comparison between triggering factors of HSV-1 reactivation and thyroid hormone alteration

	HSV-1 Reactivation	Change in Thyroid hormone levels
Stress	[59-63]	[64-68]
Fever	[69-72]	[73-76]
Local injury to face lips or eyes	[77-79]	[80]
Trauma	[81-83]	[84-86]
Surgery	[81,82,87-91]	[80,92,93]
Radiotherapy	[94,95]	[96-98]



HSV-1 TK promoter in a neuronal cell line since the regulation was not observed in other cell lines such as 293HEK and Vero (data not shown). The binding of TR to negative TREs and the outcome of histone modification in neuronal cells were not well characterized. Chromatin immunoprecipitation (ChIP) assays showed that liganded TR exhibited strong interaction to the TK promoter via TREs. The binding was significantly reduced in the absence of TH [51]. Hypoacetylation was observed at the TK promoter by TH and TR using anti-acetyl H4 Ab [51]. These results indicated that liganded TR was recruited to the TK promoter and reduced the acetylation of histone tails at the TRE region.

ii. TK was repressed by TH and TR during viral infection

Based on the results of transfection assays, infections of cells with viruses were performed to investigate the TR/TH mediated regulation in neuronal cells. RT-PCR assays showed that TK transcription was inhibited by liganded TR at high moi while the viral protein synthesis was inhibited (unpublished data). It is noted that the TK promoter activity was efficiently repressed by TR/TH at low moi [51]. These results demonstrated that liganded TR repressed TK promoter activity in neuronal cells through chromatin modification via interaction with TK TREs.

iii. Liganded TR mediated TK inhibition can be reversed by TH removal

It was hypothesized that increasing TK expression may enhance HSV-1 replication/gene expression thus promoting viral DNA replication and α expression during reactivation [47]. Results from N2aTR β cell culture

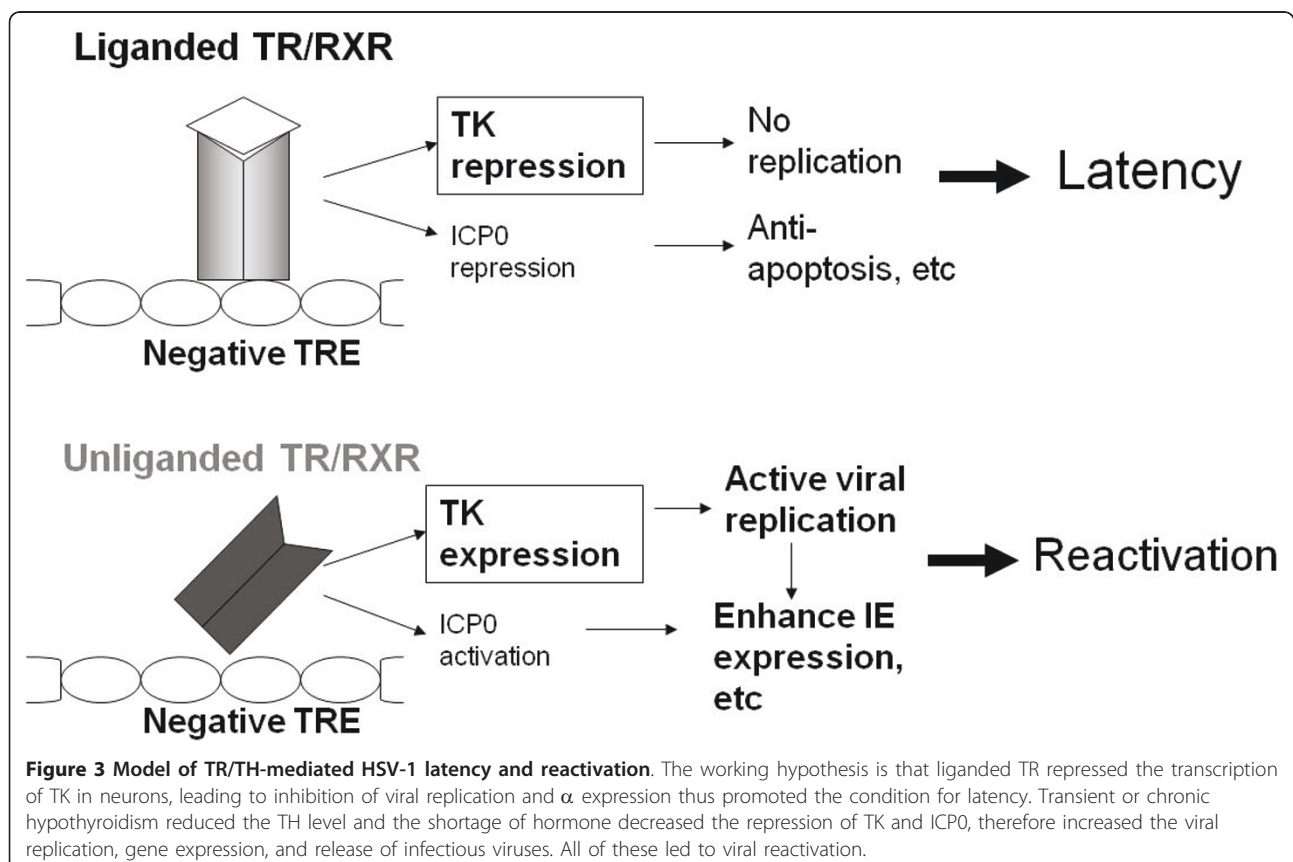
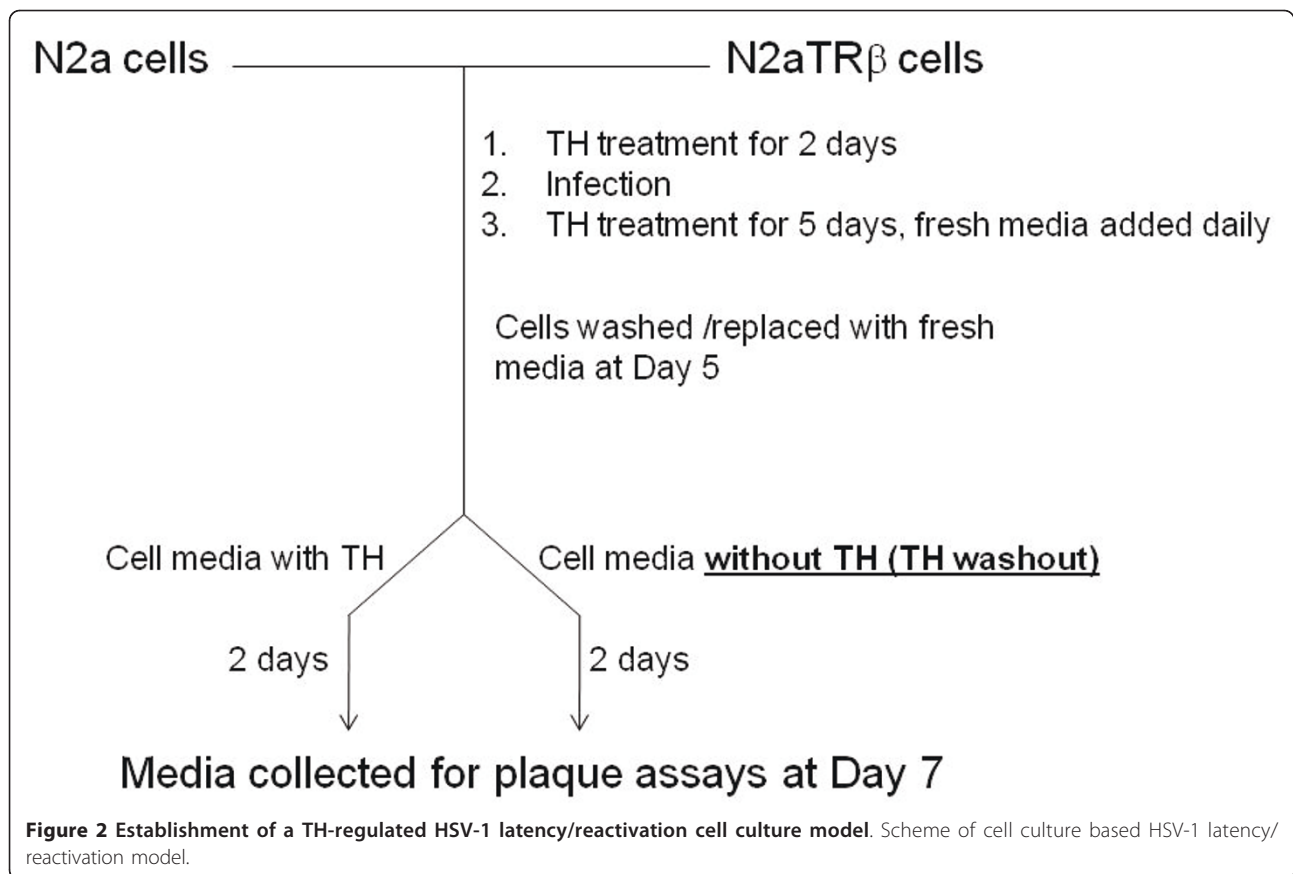
model indicated that the removal of TH de-repressed the TK inhibition [51]. In addition, the same condition of TH washout can reactivate the expression of ICP0 [50], another important HSV-1 α gene for reactivation. Together these results further support the hypothesis that TH may have implication in the HSV-1 reactivation from latency through the induction of TK and ICP0.

6. In vitro TH-mediated HSV-1 latency cell culture model

A cell culture model was established to investigate the roles of TH/TR in the regulation of HSV-1 latency/reactivation [50,51] (depicted in Figure 2). This system is based on the fact that over-expression of TR isoform β triggers N2a cells to differentiate in the presence of TH [101], mimicking the state of neurons where HSV-1 established latency. The plaque assays indicated that release of infectious virus was significantly decreased in the presence of TH with TR. Furthermore, TH washout de-repressed the virus replication and release [51]. These observations demonstrated the previous findings that TH availability played roles in the regulation of HSV-1 reactivation/latency.

7. Conclusion and future direction

A number of studies suggested the possibilities that hormone imbalance may cause virus reactivation including HSV-1. The mouse neuroblastoma cell line N2a and N2aTR β provided an efficient platform to investigate the molecular functions of TR and TH in the regulation of HSV-1 latency and reactivation.



Current progress suggested that TR/TH inhibits the HSV-1 key gene expression, leading to blockade of viral replication and α expression therefore favors maintenance of latency in neurons. Transient or chronic hypothyroidism decreases the TH level and the lack of hormone relieves the inhibition of TK and ICP0 (likely to be indirect effect through TK activation [51] and insulator effects from the LAT regulatory region [50]), results in viral replication, gene expression, release of infectious viruses, and viral reactivation (Figure 3). Additional studies showed that this TR/TH-mediated regulation was due to, at least in part, by histone modification [50,51]. In the future, the hypotheses should be tested in the animal models using TH and TR-selective thymimetic agents. This will assist in explaining the roles of TH on the maintenance of viral latency, probably by blocking the α activation in latently-infected mice upon reactivation. Conversely, treatment with TH antagonists can be tested to see if they have effects on the expression of HSV-1 ICP0 and TK, viral replication, and viral reactivation. Standard established protocols such as hyperthermia will be used for reactivation and eye swabs will be taken at the appropriate times for analysis of reactivated infectious HSV-1. Trigeminal ganglia neurons from the treated infected mice will be removed for analyses of gene expression, chromatin remodeling, and measurement of HSV-1 copy number. In addition, removal of TH production by thyroidectomy can be used to confirm the regulatory effects during reactivation.

Abbreviations

HSV: Herpes simplex virus; TH: Thyroid hormone; TR: Thyroid hormone receptor; TK: Thymidine kinase; TRE: Thyroid hormone responsive elements; LAT: Latency associate transcript; ICP0: Infected cell protein 0; ChIP: Chromatin immune-precipitation; IE: Immediate early genes

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Authors' contributions

SVH, GRB, and MDB composed and discussed the article. All authors read, agreed, and approved the final version of this manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

1. Kucharova S, Farkas R: Hormone nuclear receptors and their ligands: role in programmed cell death (review). *Endocr Regul* 2002, **36**(1):37-60.
2. Fragu P: [The history of science with regard to the thyroid gland (1800-1960)]. *Ann Endocrinol (Paris)* 1999, **60**(1):10-22.
3. Danzi S, Klein I: Potential uses of T3 in the treatment of human disease. *Clin Cornerstone* 2005, **7**(Suppl 2):S9-15.
4. Jouravel N, Sablin E, Togashi M, Baxter JD, Webb P, Fletterick RJ: Molecular basis for dimer formation of TRbeta variant D355R. *Proteins* 2009, **75**(1):111-7.
5. Martinez L, Nascimento AS, Nunes FM, Phillips K, Aparicio R, Dias SM, Figueira AC, Lin JH, Nguyen P, Apriletti JW, Neves FA, Baxter JD, Webb P, Skaf MS, Polikarpov I: Gaining ligand selectivity in thyroid hormone receptors via entropy. *Proc Natl Acad Sci USA* 2009, **106**(49):20717-22.
6. Zheng J, Hashimoto A, Putnam M, Miller K, Koh JT: Development of a thyroid hormone receptor targeting conjugate. *Bioconjug Chem* 2008, **19**(6):1227-34.
7. Machado DS, Sabet A, Santiago LA, Sidhaye AR, Chiamolera MI, Ortiga-Carvalho TM, Wondisford FE: A thyroid hormone receptor mutation that dissociates thyroid hormone regulation of gene expression in vivo. *Proc Natl Acad Sci USA* 2009, **106**(23):9441-6.
8. McEwan IJ, Nardulli AM: Nuclear hormone receptor architecture-form and dynamics: The 2009 FASEB Summer Conference on Dynamic Structure of the Nuclear Hormone Receptors. *Nucl Recept Signal* 2009, **7**:e011.
9. Teboul M, Guillaumond F, Grechez-Cassiau A, Delaunay F: The nuclear hormone receptor family round the clock. *Mol Endocrinol* 2008, **22**(12):2573-82.
10. Lopes da Silva S, Burbach JP: The nuclear hormone-receptor family in the brain: classics and orphans. *Trends Neurosci* 1995, **18**(12):542-8.
11. Hiroi Y, Kim HH, Ying H, Furuya F, Huang Z, Simoncini T, Noma K, Ueki K, Nguyen NH, Scanlan TS, Moskowitz MA, Cheng SY, Liao JK: Rapid nongenomic actions of thyroid hormone. *Proc Natl Acad Sci USA* 2006, **103**(38):14104-9.
12. Chang C, Pan HJ: Thyroid hormone direct repeat 4 response element is a positive regulatory element for the human TR2 orphan receptor, a member of steroid receptor superfamily. *Mol Cell Biochem* 1998, **189**(1-2):195-200.
13. Velasco LF, Togashi M, Walfish PG, Pessanha RP, Moura FN, Barra GB, Nguyen P, Rebong R, Yuan C, Simeoni LA, Ribeiro RC, Baxter JD, Webb P, Neves FA: Thyroid hormone response element organization dictates the composition of active receptor. *J Biol Chem* 2007, **282**(17):12458-66.
14. Li B, Carey M, Workman JL: The role of chromatin during transcription. *Cell* 2007, **128**(4):707-19.
15. Taylor TJ, Brockman MA, McNamee EE, Knipe DM: Herpes simplex virus. *Front Biosci* 2002, **7**:d752-64.
16. Rozenberg F, Deback C, Agut H: Herpes Simplex Encephalitis: From Virus to Therapy. *Infect Disord Drug Targets* 2011.
17. Lopez Garcia F, Enriquez Ascarza R, Rodriguez Martinez JC, Sirvent Pedreno AE: [Interferon therapy for herpes simplex virus infection in a 70 years old patient]. *An Med Interna* 2002, **19**(11):600-1.
18. Everett RD: ICP0, a regulator of herpes simplex virus during lytic and latent infection. *Bioessays* 2000, **22**(8):761-70.
19. Martinez PA, Diaz R, Gonzalez D, Oropesa L, Gonzalez R, Perez L, Viera J, Kouri V: The effect of highly active antiretroviral therapy on outcome of central nervous system herpesviruses infection in Cuban human immunodeficiency virus-infected individuals. *J Neurovirol* 2007, **13**(5):446-51.
20. Goel N, Mao H, Rong Q, Docherty JJ, Zimmerman D, Rosenthal KS: The ability of an HSV strain to initiate zosteriform spread correlates with its neuroinvasive disease potential. *Arch Virol* 2002, **147**(4):763-73.
21. Shah A, Farooq AV, Tiwari V, Kim MJ, Shukla D: HSV-1 infection of human corneal epithelial cells: receptor-mediated entry and trends of re-infection. *Mol Vis* 2010, **16**:2476-86.
22. Usatine RP, Tinitigan R: Nongenital herpes simplex virus. *Am Fam Physician* 2010, **82**(9):1075-82.
23. Higaki S, Inoue Y, Yoshida A, Maeda N, Watanabe H, Shimomura Y: Case of bilateral multiple herpetic epithelial keratitis manifested as dendriform epithelial edema during primary Kaposi's varicelliform eruption. *Jpn J Ophthalmol* 2008, **52**(2):127-9.
24. Jonsson MK, Wahren B: Sexually transmitted herpes simplex viruses. *Scand J Infect Dis* 2004, **36**(2):93-101.
25. Brown JC: High G+C Content of Herpes Simplex Virus DNA: Proposed Role in Protection Against Retrotransposon Insertion. *Open Biochem J* 2007, **1**:33-42.
26. Borchers K, Goltz M, Ludwig H: Genome organization of the herpesviruses: minireview. *Acta Vet Hung* 1994, **42**(2-3):217-25.
27. Weinheimer SP, McKnight SL: Transcriptional and post-transcriptional controls establish the cascade of herpes simplex virus protein synthesis. *J Mol Biol* 1987, **195**(4):819-33.
28. Burgos JS, Serrano-Saiz E, Sastre I, Valdivieso F: ICP47 mediates viral neuroinvasiveness by induction of TAP protein following intravenous

- inoculation of herpes simplex virus type 1 in mice. *J Neurovirol* 2006, **12**(6):420-7.
29. Beinert D, Neumann L, Uebel S, Tampe R: **Structure of the viral TAP-inhibitor ICP47 induced by membrane association.** *Biochemistry* 1997, **36**(15):4694-700.
30. Cun W, Guo L, Zhang Y, Liu L, Wang L, Li J, Dong C, Wang J, Li Q: **Transcriptional regulation of the Herpes Simplex Virus 1 alpha-gene by the viral immediate-early protein ICP22 in association with VP16.** *Sci China C Life Sci* 2009, **52**(4):344-51.
31. LaBoissiere S, O'Hare P: **Analysis of HCF, the cellular cofactor of VP16, in herpes simplex virus-infected cells.** *J Virol* 2000, **74**(1):99-109.
32. Gelman IH, Silverstein S: **Identification of immediate early genes from herpes simplex virus that transactivate the virus thymidine kinase gene.** *Proc Natl Acad Sci USA* 1985, **82**(16):5265-9.
33. Mark KE, Wald A, Magaret AS, Selke S, Olin L, Huang ML, Corey L: **Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults.** *J Infect Dis* 2008, **198**(8):1141-9.
34. Antinone SE, Zaichick SV, Smith GA: **Resolving the assembly state of herpes simplex virus during axon transport by live-cell imaging.** *J Virol* 2010, **84**(24):13019-30.
35. Preston CM, Efstathiou S: **Molecular basis of HSV latency and reactivation.** In *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Chapter 33.* 2 edition. Edited by: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, Yamanishi K. Cambridge: Cambridge University Press; 2007.
36. Chida Y, Mao X: **Does psychosocial stress predict symptomatic herpes simplex virus recurrence? A meta-analytic investigation on prospective studies.** *Brain Behav Immun* 2009, **23**(7):917-25.
37. Allen SJ, Hamrah P, Gate D, Mott KR, Mantopoulos D, Zheng L, Town T, Jones C, von Andrian UH, Freeman GJ, Sharpe AH, Benmohamed L, Ahmed R, Wechsler SL, Ghiasi H: **The Role of LAT in Increased CD8+ T Cell Exhaustion in Trigeminal Ganglia of Mice Latently Infected with Herpes Simplex Virus 1.** *J Virol* 2011, **85**(9):4184-97.
38. Perng GC, Jones C, Ciacci-Zanella J, Stone M, Henderson G, Yukht A, Slanina SM, Hofman FM, Ghiasi H, Nesburn AB, Wechsler SL: **Virus-induced neuronal apoptosis blocked by the herpes simplex virus latency-associated transcript.** *Science* 2000, **287**(5457):1500-3.
39. Mador N, Goldenberg D, Cohen O, Panet A, Steiner I: **Herpes simplex virus type 1 latency-associated transcripts suppress viral replication and reduce immediate-early gene mRNA levels in a neuronal cell line.** *J Virol* 1998, **72**(6):5067-75.
40. Perng GC, Slanina SM, Yukht A, Ghiasi H, Nesburn AB, Wechsler SL: **The latency-associated transcript gene enhances establishment of herpes simplex virus type 1 latency in rabbits.** *J Virol* 2000, **74**(4):1885-91.
41. Giordani NV, Neumann DM, Kwiatkowski DL, Bhattacharjee PS, McAnany PK, Hill JM, Bloom DC: **During herpes simplex virus type 1 infection of rabbits, the ability to express the latency-associated transcript increases latent-phase transcription of lytic genes.** *J Virol* 2008, **82**(12):6056-60.
42. Perng GC, Jones C: **Towards an understanding of the herpes simplex virus type 1 latency-reactivation cycle.** *Interdiscip Perspect Infect Dis* 2010, **2010**:262415.
43. Amelio AL, McAnany PK, Bloom DC: **A chromatin insulator-like element in the herpes simplex virus type 1 latency-associated transcript region binds CCCTC-binding factor and displays enhancer-blocking and silencing activities.** *J Virol* 2006, **80**(5):2358-68.
44. Jacobson JG, Ruffner KL, Kosz-Vnenchak M, Hwang CB, Wobbe KK, Knipe DM, Coen DM: **Herpes simplex virus thymidine kinase and specific stages of latency in murine trigeminal ganglia.** *J Virol* 1993, **67**(11):6903-8.
45. Kosz-Vnenchak M, Jacobson J, Coen DM, Knipe DM: **Evidence for a novel regulatory pathway for herpes simplex virus gene expression in trigeminal ganglion neurons.** *J Virol* 1993, **67**(9):5383-93.
46. Tal-Singer R, Lasner TM, Podzucki W, Skokotas A, Leary JJ, Berger SL, Fraser NW: **Gene expression during reactivation of herpes simplex virus type 1 from latency in the peripheral nervous system is different from that during lytic infection of tissue cultures.** *J Virol* 1997, **71**(7):5268-76.
47. Nichol PF, Chang JY, Johnson EM Jr, Olivo PD: **Herpes simplex virus gene expression in neurons: viral DNA synthesis is a critical regulatory event in the branch point between the lytic and latent pathways.** *J Virol* 1996, **70**(8):5476-86.
48. Lichtenstein MJ, Tilley WS, Sandler MP: **The syndrome of hypothalamic hypopituitarism complicating viral meningoencephalitis.** *J Endocrinol Invest* 1982, **5**(2):111-5.
49. Tang WW, Kaptein EM: **Thyroid hormone levels in the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex.** *West J Med* 1989, **151**(6):627-31.
50. Bedadala GR, Pinnotti RC, Palem JR, Hsia SC: **Thyroid hormone controls the gene expression of HSV-1 LAT and ICP0 in neuronal cells.** *Cell Res* 2010, **20**(5):587-98.
51. Hsia SC, Pinnotti RC, Bedadala GR, Hill JM, Palem JR: **Regulation of herpes simplex virus type 1 thymidine kinase gene expression by thyroid hormone receptor in cultured neuronal cells.** *J Neurovirol* 2010, **16**(1):13-24.
52. Walter IB, Droz B: **Nuclear and cytoplasmic triiodothyronine-binding sites in primary sensory neurons and Schwann cells: radioautographic study during development.** *J Neuroendocrinol* 1995, **7**(2):127-36.
53. Glauser L, Barakat Walter I: **Differential distribution of thyroid hormone receptor isoform in rat dorsal root ganglia and sciatic nerve in vivo and in vitro.** *J Neuroendocrinol* 1997, **9**(3):217-27.
54. Walter IB: **Triiodothyronine exerts a trophic action on rat sensory neuron survival and neurite outgrowth through different pathways.** *Eur J Neurosci* 1996, **8**(3):455-66.
55. Barakat-Walter I, Riederer BM: **Triiodothyronine and nerve growth factor are required to induce cytoplasmic dynein expression in rat dorsal root ganglion cultures.** *Brain Res Dev Brain Res* 1996, **96**(1-2):109-19.
56. Marquart M, Bhattacharjee P, Zheng X, Kaufman H, Thompson H, Varnell E, Hill J: **Ocular reactivation phenotype of HSV-1 strain F(MPE), a corticosteroid-sensitive strain.** *Curr Eye Res* 2003, **26**(3-4):205-9.
57. Higaki S, Gebhardt BM, Lukiw WJ, Thompson HW, Hill JM: **Effect of immunosuppression on gene expression in the HSV-1 latently infected mouse trigeminal ganglion.** *Invest Ophthalmol Vis Sci* 2002, **43**(6):1862-9.
58. Doherty MJ, Baxter AB, Longstreth WT Jr: **Herpes simplex virus encephalitis complicating myxedema coma treated with corticosteroids.** *Neurology* 2001, **56**(8):1114-5.
59. Padgett DA, Sheridan JF, Dorne J, Berntson GG, Candelora J, Glaser R: **Social stress and the reactivation of latent herpes simplex virus type 1.** *Proc Natl Acad Sci USA* 1998, **95**(12):7231-5.
60. Glaser R, Friedman SB, Smyth J, Ader R, Bijur P, Brunell P, Cohen N, Krilov LR, Lifrak ST, Stone A, Toffler P: **The differential impact of training stress and final examination stress on herpesvirus latency at the United States Military Academy at West Point.** *Brain Behav Immun* 1999, **13**(3):240-51.
61. Jenkins FJ, Baum A: **Stress and reactivation of latent herpes simplex virus: a fusion of behavioral medicine and molecular biology.** *Ann Behav Med* 1995, **17**(2):116-23.
62. Blondeau JM, Aoki FY, Glavin GB: **Stress-induced reactivation of latent herpes simplex virus infection in rat lumbar dorsal root ganglia.** *J Psychosom Res* 1993, **37**(8):843-9.
63. Buske-Kirschbaum A, Geiben A, Wermke C, Pirke KM, Hellhammer D: **Preliminary evidence for Herpes labialis recurrence following experimentally induced disgust.** *Psychother Psychosom* 2001, **70**(2):86-91.
64. Friedman Y, Bacchus R, Raymond R, Joffe RT, Nobrega JN: **Acute stress increases thyroid hormone levels in rat brain.** *Biol Psychiatry* 1999, **45**(2):234-7.
65. Turakulov I, Burikhanov RB, Patkhitdinov PP, Myslitskaia AI: **[Effect of immobilization stress on the level of thyroid hormone secretion].** *Probl Endocrinol (Mosk)* 1993, **39**(5):47-8.
66. Stein EJ, da Silveira Filho NG, Machado DC, Hipolide DC, Barlow K, Nobrega JN: **Chronic mild stress induces widespread decreases in thyroid hormone alpha1 receptor mRNA levels in brain—reversal by imipramine.** *Psychoneuroendocrinology* 2009, **34**(2):281-6.
67. Engstrom WW, Markardt B: **The effects of serious illness and surgical stress on the circulating thyroid hormone.** *J Clin Endocrinol Metab* 1955, **15**(8):953-63.
68. May JD, Deaton JW, Reece FN, Branton SL: **Effect of acclimation and heat stress on thyroid hormone concentration.** *Poult Sci* 1986, **65**(6):1211-3.
69. Portolani M, Cermelli C, Moroni A, Bertolani MF, Di Luca D, Cassai E, Sabbatini AM: **Human herpesvirus-6 infections in infants admitted to hospital.** *J Med Virol* 1993, **39**(2):146-51.

70. Colgin MA, Smith RL, Wilcox CL: **Inducible cyclic AMP early repressor produces reactivation of latent herpes simplex virus type 1 in neurons in vitro.** *J Virol* 2001, **75**(6):2912-20.
71. van Kraaij MG, Verdonck LF, Rozenberg-Arska M, Dekker AW: **Early infections in adults undergoing matched related and matched unrelated/mismatched donor stem cell transplantation: a comparison of incidence.** *Bone Marrow Transplant* 2002, **30**(5):303-9.
72. Sawtell NM, Thompson RL: **Rapid in vivo reactivation of herpes simplex virus in latently infected murine ganglionic neurons after transient hyperthermia.** *J Virol* 1992, **66**(4):2150-6.
73. Mustafa S, Al-Bader MD, Elgazzar AH, Alshammeri J, Gopinath S, Essam H: **Effect of hyperthermia on the function of thyroid gland.** *Eur J Appl Physiol* 2008, **103**(3):285-8.
74. Brzezinska-Slebodzinska E: **Fever induced oxidative stress: the effect on selenium status and the 5'-monodeiodinase activity, protective role of selenium and vitamin E.** *J Physiol Pharmacol* 2001, **52**(2):275-84.
75. Ljunggren JG, Kallner G, Tryselius M: **The effect of body temperature on thyroid hormone levels in patients with non-thyroidal illness.** *Acta Med Scand* 1977, **202**(6):459-62.
76. Shafer RB, Oken MM, Elson MK: **Effects of fever and hyperthermia on thyroid function.** *J Nucl Med* 1980, **21**(12):1158-61.
77. **Psychological stress and other potential triggers for recurrences of herpes simplex virus eye infections.** Herpetic Eye Disease Study Group. *Arch Ophthalmol* 2000, **118**(12):1617-25.
78. Beyer CF, Hill JM, Reidy JJ, Beuerman RW: **Corneal nerve disruption reactivates virus in rabbits latently infected with HSV-1.** *Invest Ophthalmol Vis Sci* 1990, **31**(5):925-32.
79. Khan SA, Wingard JR: **Infection and mucosal injury in cancer treatment.** *J Natl Cancer Inst Monogr* 2001, **29**:31-6.
80. Jiang YH, Tian KB, Liu WD, Fan TH, Li F: **[Thyroid hormone level change in patients undergoing oral and maxillofacial surgery].** *Shanghai Kou Qiang Yi Xue* 2007, **16**(6):611-3.
81. Marques-Silva L, Castro WH, Gomez EL, Guimaraes AL, Silva MS, Gomez RS: **The impact of dental surgery on HSV-1 reactivation in the oral mucosa of seropositive patients.** *J Oral Maxillofac Surg* 2007, **65**(11):2269-72.
82. Hyland PL, Coulter WA, Abu-Ruman I, Fulton CR, O'Neill HJ, Coyle PV, Lamey PJ: **Asymptomatic shedding of HSV-1 in patients undergoing oral surgical procedures and attending for noninvasive treatment.** *Oral Dis* 2007, **13**(4):414-8.
83. Hedner E, Vahlne A, Bergstrom T, Hirsch JM: **Recrudescence of herpes simplex virus type 1 in latently infected rats after trauma to oral tissues.** *J Oral Pathol Med* 1993, **22**(5):214-20.
84. Haviland MG, Sonne JL, Anderson DL, Nelson JC, Sheridan-Matney C, Nichols JG, Carlton EI, Murdoch WG: **Thyroid hormone levels and psychological symptoms in sexually abused adolescent girls.** *Child Abuse Negl* 2006, **30**(6):589-98.
85. Arem R, Wiener GJ, Kaplan SG, Kim HS, Reichlin S, Kaplan MM: **Reduced tissue thyroid hormone levels in fatal illness.** *Metabolism* 1993, **42**(9):1102-8.
86. Woolf PD, Lee LA, Hamill RW, McDonald JV: **Thyroid test abnormalities in traumatic brain injury: correlation with neurologic impairment and sympathetic nervous system activation.** *Am J Med* 1988, **84**(2):201-8.
87. Franco-Vidal V, Nguyen DQ, Guerin J, Darrouzet V: **Delayed facial paralysis after vestibular schwannoma surgery: role of herpes viruses reactivation—our experience in eight cases.** *Otol Neurotol* 2004, **25**(5):805-10.
88. Molloy S, Allcutt D, Brennan P, Farrell MA, Peryman R, Brett FM: **Herpes simplex encephalitis occurring after chemotherapy, surgery, and stereotactic radiotherapy for medulloblastoma.** *Arch Pathol Lab Med* 2000, **124**(12):1809-12.
89. Bourgeois M, Vinikoff L, Lellouch-Tubiana A, Sainte-Rose C: **Reactivation of herpes virus after surgery for epilepsy in a pediatric patient with mesial temporal sclerosis: case report.** *Neurosurgery* 1999, **44**(3):633-5, discussion 635-6.
90. Tenser RB, Edris WA, Hay KA: **Herpes simplex virus latent infection: reactivation and elimination of latency after neurectomy.** *Virology* 1988, **167**(1):302-5.
91. Porteous C, Bradley JA, Hamilton DN, Ledingham IM, Clements GB, Robinson CG: **Herpes simplex virus reactivation in surgical patients.** *Crit Care Med* 1984, **12**(8):626-8.
92. Hartel W, Petermann C, Petermann U, Fischer M: **[Thyroid hormone levels after surgical stress reaction (author's transl)].** *MMW Munch Med Wochenschr* 1980, **122**(43):1505-7.
93. Dagan O, Vidne B, Josefsberg Z, Phillip M, Strich D, Erez E: **Relationship between changes in thyroid hormone level and severity of the postoperative course in neonates undergoing open-heart surgery.** *Paediatr Anaesth* 2006, **16**(5):538-42.
94. Nicolatou-Galitis O, Dardoufas K, Markoulatos P, Sotiropoulou-Lontou A, Kyprianou K, Kolitsi G, Pissakas G, Skarleas C, Kouloulas V, Papanicolaou V, Legakis NJ, Velegriki A: **Oral pseudomembranous candidiasis, herpes simplex virus-1 infection, and oral mucositis in head and neck cancer patients receiving radiotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash.** *J Oral Pathol Med* 2001, **30**(8):471-80.
95. Silvano G, Lazzari G, Resta F, Buccoliero G, Pezzella G, Pisconti S: **A Herpes simplex virus-1 fatal encephalitis following chemo-radiotherapy, steroids and prophylactic cranial irradiation in a small cell lung cancer patient.** *Lung Cancer* 2007, **57**(2):243-6.
96. Airoidi M, Gabriele P, Brossa PC, Pedani F, Tseroni V, D'Alberto M, Ragona R: **Serum thyroid hormone changes in head and neck cancer patients treated with microwave hyperthermia on lymph node metastasis.** *Cancer* 1990, **65**(4):901-7.
97. Pirnat E, Zaletel K, Gaberscek S, Fidler V, Hojker S: **Early changes of thyroid hormone concentrations after (131I) therapy in Graves' patients pretreated or not with methimazole.** *Nuklearmedizin* 2004, **43**(4):129-34.
98. Nakajo M, Tsuchimochi S, Tanabe H, Nakabeppu Y, Jinguji M: **Three basic patterns of changes in serum thyroid hormone levels in Graves' disease during the one-year period after radioiodine therapy.** *Ann Nucl Med* 2005, **19**(4):297-308.
99. Park HY, Davidson D, Raaka BM, Samuels HH: **The herpes simplex virus thymidine kinase gene promoter contains a novel thyroid hormone response element.** *Mol Endocrinol* 1993, **7**(3):319-30.
100. Chatterjee VK, Lee JK, Rentoumis A, Jameson JL: **Negative regulation of the thyroid-stimulating hormone alpha gene by thyroid hormone: receptor interaction adjacent to the TATA box.** *Proc Natl Acad Sci USA* 1989, **86**(23):9114-8.
101. Lebel JM, Dussault JH, Puymirat J: **Overexpression of the beta 1 thyroid receptor induces differentiation in neuro-2a cells.** *Proc Natl Acad Sci USA* 1994, **91**(7):2644-8.

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