[Frontiers In Bioscience, Landmark, 23, 2195-2203, June 1, 2018]

Deiodinases share an evolutionarily conserved thyroid hormone-binding motif

Salvatore Benvenga[1,2,3], Fabrizio Guarneri[4]

[1]Department of Clinical and Experimental Medicine, Endocrinology, University of Messina, via Consolare Valeria, Gazzi, 98125 Messina, Italy, [2]Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina, via Consolare Valeria, Gazzi, 98125 Messina, Italy, [3]Interdepartmental Program on Molecular and Clinical Endocrinology and Women's Endocrine Health, AOU Policlinico G. Martino, via Consolare Valeria, Gazzi, 98125 Messina, Italy, [4]Department of Clinical and Experimental Medicine, Dermatology, University of Messina, via Consolare Valeria, Gazzi, 98125 Messina, Italy

TABLE OF CONTENTS

1. ABSTRACT

Human and animal thyroid hormone (TH) plasma carriers (THPC, n=426), cell surface TH transporters (CSTT, n=8,691), and TH nuclear receptors (TR, n=624) share a 49-position long TH-binding motif. Particularly conserved are positions 22-26, where a 5-residue TH-binding motif was originally detected. We extended our research to the 488 sequences of human and animal selenodeiodinases (dio-1, dio-2, dio-3). In the 10,229 sequences (THPC+CSTT+TR+deiodinases), 15/49 positions are very highly and another 18/49 highly conserved. The very highly conserved 5-residue core TH-binding motif is now W/F/Y, L/I/V/M, I/V/M/L, P, L/V/I/M. Concerning deiodinases, of the 13 conserved residues in their active centers (F121-E214, F128-E228, F139-E233), 11 (dio-1/dio-3) or 10 (dio-2) fall within the 49-position motif. Conserved in the consensus from THPC, CSTT and TR are F129/F136/F147 (position 11). Other matches of deiodinases concerned the nonapolipoprotein THPC: of particular interest, P135/P146 (dio-2/dio-3; position 9), E155/D162/E173 (position 28), S160/S167/S178 (position 33), W163/W170/W178 (position 36). The shared TH-binding domain, which is likely the product of an ancestor gene, may explain why diverse plasma and cell-associated proteins interact with TH.

2. INTRODUCTION

After synthesis by the thyrocytes and secretion into the bloodstream, iodinated thyroid hormones ((TH) T4 and T3), need (i) to be transported in plasma, (ii) to be internalized into the target cells upon interaction with plasma membrane transporters, and (iii) to exert most of their biological action genomically via binding to specific nuclear receptors (1). However, TH signaling has to be regulated by converting the prophormone T4 into the more potent T3, and by inactiving either TH into biologically inactive metabolites (2).

In humans, approximately 80% of the daily production of T3 derives from the extrathyroidal deiodination of T4. This activating deiodination of the T4 into T3 is catalyzed by type 1 and type 2 deiodinases (dio-1 and dio-2). Approximately 40% of T4 and almost all T3 produced daily are deiodinated, mostly by type 3 deiodinase (dio-3) (2). Only dio-1 acts on both the outer ring (5') and inner ring (5) tyrosyl ring, and functions as both an activator (main action) and deactivator of TH. In contrast, dio-2 is an obligate outer ring deiodinase that activates T4 signaling, while dio-3 is an obligate inner ring deiodinase that inactivates T3 and T4 signaling (2). While the TH affinity of dio-1 is low (K_m 1-2 μM), the affinity of dio-2 and dio-3 is three orders of magnitude

higher (K_m 1-4 nM). Differences among the three deiodinases also exists concerning tissue distribution. The three deiodinases are integral membrane proteins which have an approximately 50% identity in amino acid sequence. Only a small portion of dio-1 and dio-3 is associated with the plasma membrane, and only a small portion of dio-3 is associated with the endoplasmic reticulum, most of the sequence of the three deiodinases (including their active center) being cytosolic. The deiodinases share resemblance with various members of the thioredoxin family proteins. However, deiodinases have an intervening sequence that is strikingly similar (47% for dio-1 and dio-3, 60% for dio-2) to α-L-iduronidase (IDUA). It is predicted that the IDUA-like module participates to the active center of the three deiodinases (2). Critical for the enyzmatic activity of the three deiodinases is the presence of the very rare amino acid selenocysteine (SelCys) (3). SelCys is abbreviated as U in the one-letter code by the International Union of Pure and Applied Chemistry (IUPAC) (4).

Even though TH are not a ligand, but a substrate, for the three selenodeiodinases, nevertheless they physically interact with TH. Thus, we wished to test the hypothesis of whether a large TH-binding motif, that we found to be shared by human and animal know TH plasma carriers (THPC), cell surface TH transporters (CSTT) and TH nuclear receptors (TR) (5, 6), was also shared by human and animal selenodeiodinases.

3. MATERIALS AND METHODS

The amino acid sequences of human and animal deiodinases were retrieved from the Entrez Protein database (https://www.ncbi.nlm.nih.gov/protein). After manually removing replicated entries and protein fragments, we obtained a pool of 199 sequences from a total of 169 species for dio-1, 219 sequences from a total of 165 species for dio-2, 70 sequences from a total of 64 species for dio-3. The software MotiFinder (7) was used to search these sequences of dio-1, dio-2 and dio-3 for occurrences of the motif "E/Q/D/N, p, e/q/d, 0-1X, e/d/q, 0-3X, s/t, 0-14X, W/Y/F, d/e/n/q, 0-1X, a/g, l/v/i, l/m/v/i, 0-34X, **Y**/**F**/**W**, **L**/**V**/**I**/**M**, X, X, **V**/**L**/**I**/**M**, q/e/d/n, e/q/d/n, X, l/v/m, v/i/l/m, X, X, v/i/l/m, 4-10X, S/T, X, L/I/M/V, 2-3X, l/v/i/m". Consistently with our previous work (5), amino acid in the motif are those conserved, at each position, in more than 50% (written in uppercase letters and defined as "very highly conserved") or more than 33% but not more than 50% (written in lowercase letters and defined as "highly conserved") of the aligned sequences; at each position, amino acids are listed in decreasing order of frequency. Amino acids written in **bold** are those of the 5-residue motif initially found to be evolutionarily conserved in thyroxine binding sites of apolipoproteins (8, 9).

4. RESULTS

A total of 10,229 proteins were selected for our analysis. The contribution of each category of TH binding proteins (apolipoproteins, non-apolipoprotein plasma proteins, all plasma proteins, membrane transporters, nuclear receptors, deiodinases, all cell proteins) is shown in (Figure 1). Consensus motifs for each of the above categories and overall consensus for the grand total of 10,229 sequences are shown in Figure 2. Residues having a very high degree of conservation appear boldface white against a black background in all figures. Residues highly conserved appear boldface black against a gray background. Residues modestly conserved appear in regular print against no background. Consensus sequences for each of the three deiodinases appear in Figure 3.

4.1. Consensus motif of deiodinases

There was a very high level of conservation of amino acids in the approximately N-terminal three-fourths of the consensus motif (Figure 2). At 16 positions between columns 1 and 37, only one residue was present. Of course, one of such residues is U (SelCys) at position 7. In the remaining positions between columns 38 and 49, only one (no. 44) was occupied by a group of very highly conserved residues. A remarkable feature, which concerns the 5-residue hydrophobic core TH-binding motif (columns 22-26), is its imperfect nature. Indeed, the fifth position (column 26) is occupied by Tyr only, as opposed to one or more residues of the group Ile/Leu/Met/Val. In no other category of proteins, there was such "exception to the rule".

4.2. Consensus motif of deiodinases vs consensus motif of thyroid hormone plasma carriers (THPC)

These two consensus sequences (for a total of 488 and 426 proteins, respectively) share only 5 positions where a given group of amino acids is very highly conserved (no. 1, 11, 22, 23 and 44) (Figure 2). Not even the usage of residues within such a group of amino acids was identical. For instance, N (Asn) is the only amino acid at position 1 in the deiodinases, while N is the least used residue of the D/E/N/Q group in the THPC. Furthermore, two amino acid groups that are very highly conserved in deiodinases are downgraded to highly conserved in the THPC (columns no. 24, 28); the opposite phenomenon occurs at position 44. Finally, there are 3 positions (no. 15, 46 and 48) where amino acids of a given group are highly conserved in the two consensus sequences.

Relatively few residues are present in the three buffer (or gapped) positions (no. 10, 21, 41): 0-7, 4-11 and 1-2 compared with a much larger range in THPC (0-23, 0-30 and 0-7, respectively).

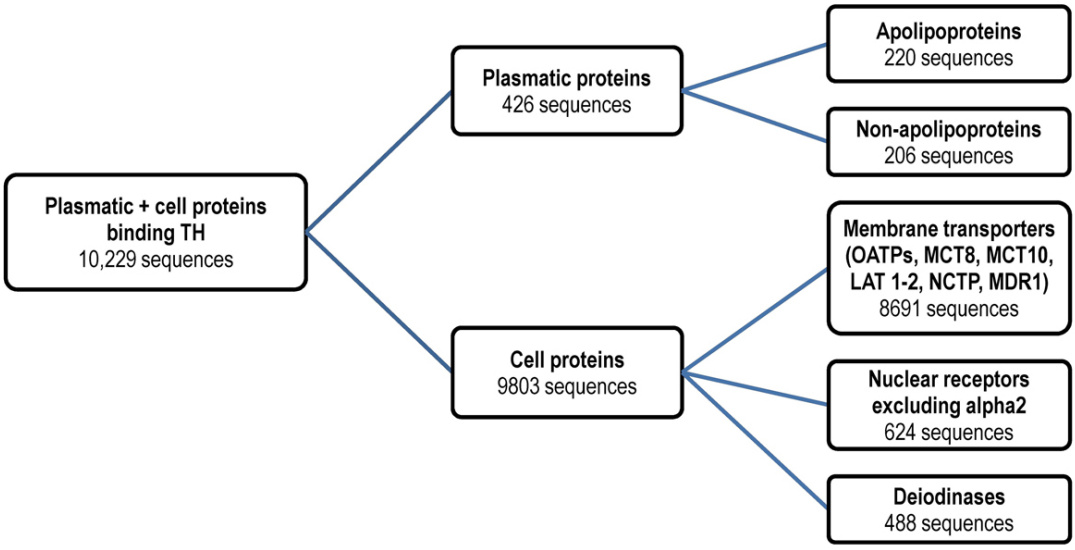

Figure 1. Number of sequences analyzed for each category of thyroid hormone binding proteins.

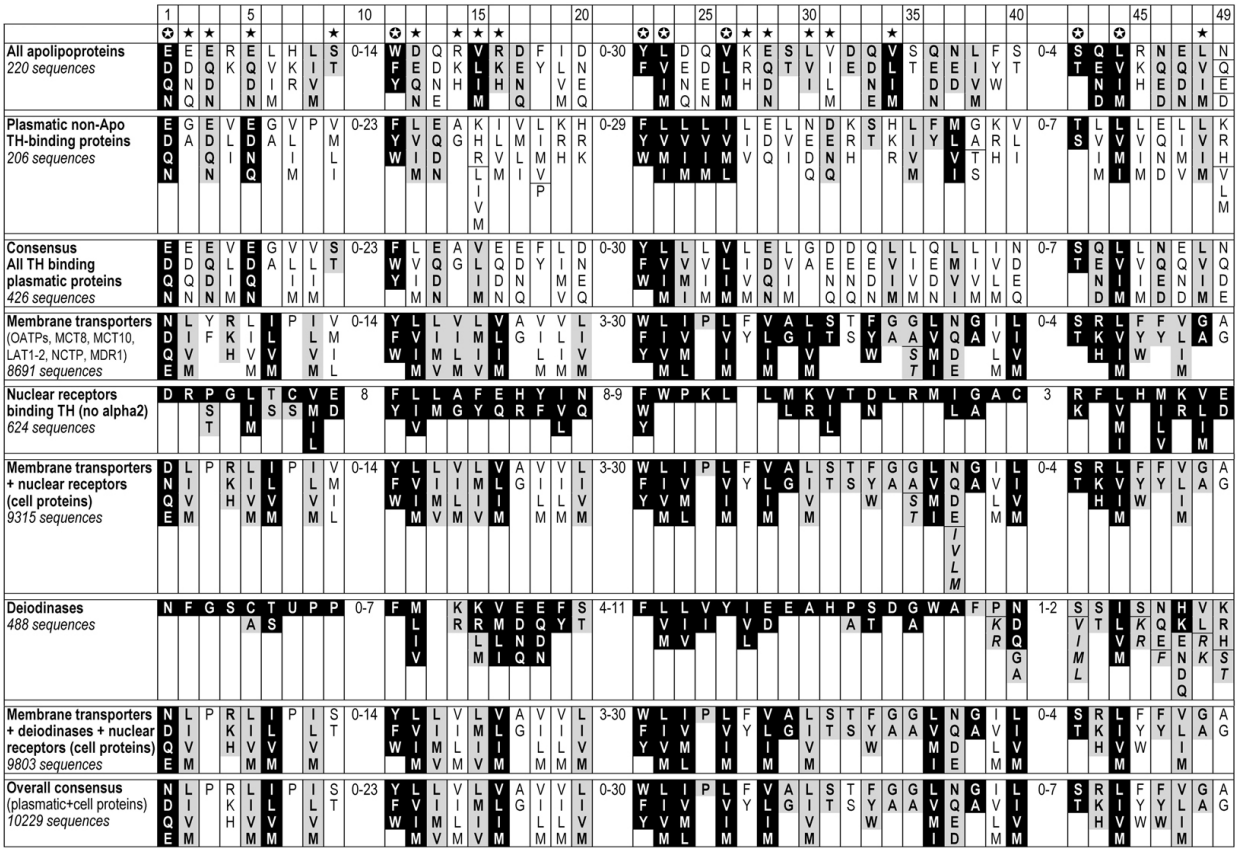

Figure 2. Consensus sequences for TH-binding plasma proteins, cell proteins and deiodinases. Based on frequency in a given position, groups of similar amino acids are written in white boldface on black background (frequency >50%) or in black boldface on gray background (frequency 34% to 50%). When the latter case occurs for two groups in the same position but their frequencies are different, amino acids belonging to the less frequent group are written in italics. In each position of the overall consensus, amino acids belonging to the same group are shown from top to bottom in decreasing order of frequency. Symbols in line 2 indicate the positions of amino acids that are very highly conserved (white star in a black circle) or highly conserved (black star) in the searched motif (5, 6).

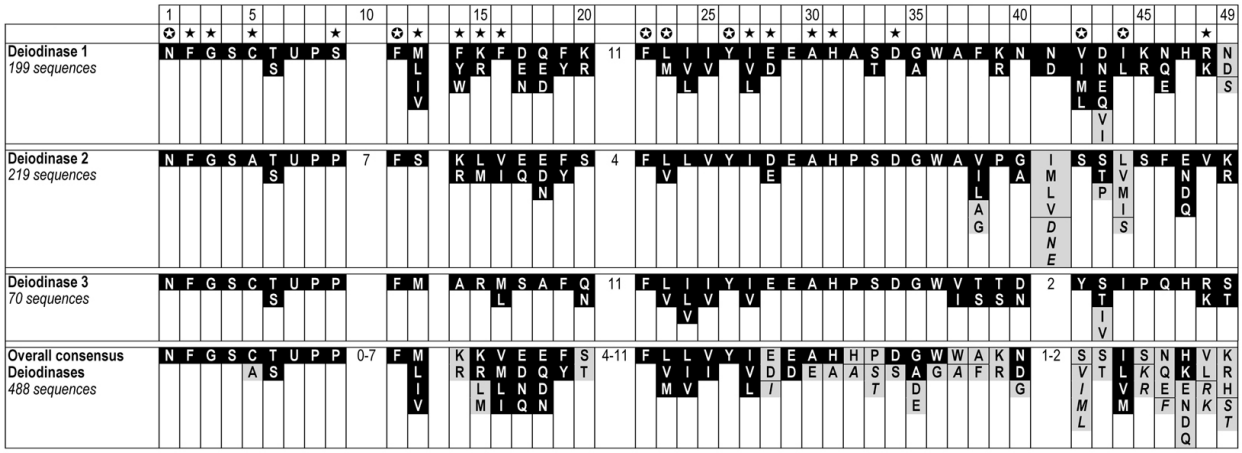

Figure 3. Consensus sequences for deiodinases. Based on frequency in a given position, groups of similar amino acids are written in white boldface on black background (frequency >50%) or in black boldface on gray background (frequency 34% to 50%). When the latter case occurs for two groups in the same position but their frequencies are different, amino acids belonging to the less frequent group are written in italics. In each position of the overall consensus, amino acids belonging to the same group are shown from top to bottom in decreasing order of frequency. Symbols in line 2 indicate the positions of amino acids that are very highly conserved (white star in a black circle) or highly conserved (black star) in the searched motif (5, 6).

Of the three consensus sequences for the three deiodinases, the one that matches the most the consensus sequence for one THPC is that of dio-1. This THPC is Apo C-III, since it shares 16 positions of very high conservation of a given group of residues, and 16 positions with either very high or high conservation (Table 1). In contrast, the THPC with the least resemblance are CBG (with all the three deiodinases) and TBG (with dio-1 only). CBG shares 5 positions of very high conservation and none of high conservation with dio-1 and dio-3, and 4 positions of very high conservation and 1 of high conservation with dio-2. TBG shares 5 positions of very high conservation and none of high conservation with dio-1 (Table 1).

Noteworthy, the 5-residue hydrophobic core TH-binding motif (columns 22-26) that one of us had originally detected as being evolutionarily conserved in apolipoproteins and being shared by other THPC (9), is only imperfectly conserved in all three deiodinases. Conserved are only the first two positions, while the fifth position is occupied by Tyr (Y) in lieu of the amino acid group I/L/M/V. This amino acid group immediately follows such Tyr (column 27), the only other proteins with I/L/V/M at column 27 being the nonapolipoprotein THPC, though at a modest degree of conservation (Figure 3). The resemblance with nonapolipoprotein THPC concerning the 5-residue motif at columns 22-26 is highlighted by (i) Phe (F) in the first position (column 22) of deiodinases matching Phe (F) as the most frequently used residue of the F/Y/W group in the first postion (column 22) of nonapolipoprotein THPC; (ii) the hierachical order L/V/M in the second position (column 23) of deiodinases matching the order L/V/M/I in nonapolipoprotein THPC; (iii) Leu (L) is the most frequently used residue of the I/L/M/V group in third position (column 24) of both deiodinases and nonapolipoprotein THPC. The resemblance extends on either side of columns 22-26, because (i) the first P (column 9) that follows SelCys (both residues participating in the active center of both dio-2 and dio-3) matches P in the nonapolipoprotein THPC, though this last P has a modest degree of conservation; (ii) F at column 11, and that participates in the active center of all three deiodinases, matches F (as the most frequently used residue of the F/Y/W group) at the same position in nonapolipoprotein THPC; (iii) such F is followed by M/L/I/V (column 12) and K/R, V/M/L/I (columns 14 and 15) in deiodinases, thus matching L/V/I/M, K/H/R and I/L/V/M in non-THPC (even though K/H/R and I/L/V/M are modestly conserved); (iv) E/D at column 28, which participates in the active center of the deiodinases, matches E/D/Q in nonapolipoprotein THPC and E/Q/D/N in apolipoprotein THPC; (v) S at column 33, which participates in the active center of the deiodinases, matches S/T in nonapolipoprotein THPC; (vi) W at column 36, which participates in the active center of the deiodinases, conservatively matches F/Y in nonapolipoprotein THPC.

4.3. Consensus motif of deiodinases vs consensus motif of cell surface TH transporters (CSTT)

These two consensus sequences (for a total of 488 and 8691 proteins, respectively) share 8 positions of a very high level of residue conservation (no. 1, 11, 12, 16, 22, 23, 24 and 44). Compared to THPC, there was more resemblance in usage of residues at such positions. Indeed, CSTT use most frequently N (Asn) at position 1, V (Val) at position 16, L (Leu) at position 22. Furthermore, one amino acid group that is very highly conserved in deiodinases is downgraded to highly conserved in the CSTT (column no. 35); the opposite occurs at another position (no. 42). Finally, there is one position (no. 15) where amino acids of a given group are highly conserved in the two consensus sequences.

Table 1. Highest and lowest number of matching positions between consensus motifs of deiodinases and consensus motifs of thyroid hormone plasma carriers (THPC), cell surface thyroid hormone transporters (CSTT) or thyroid hormone nuclear receptors (TR)

Thyroid hormone binding proteins	Deiodinase 1		Deiodinase 2		Deiodinase 3	
	Matching positions	Protein(s)	Matching positions	Protein(s)	Matching positions	Protein(s)
THPC	**16** (16+0)	Apo C-III	**13** (13+0)	Apo C-III	**13** (13+0)	Apo C-III
	5 (5+0)	CBG, TBG	**5** (4+1)	CBG	**5** (5+0)	CBG
CSTT	**13** (13+0)	MCT10	**13** (13+0)	OATP1C1, OATP1A2	**11** (11+0)	OATP3A, OATP4A1, OATP4C1
					11 (10+0)	OATP1B1
	5 (5+0)	OATP1B3	**7** (7+0)	OATP4A1, OATP4C1	**7** (7+0)	OATP1B3
TR	**8** (8+0)	TR alpha1	**5** (5+0)	TR alpha1	**10** (10+0)	TR alpha1
	7 (7+0)	TR beta1-2	**4** (4+0)	TR beta1-2	**9** (9+0)	TR beta1-2

Matches between very highly conserved (in more than 50% of the aligned sequences) groups of amino acids are typed on black background. Matches between highly conserved (in more than 33% but not more than 50% of the aligned sequences) groups of amino acids are typed on gray background. The total number of matches (very highly conserved + highly conserved) is typed boldface. In each cell of the table, the highest or lowest number of matches are shown above or below the dashed line, respectively.

Compared to THPC, there is more resemblance in the number of residues occupying the gapped positions (columns no. 10, 21 and 41): 0-7, 4-11 and 1-2 in deiodinases, and 0-14, 0-30 and 0-4 in CSTT, but 0-23, 0-30 and 0-7 in THPC.

Of the three consensus sequences for the three deiodinases, the ones that match the most the consensus sequence for one CSTT are those of dio-1 and dio-2. In detail, the consensus motif of dio-1 shares with the consensus motif of MCT10 13 positions of very high conservation of a given group of residues and none with high conservation (Table 1). A numerically identical match occurs between the consensus motif of dio-2 and those of OATPC1 or OATP1A2 (Table 1). In contrast, the CSTT with the least resemblance is OATP1B3, since it shares with dio-1 5 positions of very high conservation of a given group of residues, and none with high conservation (Table 1).

4.4. Consensus motif of deiodinases vs consensus motif of TH nuclear receptors (TR)

These two consensus sequences (for a total of 488 and 624 proteins, respectively) share 6 positions of a very high level of residue conservation (no. 1, 11, 12, 22, 44 and 47). There was no resemblance in usage of residues at these 6 positions. Furthermore, one amino acid group that is very highly conserved in deiodinases is downgraded to highly conserved in the THPC (column no. 6); the opposite phenomenon occurs at three positions (no. 45, 47 and 48). There are no positions where a given group of aminoacids is highly conserved at the same position in the two consensus sequences.

Compared to CSTT, there is higher resemblance in the number of residues occupying the gapped positions (columns no. 10, 21 and 41): 0-7, 4-11 and 1-2 in deiodinases, and 8, 8-9 and 3 in TR; but and 0-14, 0-30 and 0-4 in CSTT.

Of the three consensus sequences for the three deiodinases, the one that matches the most the consensus sequence for one TR is that of dio-3. This TR is TR alpha1, since it shares 10 positions of very high conservation of a given group of residues, and none with high conservation (Table 1). In contrast, the TR with the least resemblance is TR beta1-2, since it shares with dio-2 4 positions of very high conservation of a given group of residues, and none with high conservation (Table 1).

4.5. Overall consensus (based on 10,229 human and animal sequences)

As shown in Figure 1, the basic schema that had resulted from 426 sequences of human and animal THPC (5) and confirmed by adding 9,315 cell proteins (CSTT and TR) (6) continued to hold upon adding the sequences from 488 human and animal deiodinases. In the 10,229 sequences, 15 positions are very highly conserved and another 18 positions are highly conserved. The very highly conserved 5-residue core TH-binding motif (columns 22-26) now consistes of the stretch W/F/Y, L/I/V/M, I/V/M/L, P, L/V/I/M. Noteworthy, the hierarchy of usage L/I/V/M occurs at a total of 7 positions (no. 2, 5, 20, 22, 29, 40 and 44).

4.6. Relationship of the catalytic site of the deiodinases with the deiodinase consensus motif

In the three human deiodinases Bianco *et al*. (10) and Callebaut *et al*. (11) identified a highly conserved carboxy-termi-nal segment (from amino acid 105 of dio-1, 112 of dio-2 or 123 of dio-3 to the

Table 2. Comparison between conserved positions in the catalytic domain of each human deiodinase (2, 10, 11) and the corresponding consensus motif

Deiodinase 1 (accession number: P49895.3)		Deiodinase 2 (accession number: Q92813.4)		Deiodinase 3 (accession number: AAB35616.2)	
Position in the amino acid sequence	**Position in the consensus motif**	**Position in the amino acid sequence**	**Position in the consensus motif**	**Position in the amino acid sequence**	**Position in the consensus motif**
F121	F-2	F128	F-2	F139	F-2
S123	S-4	S130	S-4	S141	S-4
U126	U-7	U133	U-7	U144	U-7
S128	S-9	P135	P-9	P146	P-9
F129	F-11	F136	F-11	F147	F-11
E155	E-28	D162	D/E-28	E173	E/D; I-28
E156	E-29	E163	E-29	E174	E/D-29
H158	H-31	H165	H-31	H176	H-31 A-31
S160	S/T-33	S167	S-33	S178	S-33
W163	W-36	W170	W-36	W181	W-36
H174	H-47	H185	not within motif	H193	H-47
S212	not within motif	A226	not within motif	Y231	not within motif
E214	not within motif	E228	not within motif	E233	not within motif

SelCys is abbreviated as U in the one-letter code by the International Union of Pure and Applied Chemistry (IUPAC). Amino acids which are very highly conserved in consensus sequences (more than 50%) are typed in white boldface on black background. Amino acids which are highly conserved in consensus sequences (more than 33% but not more than 50%) are typed in black boldface on gray background.

end of the respective proteins) and, within it, an “active center”, with experimentally demonstrated functional importance (segment 115-129 of dio-1, 122-136 of dio-2 and 133-147 of dio-3) (10). With small differences, this carboxy-terminal segment and its “active center” were found to be highly conserved also across different species. Subsequently, Schweizer *et al*. (12, 13) defined the three-dimensional structure of the catalytic domain of murine dio-3, confirming that it is located in the carboxy-terminal part of the molecule. Also, they identified the amino acids involved in the interaction with the ligand. In their numbering, these amino acids were S167, U170 (although it was substituted with a cysteine in their experiment), E200, H202, H219, E259 and R275, which correspond to S141, U144, E174, H176, H193, E233 and R249, respectively, in the numbering used by Bianco *et al*. (10).

As shown in Table 2, most of the important amino acids (including SelCys) that form the catalytic site of each deiodinase fall within the segments corresponding to our TH-binding associated consensus motif, namely 120-176 of dio-1, 127-183 of dio-2 and 138-195 of dio-3. This holds true even when using more recent data (12, 13), as shown in Table 3.

To date, the only three-dimensional model of deiodinases available in public domain databases is that of the aforementioned catalytic domain of murine dio-3 (12). We retrieved this model (accession code: 4TR3) from the Molecular Modeling Data Base (https://www.ncbi.nlm.nih.gov/Structure/MMDB/mmdb.shtml)(14) of the NCBI (National Center for Biotechnology Information) to further confirm the correspondence between our motif and the functionally important domains and positions reported in literature. Correspondence with data reported by Bianco *et al*. (10) is shown in Figure 4, while correspondence with data reported by Schweizer *et al*. (12, 13) is shown in Figure 5. It is evident that our motif includes the majority of fundamental amino acids and a relevant portion of the surrounding protein structure.

5. DISCUSSION

Here we vhave verified our hypothesis that the large TH-binding motif is conserved in selenodeiodinases from *Homo sapiens* and a total of 198 other species.

Because dio-1 and dio-3 are attached to the plasma membrane, though most of their sequence is cytosolic, and because there are striking resemblances between all deiodinases and nonapolipoprotein THPC, a special physical relationship can somehow take place between the TH carried by the THPC in the extracellular fluid and deiodinases, with dio-1 and dio-3 ready to activate/deactivate TH immediately after TH entry into the cells. The remarkable redundancy of nonapolipoprotein THPC, and with very wide TH binding affinity, can be explained by the importance of the postulated physical relationship, so that this relationship has to be defended with the availability of as many carriers as possible.

Table 3. Comparison between amino acids involved with ligand binding in the catalytic domain of murine deiodinase 3 (12, 13) and the corresponding consensus motif. Amino acids are numbered according to Bianco *et al*. (10).

Deiodinase 3 (accession number: AAL23960.1)	
Position in the amino acid sequence	**Position in the consensus motif**
S141	S-4
U144	U-7
E174	E/D-29
H176	H-31 A-31
H193	H-47
E233	not within motif
R249	not within motif

SelCys is abbreviated as U in the one-letter code by the International Union of Pure and Applied Chemistry (IUPAC). Amino acids which are very highly conserved in consensus sequences (more than 50%) are typed in white boldface on black background. Amino acids which are highly conserved in consensus sequences (more than 33% but not more than 50%) are typed in black boldface on gray background.

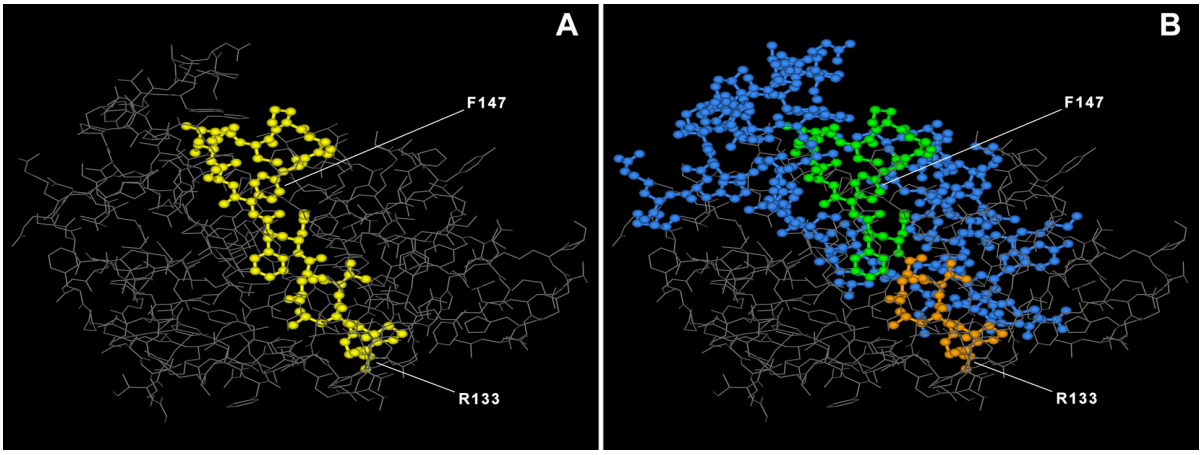

Figure 4. Schematic representation of the catalytic domain of murine deiodinase 3 (accession code: 4TR3). Notable amino acids are shown in "ball and stick" mode, others in "wireframe" mode. Amino acids are numbered according to Bianco *et al*. (10). a) amino acids which constitute the "active center" of the molecule according to Bianco *et al*. (10) are shown in yellow. b) Amino acids corresponding to the TH-binding motif discussed in this paper are shown in light blue, or in green when they match those of the "active center" (see panel a). The other amino acids of the "active center" are shown in orange

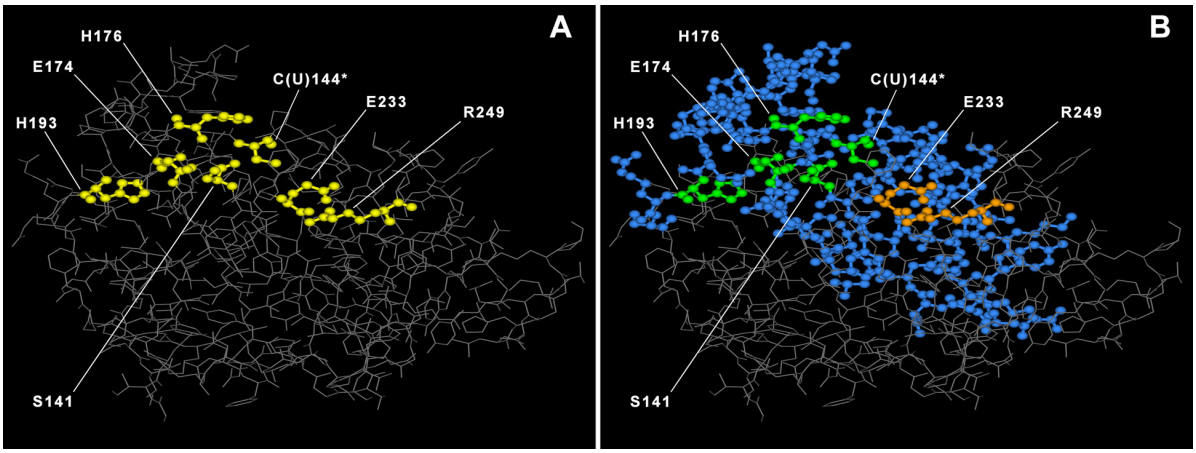

Figure 5. Schematic representation of the catalytic domain of murine deiodinase 3 (accession code: 4TR3). Notable amino acids are shown in "ball and stick" mode, others in "wireframe" mode. Amino acids are numbered according to Bianco *et al*. (10). *The three-dimensional model published by Schweizer *et al*. (12) has a cysteine (C) in this position, but the actual protein has a selenocysteine (U). a) amino acids which are involved in ligand binding according to Schweizer *et al*. (12) are shown in yellow. b) Amino acids corresponding to the TH-binding motif discussed in this paper are shown in light blue, or in green when they match those involved in ligand binding (see panel a). The other amino acids involved in ligand binding are shown in orange.

In summary, a variety of plasma, cell membrane and cell nucleus proteins so diverse genetically and functionally share the property of binding TH because they share a local region of homology, which we refer to as a large TH binding motif. It is likely that the TH-binding domain of proteins originated from a common ancestor gene, with "variations on the theme" at certain positions dictated by localization in the body (fluids, cell, nucleus) and overall function of the single proteins. In brief, starting from their secretion by the thyrocyte and ending with their inactivation, the journey into the body of iodinated TH is a continuous relay among proteins that share a TH-binding domain.

6. REFERENCES

1. P. M. Yen, G. A. Brent. Genomic and nongenomic actions of thyroid hormones. In: Werner and Ingbar's The Thyroid: a fundamental and clinical text, 10th ed. Eds: LE Braverman, DS Cooper, Wolters Kluwer, Lippincott Williams & Wilkins, Philadelphia, 127-138 (2013)

2. A. C. Bianco, B. W. Kim. Intracellular pathways of iodothyronine metabolism. Implications of deiodination for thyroid hormone action. In: Werner and Ingbar's The Thyroid: a fundamental and clinical text, 10th ed. Eds: LE Braverman, DS Cooper, Wolters Kluwer, Lippincott Williams & Wilkins, Philadelphia, 103-126 (2013)

3. T.M.Ortiga-Carvalho, M. I. Chiamolera, C. C. Pazos-Moura, F. E. Wondisford: Hypothalamus-pituitary-thyroid axis. *Compr Physiol* 6, 1387-1428 (2016)
DOI: 10.1002/cphy.c150027
PMid:27347897

4. IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN) and Nomenclature Committee of IUBMB (NC-IUBMB): Newsletter 1999. *Eur J Biochem* 264, 607-609 (1999)

5. S. Benvenga, F. Guarneri: Conservation in the phylum of the local homology of apolipoproteins with the thyroid hormone plasma carriers. *Rev Endocr Metab Disord* 17, 537-544 (2016)
DOI: 10.1007/s11154-016-9379-7
PMid:27549767

6. S. Benvenga, F. Guarneri: Thyroid hormone-interacting cell and plasma proteins share a common motif. *Front Biosci* (2018), in press. *Front Biosci (Schol Ed)* 10, 326-336 (2018)
DOI: 10.2741/s519

7. F. Guarneri, B. Guarneri: Bioinformatic analysis of HLA-linked genetic susceptibility to immunoallergic diseases: the MotiFinder software. *Ann Ital Dermatol Allergol* 64, 69-75 (2010)

8. S. Benvenga, H.J. Cahnmann, D. Rader, M. Kindt, A. Facchiano, J. Robbins: Thyroid hormone binding to isolated human apolipoproteins A-II, C-I, C-II, and C-III: homology in thyroxine binding sites. *Thyroid* 4, 261-267 (1994)
DOI: 10.1089/thy.1994.4.261
PMid:7833661

9. S. Benvenga: A thyroid hormone binding motif is evolutionarily conserved in apolipoproteins. *Thyroid* 7, 605-611 (1997)
DOI: 10.1089/thy.1997.7.605
PMid:9292950

10. A. C. Bianco, D. Salvatore, B. Gereben, M. J. Berry, P. R. Larsen: Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev* 23, 38-89 (2002)
DOI: 10.1210/edrv.23.1.0455
PMid:11844744

11. I.Callebaut, C. Curcio-Morelli, J. P. Mornon, B. Gereben, C. Buettner, S. Huang, B. Castro, T. L. Fonseca, J. W. Harney, P. R. Larsen, A. C. Bianco: The iodothyronine selenodeiodinases are thioredoxin-fold family proteins containing a glycoside hydrolase clan GH-A-like structure. *J Biol Chem* 278, 36887-36896 (2003)
DOI: 10.1074/jbc.M305725200
PMid:12847093

12. U.Schweizer, C. Schlicker, D. Braun, J. Kohrle, C. Steegborn: The crystal structure of mammalian selenocysteine-dependent iodothyronine deiodinase suggests a peroxiredoxin-like catalytic mechanism. *Proc Natl Acad Sci U S A* 111, 10526-10531 (2014)
DOI: 10.1073/pnas.1323873111
PMid:25002520 PMCid:PMC4115520

13. U.Schweizer, C. Steegborn: New insights into the structure and mechanism of iodothyronine deiodinases. *J Mol Endocrinol* 55, R37-52 (2015)

14. T.Madej, C. J. Lanczycki, D. Zhang, P. A. Thiessen, R. C. Geer, A. Marchler-Bauer, S. H. Bryant: MMDB and VAST+: tracking structural similarities between macromolecular complexes. *Nucleic Acids Res* 42 (Database issue), D297-303 (2014)

Key Words: Thyroid hormones, Selenodeiodinases, Thyroid hormone deiodination, Amino acid sequence homology, Motifs

Send correspondence to: Fabrizio Guarneri, Department of Clinical and Experimental Medicine, Dermatology, via Consolare Valeria, Gazzi, 98125 Messina, Italy, Tel: 39 090 2212890, Fax: 39 090 2927691, E-mail: f.guarneri@tiscali.it