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# Physiological Regulation of E-Cadherin Adhesiveness

**María F Izaguirre, Carolina D Galetto and Víctor H Casco***

*Laboratorio de Microscopia Aplicada a Estudios Moleculares y Celulares, Facultad de Ingeniería (Bioingeniería-Bioinformática), Universidad Nacional de Entre Ríos. Ruta 11, Oro Verde, Entre Ríos, Argentina*

***Corresponding author:** Casco VH, Laboratorio de Microscopia Aplicada a Estudios Moleculares y Celulares, Facultad de Ingeniería (Bioingeniería-Bioinformática), Universidad Nacional de Entre Ríos. Ruta 11, Oro Verde, Entre Ríos, Argentina, E-mail: vcasco@bioingenieria.edu.ar

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## Abstract

Physiological controls on cell adhesion mediated by E-cadherin have been frequently focused in the proliferation restraining. This can be given both by contact inhibition *via* the regulation of homotypic cadherin expression, by the control of adhesive strength, or even for the activation of proliferation mediated by growing factors. However, few studies have been conducted to evaluate the possible effects of hormones on the cell-cell adhesion mechanisms, during animal development and the maintenance of adult tissues and organs. Thus, the analysis of thyroid hormone influence on E-cadherin adhesive potential result highly challenging and promising field of research in cell biology.

**Keywords:** Cadherin; Thyroid hormones; Cell adhesion

## Introduction

Growth factors are responsible for the crosstalk between cell proliferation, migration, and adhesion. As was early determined, the binding of the hepatocyte growth factor (HGF) to its receptor c-Met, causes cell-cell dissociation coupled to endocytosis of both E-cadherin and c-Met [1-3]. Fibroblastic growth factor (FGF) also induces E-cadherin endocytosis along with Fibroblastic growth factor receptor-1 (FGFR1), *via* a classical clathrin-mediated pathway [4]. In contrast, stimulation by Epidermal growth factor (EGF) causes Rac-1-dependent E-cadherin internalization by macropinocytosis, internalized-E-cadherin association with the sorting nexin 1 (SNX-1) preventing its degradation and facilitating the recycling back to the cell surface for AJs maintenance (Figure 1) [5].

Therefore, different growth factors-signaling pathways within the same cell can lead to very different fates for the E-cadherin internalization and surface-stabilization, possibly to achieve differentiated cell effects. Moreover, the co-regulation of E-cadherin and growth factor signaling is particularly prominent in various examples of Mesenchymal-Epithelial Transition (EMT) and tumorigenesis. Tumoral growth factor (TGFβ) signaling seems to be a key regulator for E-cadherin expression loss in response to Ras-Raf signaling during EMT [6-31]. E-cadherin mutants, in turn, reduce interactions between E-cadherin and EGFR, inducing EGFR dimerization, resulting in increased cell surface motility, enhanced activation of tumoral cells, and also E-cadherin internalization [3].

In contrast to growth factors-signaling on cell junctions, the hormonal physiological regulation of junctional communication has been scarcely analyzed. The most studies have evaluated hormonal regulation of gap junction-proteins expression, formation and/or maturation [13,15,32-50]. A long time ago we have focused on unraveling the functioning of E-cadherin mediated epithelial adhesion junctions during vertebrate development, and under hormonal influence [18,19,26-29]. Interesting, recently it was detected that the distribution/expression of N-, E- and VE-cadherin's as well as α-catenin and F-actin were significantly altered in pancreatic islet cells of obese and diabetic mice [14]. In addition, it was found that the glucocorticoids promote respiratory epithelial barrier integrity by inducing protocadherin-1 expression [35].

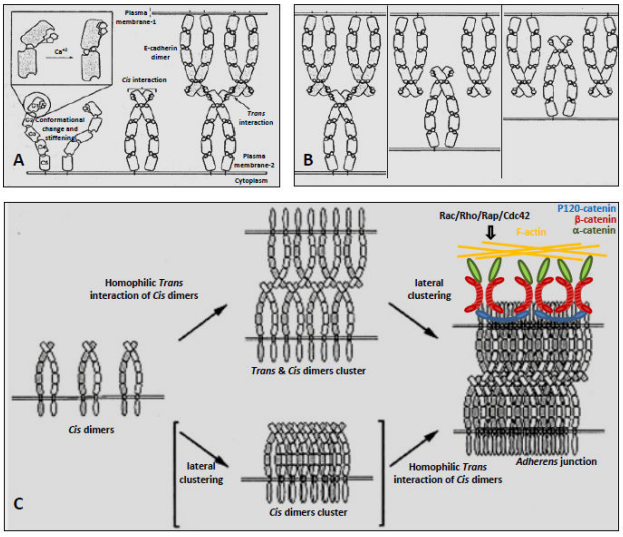


**Figure 1:** Interaction of *Cis* dimers.

## Genomic and Non-Genomic Actions of Thyroid Hormones

It is widely recognized that thyroid hormones (TH) modulate energy metabolism, having a great influence on growth and development by independent mechanisms [51-61]. While thyroid calorigenesis is influenced predominantly *via* nuclear receptors that mediate synthesis of mitochondrial respiratory complexes and cell membrane sodium-potassium ATPase, it has been suggested that many of the TH effects over development are mediated *via* growth factors [16]. TH binding to thyroid hormone-nuclear receptors (TR), which

belong to the nuclear hormone receptor superfamily of transcription factors [39], stimulates growth hormone (GH) synthesis, and probably potentiates GH stimulation on somatomedin (SM) production as well as, the erythropoietin (EP) production, being nerve growth factor (NGF) and epidermal growth factor (EGF), key players for erythrocyte production, autonomic and central nervous system maturation, and epidermal development, respectively [16].

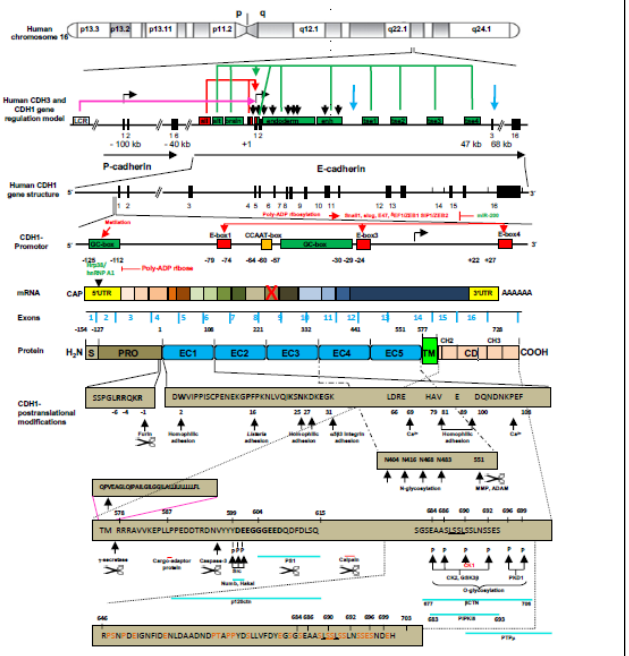


**Figure 2:** Gene transcription.

The cellular action of THs through TRs involves, the conversion of L-T4 to T3 and this binds to heterodimers of retinoic acid X-receptors (RXRs)-TRs, which together, in turn, bind to T3 response elements located within the genomic regions of target genes, mediating TH-regulated gene expression [41,45,62]. The general model for TH action in the nucleus propose that in the absence of T3, the TR-RXR heterodimeric complexes interact with co-repressor proteins inhibiting the target gene transcription (Figure 2). When nuclear T3 concentration increases, it binds to receptor complexes displacing the co-repressors and recruiting the co-activators to activate the T3-dependent target genes transcription. In addition to TR-mediated genomic actions, it has been revealed that THs also exert rapid non-genomic actions mediated by cell membrane receptors. Thus, integrin αvb3 is a cell membrane specific receptor for T4 and T3, which activate the mitogen-activated protein kinase (MAPK) intracellular cascade (Figure 2) [11,12]. TH-dependent MAPK activation modulate the membrane potential by regulation of ion transporters channels, $Na^+/K^+$ exchanger, $Ca^{2+}$-ATPase, regulating the sub-membrane actin cytoskeleton and the intracellular protein trafficking [12,33]. TH-activated MAPK, in turn, can rapidly translocate to the nucleus inducing serine phosphorylation of TRs, thereby promoting angiogenesis and tumor cell proliferation [10,11]. THs also promote the protein serine phosphorylation *via* MAPK, regulating transcriptional activity of p53, STAT1a and STAT3 (Figure 2) [42,43,56].

The thyroid hormone receptor domain of integrin αvβ3 is at, or near the Arg-Gly-Asp (RGD) recognition site [2,9]. Another aspect to be considered is that T3 exerts its actions depending on the isoform of the receptor involved. Thus, TRα regulate the mitochondrial gene expression and metabolic function [61]. In addition, TRα or TRβ forms could act through the formation of a cytoplasmic complex with the PI3K-p85 subunit inducing the protein kinase B/Akt nuclear translocation (Figure 2) [23]. *THRA* and *THRB* genes encode the TRα and TRβ isoforms respectively, which are ubiquitously expressed [62]. Moreover, depending on species, tissue or experimental systems, there are predominant TR cell isoforms, and each gene can generate different proteins using different promoters and/or alternative splicing [55,62].

*Xenopus* have two *TRα* genes and two *TRβ* genes due to tetraploid condition although when *Xenopus laevis* is a functional diploid organism, its genome shows several features reminiscent of its allotetraploid origin. Alternative splicing of the TRβ transcripts gives rise to two different isoforms for each *TRβ* gene [55]. In mammals, two genes encode for the T3 nuclear receptors TRα and TRβ [63]. Each gene generates different proteins using different promoters and/or alternative splicing [43,55,63]. The TRα locus codes for four isoforms, but only TRα1 can bind both T3 and DNA [1-63]. TRα1 and TRα2 result from the alternative splicing of a primary transcript [34]. TRΔα1 and TRΔα2 result from the alternative splicing of a secondary transcript, starting from an internal promoter that is located in the intron 7 [8]. TRα2, TRΔα1, and TRΔα2 behave as antagonists of TRα1 on its target genes through a mechanism that has not been characterized yet [8,34,48]. TRα1 and TRα2 have a widespread, ubiquitous expression, whereas the short TRΔα1 and TRΔα2 isoforms display restricted expression patterns [17]. The TRβ locus codes for four isoforms, including three receptors, TRβ1, TRβ2, and TRβ3, that result from three different transcription start sites [17,22]. The TRΔβ3 lacks the DNA-binding domain and behaves like a competitive inhibitor of the three TRβ and TRα1 receptors. Moreover, TRβ3 and TRΔβ3 were only described in the rat genome [60]. TRβ1 displays a ubiquitous expression and is the main TR isoform expressed in the liver. TRβ2 expression is restricted to the pituitary gland, the hypothalamus-TRH neurons, the developing retina, and the inner ear. TRβ3 is expressed in liver, kidney and lung, whereas TRΔβ3 is present in skeletal muscles, heart, spleen, and brain [17,60]. Interesting, almost all the TR isoforms are expressed in intestinal epithelial cells [47,48].

Usually, the T3-concentrations that lead to TRE-dependent responses occur in the picomolar range, whereas the minimum T3-concentrations, which activate Akt and eNOS are somewhat higher, within the TR-dissociation constant value (i.e., 0.1-1 nM) [62]. It is unknown why higher concentrations of T3 are required for Akt and eNOS activation compared with that of TRE-dependent responses [23]. Through the tissular differential TR-expression, TRα1 or TRβ1 mediate the activation of PI3-kinase/Akt/eNOS or PKB-mTOR-p70(S6K) pathways [7,23]. Additionally, due most of T3 is bound to carrier proteins such as thyroxine-binding globulin (TBG), albumin, and thyroid-binding pre-albumin *in vivo*, only 0.3% of T3, and 0.03% of T4 are unbound and free to interact with TR, and to produce biological activity [60]. In murine thyrocytes, TRβ1 is able to inhibit the Wnt/β-catenin pathway, through its interaction and consequent sequestration of β-catenin, resulting in cell proliferation down-modulation (Figure 3) [20].

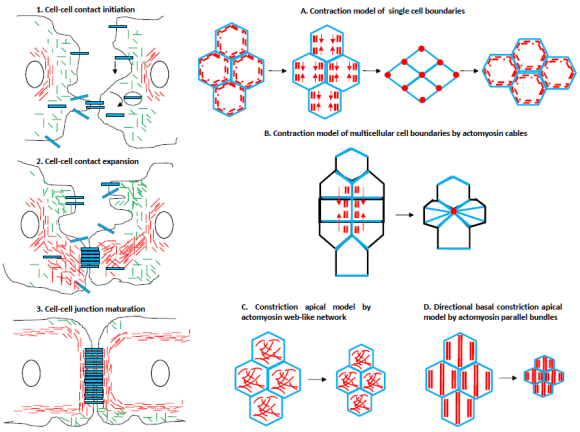


**Figure 3:** Cell proliferation down-modulation.

Nowadays, numerous evidences shown the TH parallel action on membrane receptors, cytoplasmic partners and HT-target genes, such as genes involved on adhesive contacts, and cell proliferation/differentiation functions [21,23,27,28,36-38,44 ,49,57,58].

## Thyroid Hormones as Specific Regulators of Cell Adhesion Mediated by E-Cadherin

Analogous to the positive T3-responsive *RTHB* gene (RTβ), we found that E-cadherin, β- and α-catenin genes are upregulated at 24 h T3-postreatment [6,19,51,54]. A similar performance is exhibited by the Rac1 small GTPase. On the contrary, occludin and Rap1 expression become more significant at day 5 of T3-treatment. Similar to IFABP behavior, a negative T3-responsive gene [53], the Rho small GTPase decreased at day 5 of T3-treatment. The p120-catenin, Arp2 actin-nucleation protein, Cdc42 and ZO-1 mRNA levels remain practically unchanged both at 24 h and day 5 of T3-treatment, as well as during spontaneous metamorphosis [18,19]. Supporting these results, putative TRE were found *in X. laevis* E-cadherin, β-catenin, α-catenin and *Rac1* genes, but not in the *p120-ctn* gene, using bioinformatics tools [18]. While one TRE was found in 5'UTR and intron-1 of E-cadherin, and β-catenin and *Rac1* genes respectively, three TRE were found in *α-catenin* gene (TRE1 in 5'UTR and TRE2 and TRE3 in intron-1) [18].

The duo-expression analysis of guanine nucleotide exchange factors (GEFs) and GTPase-activating protein (GAP) for each small GTPase pairs: Rac1-TIAM/GAP12; Rap1-C3G/SPA1; Cdc42FRG/Rich and RhoA-GEF18/p190-GAP was less conclusive, but its genes do not respond directly to T3. Only Rac1-GAP12 showed a significant physiological increase at 5 days of T3- induction correlated with decrease of Rac1 and increase of Rap1. These results mainly suggest non-genomic control mechanisms on their GEFs/GAPs and/or others involved [19]. Moreover, the morphometric ultrastructural analysis of *X. laevis* digestive tract provided very relevant data. While the numbers of tight junctions (TJ) are not modified during T3-treatment, supporting their role in the maintenance function of the epithelial barrier from larval stages to juvenile stages, adherens junctions (AJ) and desmosomes (Dm) led the major changes in epithelial remodeling. At 24 h of T3 treatment while AJ number remain constant, Dm significantly decreased. However, the cell-cell distance of AJ and Dms significantly increased, suggesting the increase of epithelial adhesive plasticity, promoting cell proliferation and migration during gastrointestinal remodeling. At 5 days of T3-induction in agreement with a differentiated epithelium, the cell-cell distances of AJ and Dm return to those of mature epithelia, now of juvenile anurans. In contrast, a significant decrease of AJ and a significant increase of Dm were produced correlated with an impressive increase of apical complex junctions (ACJ), features of epithelial barrier strengthening (Figure 1). In addition, the morphometric IHC analysis has demonstrated that T3 exerts a positive regulatory effect on E-cadherin and β- and α-catenin expression and *de novo* synthesis in stomach epithelium during metamorphosis (Figure 2) [28].

From these results we can conclude that T3 mediates genomic response on E-cadherin, β-, α-catenin and Rac1 gastrointestinal genes, rapidly responding to adhesive plasticity and promoting lamellipodia formation, necessary during epithelial remodeling. In contrast, the master regulator of junctional E-cadherin stability, p120-catenin does not respond to T3, whereas Rap1 indirectly reacts to T3 during the reestablishment of mature epithelium. Rap1 is involved in the regulation of epithelial cell adhesion and migration. Rap1 is required for homotypic E-cadherin interactions [24]. Ligation of the extracellular domain of E-cadherin enhances Rap1activity, which in turn is necessary for the proper targeting of E-cadherin molecules to maturing cell-cell contacts [24]. In the presence of Rap1, afadin/nectin-partner and p120-catenin reduce endocytosis of E-cadherin that is not engaged in homophilic interactions and thereby further accumulates non-trans-interacting E-cadherin to the nectin-based cell-cell adhesion sites for the formation of AJ [25]. Rap1 contributes, in turn, to intestinal epithelial barrier stabilization *in vivo* [59]. Afadin is important for proper Rap1 activation and control of epithelial barrier function under basal and inflammatory conditions *in vivo* and *in vitro*. However, the exact mechanism by which Rap1 regulates these processes remains to be elucidated in future studies. Some studies suggest that active Rap1 stabilizes the barrier by dampening acto-myosin contractility through the regulation of RhoA/ROCK-mediated actin dynamics [52].

## Conclusion

Recently, we have proven that T3 is a key mediator of genomic response on E-cadherin, β-, α-catenin and Rac1 *X. laevis* gastrointestinal genes, which rapidly responding to adhesive plasticity, promoting lamellipodia formation, necessary during epithelial remodelling. Conversely, the master regulator of junctional E-cadherin stability, p120-catenin does not respond to T3, whereas Rap1 indirectly reacts to T3 during the re-establishment of mature epithelium. These behaviours open the possibility for alternative treatments to control proliferative disorders as colon cancer and other epithelial dysfunction diseases.

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