Thyroid Embryogenesis

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1.1 Where Does the Adult Thyroid Come from?

The thyroid gland has a characteristic shape consisting of two elongated lobes connected by a narrow isthmus. In humans, it is located in front of the trachea at the base of the neck, between the thyroid cartilage and the V-VI tracheal ring. The gland has a distinctive histological organization characterized by the presence of spheroidal structures, called follicles. Follicles consist of a closed cavity (follicular lumen) surrounded by a layer of epithelial cells known as thyroid follicular cells (TFC) devoted to the production and export of thyroid hormones. In addition to TFCs, the most abundant other endocrine cells, C cells responsible for calcitonin production, are scattered in the interfollicular space.

The processes leading to the formation of the adult thyroid involve both the assembly of distinct embryonic structures originated in different locations (the *thyroid anlage* and the ultimobranchial bodies) and the differentiation of multipotent cells toward a highly specialized phenotype. Such processes require the harmonized action of genetic factors acting outside (extrinsic) and inside (intrinsic) the precursors of thyroid cells [1].

Thyroid development in humans (summarized in O'Rahilly [2] and more recently in Polak [3]) has been accurately described, at microscopic level, since the first

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decades of the 1900s. In the last 20 years, the molecular pathways underlying thyroid organogenesis have been systematically analyzed in animal models, mostly in mice. *Zebrafish* (Danio rerio), a tropical freshwater teleost fish, has also been used as a valuable tool in developmental biology including thyroid morphogenesis [4]. Data from animal models and insights from patients presenting thyroid dysgenesis (i.e., impaired thyroid development) have allowed to dissect the genetic mechanisms controlling the development of the thyroid gland that are to a large extent conserved among vertebrates [5].

1.2 A Morphological Description of Thyroid Development in Humans

The adult thyroid gland is assembled from different embryonic components: a median component (the thyroid bud, derived from the *thyroid anlage*) and two lateral structures (the ultimobranchial bodies).

According to Weller [6], in human embryos the "median thyroid primordium" (*thyroid anlage*) is visible at Carnegie stages (C)9 (length crown-rump ca. 1.5–2.5 mm; 1–3 pairs of somites; ca 20 days) as a fold in the ventral wall of the primitive pharynx. At this stage, the thyroid primordium consists of an accumulation of endodermal cells; the cells are closely packed but do not appear different from the other cells of the surrounding endoderm. At C10, embryonic day (E) 22, the thyroid primordium is clearly evident as a midline endodermal thickening in the floor of the primitive pharynx caudal to the region of the first branchial arch which forms the *tuberculum impar*. This thickening, 2 days later at CS 11, forms a small endodermal pit-like depression and then an outpouching of the endoderm so that the thyroid appears as a bud (spherical nodule) [2]. The thyroid bud is a nonhomogeneous structure, formed by high and pseudostratified epithelial cells different from those lining the pharynx [7]. As a consequence of the outgrowth and budding of the thyroid anlage, the developing thyroid by E26 appears as a flask-like structure with a narrow neck. This structure becomes an endodermally lined diverticulum that starts from the midline of the dorsum of the tongue and extends caudally. The distal part of the diverticulum represents the anlage of the gland itself connected with the floor of the pharynx by the thyroglossal duct. By E30, the thyroid anlage becomes larger while the thyroglossal duct becomes rather thinner and starts to fragment by CS 15 (ca 7–9 mm; E33). At CS16, the developing thyroid is a bilobate structure still not connected with the pharynx [6]. Finally, the thyroid reaches its destination in front of the trachea between E45 and E50 and shows its definitive external form - two lobes connected by the narrow isthmus – by CS20 (ca 18–22 mm; ca E51).

The ultimobranchial bodies (UBBs) – the so-called lateral thyroid component - are first evident at E24, as an outpouching of the ventral region of the fourth pharyngeal pouches. By E35, UBB primordia appear as long-necked flasks which start to migrate a few days later, losing any connection with the pharynx. After a ventral to caudal migration, UBBs are visible in close contact with the developing thyroid

at CS18 (E44). Then, the two structures merge; around E55, cells from UBBs and median thyroid are completely fused.

The subsequent formation of the peculiar follicular organization of the thyroid requires several weeks [8]. This process begins after 7 weeks of gestation when thyroid tissue is composed of strands of unpolarized thyroid cells. By the 10th week, small canaliculi appear in the thyroid tissue. Then, these small canaliculi enlarge, and around the 11th week, small follicles are clearly visible Progressive follicular growth occurs by the 12th week onward [9]. T4 is first detected at the 11th week, but a robust hormone production begins around 15-16 weeks [10].

1.3 Thyroid Development in Animal Models

1.3.1 Ontogenesis

The process of gastrulation divides the embryonic epiblast into three germ layers, ectoderm, mesoderm, and endoderm, the most internal layer of the vertebrate embryo (Fig. 1.1a). Embryos of different vertebrate species show divergent morphogenetic modes; however, after gastrulation and just before the organogenesis processes begin, all embryos share similar body plans when the endoderm generates a primitive gut tube. The tube, which runs along the anterior-posterior (craniocaudal) axis of the embryo, is subdivided into the foregut - the most anterior (cranial) region of the tube, midgut, and hindgut (Fig. 1.1b). The endoderm contributes to a remarkable number of cell lineages which form the epithelial components of many organs, such as intestine, liver, pancreas, stomach, lungs, thymus, and thyroid, the anterior-most organ that originates from the foregut.

Shortly after formation, the gut tube is formed of a single layer of largely unspecified epithelial-like cells. Subsequently, due to complex phenomena, only partially clarified, the endodermal cells acquire a positional identity along the anterior-posterior axis, and distinct groups of cells can be identified by the expression of specific signaling molecules and transcription factors. Endodermal cells are recruited into specific cell lineages (this initial, still reversible, step of the differentiation program is called *specification*); as a consequence, the tube, previously monotonous, is patterned in defined domains (*endoderm regionalization*). In many cases, the first visible event is the appearance of a multilayered structure from which, eventually, organ primordia emerge as outpockets (buds) from the tube (Fig. 1.1b).

As in humans, also in mouse embryos (19.5 day-long gestation), the earliest morphological proof of thyroid specification is the appearance, at E 9–9.5, of an endodermal thickening in the ventral wall of the primitive pharynx (Fig. 1.2). However, a day before this thickening is evident, a group of cells of the pharynx endoderm (*thyroid anlage*) is distinguishable from any other endodermal cells for the simultaneous expression of the transcription factors Nkx2-1, Pax8, Foxe1, and Hhex [11]. These cells can be defined as precursors of thyroid follicular cells (pTFC), i.e., developing thyroid cells that do not yet synthesize thyroid hormones. It is worth noting that, even if the ultimobranchial bodies participate in the organogenesis of the gland, thyroid

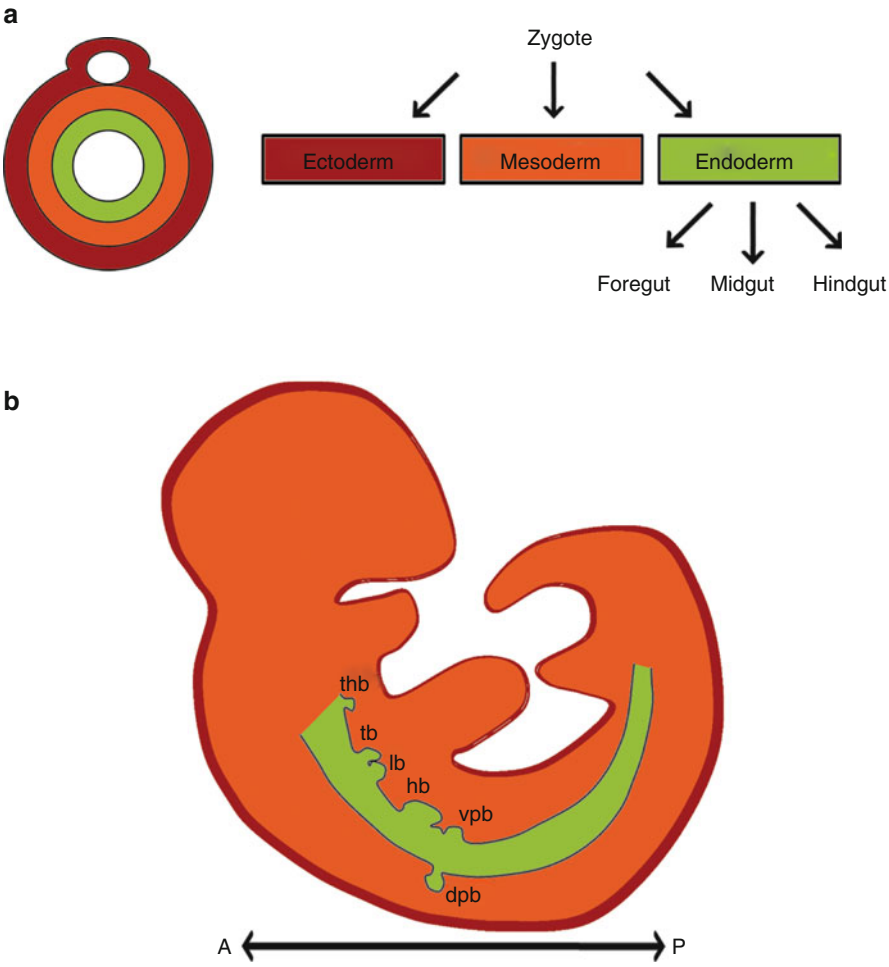

Fig. 1.1 Early stage of mammalian development. Panel **a**: Schematic cross-section of a mammalian embryo after gastrulation. The position of three germ layers, ectoderm (*brown*), mesoderm (*orange*), and endoderm (*green*) is indicated. The endoderm is the internal-most layer of the embryo. Panel **b**: The endoderm lineage. The endoderm generates a primitive gut tube which runs along the anterior-posterior axis of the embryo. The tube is subdivided into the foregut (the most anterior region of the tube), midgut and hindgut. Panel **c**: Schematic representation of an E10 mouse embryo. The embryonic structures derived from ectoderm, mesoderm and endoderm are indicated in brown, orange and green respectively. At this stage the primordia of organs derived from the foregut are evident as buds (outpockets) from the primitive endodermal tube. *thb* thyroid bud, *tb* trachea bud, *lb* lung bud, *hb* liver bud, *vpb* ventral pancreatic bud, *dvb* dorsal pancreatic bud. A ← → P: anterior-posterior axis of the embryo (Courtesy of Dott. MT De Angelis)

hormone-producing cells derive only from the thyroid anlage. This assumption has been proven formally using lineage studies in zebrafish [12] but not yet in mammals where thyroid primordium and UBBs merge in the definitive gland.

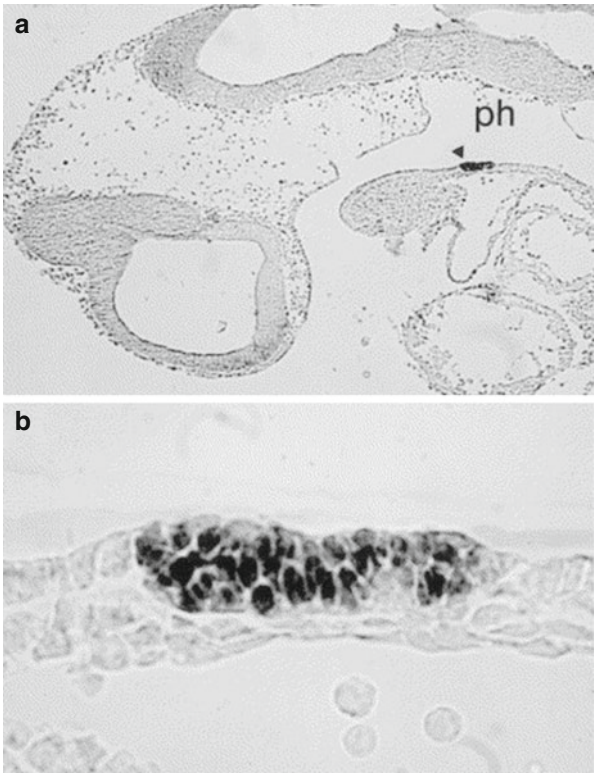

Fig. 1.2 Thyroid anlage in mouse embryo. Panel **a**: Sagittal section of mouse embryo at E9.5. Precursors of Thyroid follicular cells are specifically stained with anti Pax8 antibody. Thyroid anlage (*arrow head*) appears as a restricted area of the endodermal epithelium of the pharynx floor (*ph*). Panel **b**: Enlargement of the same section (From: Missero et al. [44])

The *prime mover* responsible for the specification of the thyroid anlage in mice is still rather obscure. However, data obtained in other organisms such as zebrafish and chicks have been offering valuable information to extend our knowledge of early steps of thyroid development in mammals.

The development of some endoderm-derived organs (liver, pancreas, lungs) requires inductive signals from the surrounding mesoderm. In the case of the thyroid, we know that in the mouse by E8.5, the *thyroid anlage* is very close to the aortic sac, from which embryonic heart outflow and pharyngeal arteries originate [13]. The developing thyroid could be targeted by signals coming from the cardiac mesoderm or endothelial lining of the aortic sac. This hypothesis has received strong support by studies in zebrafish [14]. It has been demonstrated that early thyroid development absolutely requires both the expression of the transcription factor Hand2 in the cardiac mesoderm surrounding the thyroid anlage and fibroblast growth factor (FGF)-signals. In humans, a cross-talk between the developing thyroid and heart is supported by epidemiological studies. In fact, a number of patients affected by thyroid dysgenesis also present cardiac malformations at birth [15]; furthermore, DiGeorge syndrome includes both congenital heart defects and an increased risk of congenital hypothyroidism [16].

1.3.2 Translocation and Lobe Formation

In mouse embryos, by E9.5 the thyroid anlage expands and then forms a bud that moves caudally in the surrounding mesenchyme. In the early phase of morphogenesis, the proliferation rate of pTFC is lower than that of the other endodermal cells [13]. Hence, enlargement of the developing thyroid probably depends on the recruitment of other endodermal cells of the primitive pharynx into the thyroid anlage.

The migration of pTFC is a notable feature of thyroid organogenesis. Morphogenesis of the neck encompasses a number of events that can contribute to the translocation of pTFC in the direction of the trachea. However, translocation mostly involves active migration of the precursor cells, which probably move through a process of "collective cell migration" by which cells move in concert without completely disrupting their cell-cell contacts [17]. The genetic basis of the thyroid bud migration has been, at least in part, elucidated; the presence of transcription factor Foxe1 in pTFC is required for thyroid bud migration [11, 18].

At E11.5, after the thyroid primordium is no longer connected to the pharynx, the process of lobulation begins, attested by a lateral enlargement of the developing thyroid; one day later, thyroid appears as an elongated structure close to third pharyngeal arch arteries that will participate in the formation of the definitive carotid vessels. These reports suggest that inductive signals originating from adjacent vessels could be relevant in the lobulation of the gland. This hypothesis was validated using genetically modified mice deprived of sonic hedgehog [19] (a morphogen relevant in vertebrate organogenesis) or Tbx1 [16] (a transcription factor regulated by sonic hedgehog itself). In these models, the development of vessels is impaired, and the thyroid bud does not stay in contact with them. At the same time, the lobulation process is disturbed, and the gland does not separate into two distinct lobes but appears as a single mass. However, in addition to extrinsic signals, pTFC specific mechanisms are required for correct lobulation. In fact, in mice partially deficient for both the transcription factors Nkx2-1 and Pax8, thyroid hemiagenesis is frequently observed [20].

1.3.3 Functional Differentiation and Enlargement

By E14, precursors of TFCs proliferate and begin to undergo a differentiation program completed at E16.5, when the thyroid is composed by *bona fide* adult TCFs, able to synthesize thyroid hormones. TCFs express, according to a precise temporal pattern, a number of specific proteins such as thyroglobulin (Tg), TSH receptor (Tshr), thyroid peroxidase (TPO), sodium/iodide symporter (NIS), thyroid NADPH oxidases (Duox's), and pendrin (PDS). At the same time, the gland accomplishes the proper follicular organization required to guarantee a correct hormone supply to the organism.

In the postnatal thyroid, mechanisms triggered by TSH upon its interaction with Tshr are extremely relevant in the regulation of both proliferation and function of

TFCs. The finding that in the mouse Tshr is detectable in thyroid cells by E14 and TSH by E15 could suggest a role for TSH/Tshr signaling in the control of functional differentiation and proliferation of TFC in the developing thyroid. However, in mouse embryos lacking a functional Tshr, the size of the fetal thyroid is quite similar to that in wild-type mice [21]. In addition, the number of proliferating cells in the thyroid is comparable in mutants and wild-type embryos. On the contrary, adult mice lacking TSH signaling have a clearly hypoplastic thyroid. These data indicate that in the mouse, TSH/Tshr signaling does not have a relevant effect on the proliferation of thyroid cells during embryonic life [22]. This scenario could be different in humans. In fact, in the mouse, thyroid organogenesis is complete just at the end of gestation, and the functions of the hypothalamic-pituitary-thyroid axis are accomplished only after birth. In humans,, the thyroid is realized by 12–13 weeks; during the rest of gestation, the thyroid continues to grow and the hypothalamic-pituitary-thyroid axis is functioning. While the role of Tshr/TSH signals in controlling the growth of fetal thyroid remain rather obscure, molecular analysis reveals that both TPO and NIS are almost absent in mouse embryos lacking a functional Tshr. Thus, TSH induced signals are required to express key molecules for hormone biosynthesis and to complete the differentiation program of the thyroid follicular cells [21].

Finally, TSH signaling is not required for folliculogenesis because normal thyroid follicles are present in mouse embryos lacking a functional Tshr. Signals from endothelial cells are relevant in forming follicles. In fact, in animal models characterized by a thyroid-specific severe reduction of vascular density, the gland appears as a multilayer mass of nonpolarized cells [23].

1.3.4 Merging of Ultimobranchial Bodies

In placental mammals, the ultimobranchial bodies are embryonic transient structures derived from the fourth pharyngeal pouch, which will merge with the developing thyroid.

In mice by E10, the fourth pharyngeal pouches are detectable as lateral extroflexions of the primitive foregut expressing the transcription factor Islet1 [24]. One day later, the caudal portion of the pouches grows forming UBB primordia identified for the expression of the factors Hes-1 [25], Isl1, and Nkx2-1 [26]. UBBs begin to migrate and reach the primordium of the thyroid at E13. By E14.5, UBB cells begin to disperse within the thyroid parenchyma, and only remnants of UBBs can be distinguished in the thyroid gland.

The expression of Nkx2-1 is required for the survival of UBBs [26], while Hes-1 plays a role in the merging of these structures into the thyroid [25]. UBB defects have been also described in animal models with an impaired expression of Hox3 genes, encoding factors involved in the morphogenesis of several structures. In these models, UBBs do not merge into the thyroid but remain as bilateral vesicles composed exclusively of calcitonin-producing cells (persistent ultimobranchial bodies) [27].

1.4 Thyroid Toolkit Genes

The generation of an increasing number of mouse models carrying mutations *on demand* of specific loci has been offering biomedical research an invaluable tool for the identification of the functions of proteins *in vivo* and the dissection of the pathways underlying developmental processes. Also in the case of the thyroid, a large part of our knowledge of molecular mechanisms of its morphogenesis is due to studies of phenotype mice, in which genes encoding proteins expressed during thyroid development have been inactivated by gene targeting (knockout mice).

Molecular genetics of thyroid development was inaugurated by the discovery of a number of transcription factors expressed in the thyroid anlage, Nkx2-1 (formerly called TTF-1), Foxe1 (formerly called TTF-2), Pax8, and Hhex. These genes, which can be considered thyroid "toolkit genes," remain expressed in both precursor and differentiated thyroid follicular cells. Although these factors are also expressed in other tissues, the coexpression of all four is a peculiar hallmark of thyroid cells [11].

In the next paragraphs, the focus will be on the role of these genes as deduced by their distribution and by the phenotype of knockout animals; the consequences of mutations in these genes in the pathogenesis of thyroid diseases will be exhaustively treated in later chapters.

1.4.1 Nkx2-1

During embryonic life, Nkx2-1 is expressed in the developing brain, lungs, and thyroid. In the brain, the factor is present in some areas of the developing diencephalon, such as the hypothalamic areas and the infundibulum, and in the neurohypophysis [28]. As for the lungs, Nkx2-1 is detectable in the epithelial cells of the developing trachea and lungs. In the thyroid, it is expressed in both precursor and differentiated TFC, in the C cells [26], and in the epithelial cells of the fourth pharyngeal pouches forming the ultimobranchial body. In human embryos, the expression pattern of Nkx2-1 is not different from that of mice [29]. The phenotype of *Nkx2-1* knockout mice reflects the expression domain of this gene: severe defects in lung and forebrain morphogenesis, lack of pituitary and thyroid [30]. Notably, in absence of Nkx2-1, the thyroid anlage forms and buds, but already by E10 the thyroid primordium appears smaller than in wild-type embryos and soon undergoes degeneration. The ultimobranchial bodies undergo the same process and disappear by E12 [26]. Thus, Nkx2-1 is required not for the initial specification of both follicular and parafollicular thyroid cells but for the survival of these cells. In addition, Nkx2-1 is also involved in the folliculogenesis. In fact, in mice in which this gene is made inactive by the middle of organogenesis, the postnatal thyroid shows a reduced number of dilated follicles [31].

1.4.2 Pax8

During embryonic life, Pax8 is expressed since E8.5 in the kidneys, brain, and thyroid primordium [32]. In the developing kidney, at an early stage, Pax8 is expressed in the nephrogenic cord and in mesonephric tubules; then, it is present in the cortex of the metanephros. In the brain, Pax8 is transiently expressed in the myelecephalon, through the entire length of the neural tube, otic vesicle, and at the midbrain-hindbrain boundary. In the thyroid, Pax8 is expressed in the thyroid follicular cells and in their precursors. In *Pax8* knockout embryos, the thyroid primordium forms, buds from the gut, and begins its migration [33]. However, the thyroid primordium is almost undetectable by E12. In newborn mice, the thyroid lacks thyroid follicular cells and is composed almost completely of calcitonin-producing C cells. The animals are affected by a severe hypothyroidism and die within 2–3 weeks after birth. In mice in which the *Pax8* gene is inactivated in the late fetal life, the thyroid shows a severe hypoplasia and reduced expression of genes required for hormone biosynthesis. Thus, Pax8 is required for the survival and the differentiation of thyroid follicular cells.

1.4.3 Foxe1

At variance with Nkx2-1 and Pax8, whose presence in the gut is restricted to the thyroid anlage, during development Foxe1 is expressed in tissues which are developed from the pharynx and pharyngeal arches: thyroid, tongue, epiglottis, palate, choanae, and esophagus [34]. In addition, Foxe1 is also detected in the whiskers and hair follicles, which derive from the ectoderm [35].

Foxe1 knockout mice die within 48 h of birth [18]. These mice display a severe cleft palate, an absent thyroid or ectopic thyroid, and lack of thyroid hormones. In embryos in absence of Foxe1 at E8.5, the thyroid anlage is specified, but at E9.5 thyroid precursor cells are still on the floor of the pharynx, showing a clear defect of migration. At later stages of development, in the absence of Foxe1, thyroid follicular cells either disappear or form a sublingual small thyroid remnant. In conclusion, Foxe1 has a specific role in controlling the migration of thyroid follicular cell precursors but is not relevant for the specification and differentiation of the thyroid anlage.

1.4.4 Hhex

Hhex is expressed during embryonic life in several organs derived from the foregut endoderm including the thyroid [36]. In the adult, in addition to the thyroid, Hhex expression is maintained in the liver and lungs. In absence of this factor, many developmental processes are impaired and *Hhex* knockout embryos die at

midgestation (E13.5-E15.5); they show severe defects in the liver, forebrain, heart, and thyroid [37]. At E8.5, the thyroid anlage is visible, but already at E9.5, the thyroid primordium is absent or severely hypoplastic. These data suggest that Hhex is required for the survival of precursors of TFC.

1.4.5 Gene Interactions

As summarized above, knockout mice demonstrate that Nkx2-1, Hhex, Pax8, and Foxe1 are required for correct thyroid development. In addition, these transcription factors are linked in a regulative network during the process of thyroid development [11].

In the thyroid anlage, at E9, the expression of Titf1, Hhex, and Pax8 is not dependent on the expression of each other, since the absence of any of these genes does not affect the expression of the others. At a later stage, Nkx2-1, Hhex, and Pax8 contribute to a common network of reciprocal regulatory interaction since each of them controls the maintenance of the expression of the others. The concurrent presence of Nkx2-1, Hhex, and Pax8 is required for the expression of Foxe1. According to this scenario, in the developing human thyroid, the expression of both NKX2-1 and PAX8 precedes the onset of FOXE1 expression [29].

1.5 How Many Genes to Build the Thyroid?

It is obvious that other genes, in addition to *Nkx2-1*, *Foxe1*, *Pax8,* and *Hhex*, are required for a correct thyroid morphogenesis. The global gene expression of the thyroid bud at E10.5 has been defined and compared to genes expressed in the whole embryo. Using this approach, it has been possible to identify a list of about 450 genes strongly enriched in the thyroid bud. It is plausible that this list includes many novel genes required for thyroid morphogenesis [38].

On the other hand, the study of the phenotype of knockout mice has revealed an important role in the development of the gland for some genes which are not thyroid specific but are expressed in many tissues. Some of these genes are described below.

1.5.1 Nkx2-5

Nkx2-5, like *Nkx2-1*, is a gene belonging to the Nkx2 family. It is transiently expressed in the thyroid anlage [39]. In *Nkx2-5* knockout embryos, the number of thyroid precursor cells is strongly reduced, and the developing thyroid appears hypoplastic [40]. The mutant embryos die at early stages of development, and hence, it is not possible to address the role of this factor in the differentiated thyroid. However, in humans, mutations in *NKX2-5* have been associated with thyroid dysgenesis [40].

1.5.2 Fgfr2

Proteins belonging to the Fgf family recognize and activate specific receptors (Fgfr) present in many types of epithelial cells. pTFCs express Fgr2-IIIb (fibroblast growth factor receptor 2, isoform IIIb), a tyrosine kinase receptor able to bind specific Fgfs that are expressed in the mesenchyme. A relevant role of FGF/FGFR interactions in thyroid morphogenesis is demonstrated by the absence of the thyroid gland in knockout mice for Fgr2-IIIb [41].

1.5.3 Hox3 Genes

Hoxa3 is expressed in many tissues, including the developing thyroid, and in the precursors of C cells. As described above (see 1.3.4), in *Hoxa3* knockout mice, ultimobranchial bodies do not merge into the thyroid [27]. In addition, a reduction in the number of thyroid follicular cells and hypoplasia of the thyroid have been described. These defects appear more severe in mice carrying simultaneous mutations in *Hoxa3* and in its paralogs *Hoxb3* and *Hoxd3* genes [42].

1.6 From Embryology to Clinical Practice

The animal models described above demonstrate that mutations in a number of genes involved in thyroid morphogenesis cause defects in thyroid development, i.e., cause congenital hypothyroidism with thyroid dysgenesis (CHTD). According to the "medicine translational approach," it seemed conceivable to investigate whether patients affected by CHTD carry mutations either in the toolkit thyroid genes or in other genes known to be relevant for thyroid morphogenesis. This working hypothesis was revealed to be correct, and it has been currently reported that about 3–5 % of cases of CHTD are associated with mutations in either the toolkit thyroid genes or other genes (mainly *TSHR*) [3, 5]. This data indicate that, albeit in only a small fraction of human patients, CHTD is caused by inheritable genetic defects. However, some points are worth highlighting:

(a) The mode of transmission of inheritance of the phenotype could be different between humans and mice. Humans carrying heterozygous mutations in either *NKX2-1* or *PAX*8 are affected by CH, while mice heterozygous for either *Nkx2-1* or *Pax8* do not present an overt hypothyroidism.
(b) In mice, Foxe1 is required for thyroid bud migration. In humans, impaired thyroid migration (ectopic thyroid) has never been found to be associated with mutations in the *FOXE1* gene.
(c) There is no model for thyroid agenesis, i.e., absence of the gland due to an impaired specification of thyroid bud. Genes required for the initiation of thyroid morphogenesis are still unknown in mammals.

(d) Some cases of CHTD could be due to mutations in not yet identified genes. The identification of new genes and mechanisms involved in thyroid development will be valuable for the elucidation of the molecular pathology of thyroid dysgenesis.

1.7 Making Thyroid *In Vitro*

A recent spectacular achievement by the group of Costagliola [43] (see also Chapter XX – Antonica) has demonstrated that it is possible to form functional thyroid tissue starting from multipotent mouse embryonic stem cells. This work demonstrates that the forced expression of Nkx2-1 and Pax8, combined to exposure to TSH, leads stem cells to differentiate into functional TFC that reorganize in follicles, thus reinforcing the important role of these factors in thyroid differentiation. In addition, this seminal accomplishment opens the way to different approaches for the therapy of thyroid diseases and provides an excellent model to investigate in better detail the processes leading to thyroid formation and function.

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