Embryology of the Parathyroid Glands

2

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2.1 Introduction

The parathyroid glands develop from the pharyngeal pouches, transient endodermal outpocketings that also form the thymus and ultimobranchial bodies in vertebrates. The parathyroids vary in number and final location in different vertebrates, including in humans and mice. Despite its importance in calcium physiology, the molecular regulators and cellular events underlying parathyroid organogenesis have only recently begun to be elucidated, in part due to their small size, nondescript shape, and variable locations. Recent work has identified some of the key molecular regulators of parathyroid organogenesis, including the transcription factors GCM2, GATA3, and TBX1, and the sonic hedgehog (SHH) signaling pathway, and the morphogenetic events leading to their development have begun to be defined. The parathyroid glands develop from a shared initial organ primordium with the thymus glands, leading to interesting connections between these two organs with diverse functions. Finally, a recent study has shown that parathyroid cell fate may be unstable during late fetal development. Further understanding of the mechanisms controlling parathyroid specification and embryonic development could contribute to better understanding of parathyroid biology and improved treatment for hypoparathyroidism in humans.

2.2 Anatomy of Parathyroid Organogenesis

Parathyroids originate from the posterior pharyngeal pouches, transient bilateral endodermal outpocketings that form from the pharynx during embryogenesis. The number of parathyroids and which pouches they originate from is species specific; humans and birds (chickens) have four parathyroids arising from the 3rd and 4th pharyngeal pouches (pp) [1–4], while mice have two parathyroids that come from the 3rd pp [5]. Nearly all of the information we have regarding parathyroid organogenesis has come from studies in mice, facilitated by the identification of the early regulator of parathyroid differentiation, *glial cells missing 2*, or *Gcm2* [6]. The expression of *Gcm2* throughout parathyroid organogenesis allowed the tracking of parathyroid-fated cells throughout embryonic development and has been a key to the recent developments in understanding parathyroid organogenesis.

Initial parathyroid organogenesis is closely linked to thymus organogenesis – these organs arise from different regions of the same pouches, and during development they undergo a series of morphogenetic events to form separate organs (reviewed in [7]). The initial parathyroid domain forms in the dorsal-anterior region of the pp and

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the forming pp-derived organ primordia, the ventral domain of which constitutes the developing thymus. These primordia must (in mice and humans) detach from the pharynx via localized apoptosis [7, 8]. The thymus and parathyroid domains separate from each other by less well-understood mechanisms, likely involving both differential cell adhesion, involvement of the surrounding neural crest cells (NCCs), and physical forces derived in part from thymus migration [5, 9]. Current evidence suggests that while the thymus lobes actively migrate, via the activity of the NCC-derived capsule [10]; the parathyroids do not themselves migrate but are "dragged" along by the migrating thymus lobes until the separation process is complete. This process introduces variability in their final locations, most often near the lateral aspects of the thyroid gland, but can be nearly anywhere in the neck region.

As a result of this connection during early organogenesis, the thymus and parathyroids have been often studied together and have been suggested to have functional overlap as well. These issues are discussed at the end of this chapter; the majority of this chapter will focus on the current knowledge of the molecular regulation of parathyroid cell fate specification and differentiation during organogenesis.

2.3 Molecular Regulators of Initial Parathyroid Specification

2.3.1 Transcription Factors

Because of their small size, variable location, and rather indistinct shape, little was known about parathyroid gland organogenesis until the identification of the early parathyroid marker *Gcm2*. *Gcm2* encodes a transcription factor related to the *glial cells missing* gene, originally identified in *Drosophila* as a molecular switch between neural and glial cell fate (reviewed in [11]. Although *Gcm2* does not have this same function in mammals, it plays a critical role in parathyroid development [12]. However, *Gcm2* expression does not appear to specify parathyroid cell fate or define the parathyroid domain during initial organogenesis. In the absence of *Gcm2*, the parathyroid domain (or at least a domain that expresses some parathyroid-related genes) appears to be specified at E10.5. This domain then undergoes rapid and coordinated apoptosis at about E11.5–12 [13]. Thus, other transcription factors and signaling pathways must specify parathyroid fate. While several candidates have been identified, the transcriptional network that specifies cell fate, and directly or indirectly upregulates *Gcm2* expression, has still not been clearly articulated.

A suite of genes including *Hoxa3*, *Pax1*,*9*, *Eya1*, and *Six1*,*4* have been proposed to constitute a Hox-Pax-Eya-Six network that controls early pouch patterning and organogenesis. While single and double mutants for these genes generally result in parathyroid agenesis or severe hypoplasia, the exact structure of such a network and whether these genes act individually or in concert to affect parathyroid fate specification is less clear. The first to be identified was *Hoxa3* [14]. Null mutants are aparathyroid and athymic, and due in part to the classical role of HOX proteins in specifying regional identity, the prevailing model has been that *Hoxa3* specifies 3rd pp identity and patterning [15]. However, recent evidence has demonstrated that in *Hoxa3* mutants, *Gcm2* is expressed its normal domain, but at very low levels indicating that *Hoxa3* upregulates *Gcm2* but is not required to specify parathyroid fate [16, 17]. Whether this regulation is direct or indirect is unknown; however, evidence from $Hoxa3^{+/-}Pax1^{-/-}$ mutants suggests that *Hoxa3* may work with the paired box transcription factor PAX1. *Pax1* single mutants have normal initial *Gcm2* expression, but do not maintain it, resulting in significant parathyroid hypoplasia [18]; this phenotype is exacerbated in $Hoxa3^{+/-}Pax1^{-/-}$ compound mutants. *Eya1* and *Six1*,*4* have also been shown to be required for *Gcm2* expression, and mutants result in loss through apoptosis. As loss of *Gcm2* itself is sufficient to cause apoptosis, it is possible that the effects of all of these genes, either individually or as a pathway or network, are mediated by their effect (direct or indirect) on *Gcm2* expression.

The two best candidates for transcriptional regulators that specify parathyroid fate are TBX1 and GATA3, both of which are expressed in the parathyroid domain in the 3rd pp and have been implicated in regulating *Gcm2*. *Tbx1* expression is correlated spatially and temporally with *Gcm2*, and its expression in the 3rd pp is unaffected in *Gcm2* null mutant mice [13], indicating that it acts upstream of, or in parallel to, Gcm2. However, recent work from the author and collaborators has shown that ectopic expression of *Tbx1* in the 3rd pp outside the parathyroid domain is not sufficient to induce *Gcm2* expression [19], and *Tbx1* null mutants do not form the caudal pouches at all [20]. Thus, it is unclear whether TBX1 plays any specific role in parathyroid specification or organogenesis and, if so, whether it regulates *Gcm2* expression directly or indirectly. In contrast, GATA3 has been shown to directly bind to the *Gcm2* promoter region and upregulate its expression, and *Gcm2* levels are reduced even in heterozygotes [21]. Whether GATA3 plays a role in organ fate specification is less clear. *Gata3*$^{+/-}$ heterozygotes have fewer *Gcm2-expressing* cells, suggesting that GATA3 could affect cell fate [21]. However, this possibility has not been directly investigated.

The final candidate gene identified so far is *Sox3*. Human mutations in Sox3 are associated with hypoparathyroidism, and *Sox3* is expressed in the 3rd pp and developing parathyroids in mice [22]. However, no direct connection has so far been made between *Sox3* and *Gcm2* expression or other aspects of parathyroid organogenesis, so its specific role is still unknown. Thus, while all of these transcription factors have been shown to affect organogenesis and patterning, the identity of the direct targets for these transcription factors and clear evidence for a role in specifying parathyroid cell fate, as opposed to promoting *Gcm2* expression, is lacking.

2.3.2 Signaling Pathways

While transcriptional regulators generally act cell autonomously, signaling pathways can act either within or between tissues to influence cell fate and/or differentiation. Thus, signals that specify parathyroid fate could be expressed either within the endoderm or in the adjacent NCC mesenchyme, and there is evidence for both. Three signaling pathways, SHH, BMP4, and FGF8/10, have been implicated as positive or negative regulators of parathyroid fate in the 3rd pp in mice and are discussed below. All of them are expressed within the endoderm. However, data from *Splotch* mutant mice, which have a deficiency in NCCs, have shown that the size of the parathyroid domain within the pouch is in part determined by signals from the surrounding NCCs [23]. Thus, signals coming from either or both cell types during patterning could influence the location and size of the parathyroid domain within the endoderm.

The earliest identified signaling pathway to influence parathyroid fate within the pouch endoderm is *sonic hedgehog* (SHH). *Shh* null mutant mice fail to establish a prospective parathyroid domain or express *Gcm2*, and thymus fate spreads to encompass the entire pouch [24]. However, there are conflicting data on whether SHH is acting directly within the endoderm or indirectly (either from adjacent endoderm or through a NCC-mediated mechanism) to establish parathyroid fate [24, 25]. Intriguingly, *Tbx1* is known to act downstream of SHH signaling in heart development [26], raising the possibility that SHH acts in part through inducing *Tbx1* in this case as well. However, gain of function studies in the author's lab, in which ectopic SHH signaling in other domains of the 3rd pp in mouse embryos induced *Tbx1*, but not *Gcm2*, indicate that this pathway is not sufficient to turn on *Gcm2* outside the normal parathyroid domain [19]. These data indicate that either other SHH targets, or additional signals or pathways, may be required to fully induce the parathyroid pathway.

The fibroblast growth factor (FGF) signaling pathway has also been implicated in suppressing parathyroid fate and/or differentiation. The main *Fgf* gene implicated in 3rd pp patterning and development in mice is Fgf8, but as *Fgf8* null mutants fail to form the caudal pouches, loss of function approaches is limited. However, members of the sprouty (*Spry*) class of FGF inhibitors

are expressed in the 3rd pp in mice, and mutations in these genes cause enhanced and ectopic FGF signaling throughout the pouch at E10.5 and later [7]. In *Spry1,2* double mutants, parathyroid size is reduced, and Gcm2 expression is delayed, indicating that excessive FGF signaling can suppress parathyroid specification and differentiation. This effect was suppressed by reducing the dosage of *Fgf8*, which is normally expressed in the ventral endoderm and off by E11.5. However, FGF10 is also expressed in the NCC mesenchyme adjacent to the dorsal domain, so some of the effect of FGF signaling on the parathyroid domain may come from FGF10. These results suggest that the effects of FGF signaling on parathyroid organogenesis may occur quite early and from both the within the endoderm and from the NCC mesenchyme, to restrict parathyroid fate to the most dorsal domain of the pouch.

The last signaling pathway that has been implicated in parathyroid fate specification is the BMP pathway, specifically BMP4. The role of BMP4 is less clear, as there is evidence for both a positive and a negative role. Like *Fgf8*, *Bmp4* expression is not expressed in the parathyroid domain but is restricted to the ventral thymus domain. In the SHH null, *Bmp4* expansion throughout the 3rd pp is coincident with loss of the parathyroid domain and expansion of thymus fate. Furthermore, the expression of the BMP inhibitor Noggin in the NCC mesenchyme surrounding the dorsal parathyroid domain suggests that suppressing BMP signaling is important for parathyroid fate or differentiation. Taken together, these data have been interpreted to indicate a SHH-BMP mutual antagonism in establishing parathyroid and thymus cell fate in the 3rd pp [5]. However, evidence from chick showed that inhibition of BMP signaling (via ectopic Noggin) suppressed *Gcm2* expression, at least at early stages of pouch development, suggesting that BMP signaling is at least transiently a positive regulator of *Gcm2* expression and parathyroid differentiation in this system. Thus, the role of BMP signaling in parathyroid fate specification and/or differentiation, and whether there are species-specific differences in this process, will require further investigation.

2.4 Differentiation and Survival of Parathyroids: *Gcm2*

Once the parathyroid domain is established, upregulation of *Gcm2* expression is necessary and sufficient for parathyroid differentiation and survival. *GCM2* is also known to be important in human parathyroid development, as both dominant negative [27] and loss-of-function [28] *GCM2* alleles are associated with hypoparathyroidism in humans (see also Chap. 14). In the *Gcm2* null mutant mouse, the parathyroid domain is specified, as evidenced by normal expression of the parathyroid-associated genes *Tbx1*, *Ccl21*, and *Casr* (*calcium-sensing receptor*) in the dorsal domain at E10.5 and failure of the thymus domain to expand into this region [13]. However, these cells fail to upregulate *parathyroid hormone* (*Pth*) at E11.5 and undergo coordinated apoptosis soon after, by E12.5. GCM2 also works with the transcription factor MAFB to upregulate *Pth* gene expression [29]. *MafB* mutation also affects parathyroid separation from the thymus and may itself be regulated by GCM2.

Thus, upregulation of *Gcm2* is a critical step in early parathyroid differentiation and survival. *Gcm2* continues to be expressed in parathyroids after the early stages of differentiation, and the loss of parathyroids after downregulation of *Gcm2* expression in *Hoxa3* and *Pax1* mutants suggests that it may still be required for parathyroid survival at least during fetal development. However, in the absence of conditional deletion of *Gcm2* at later stages, it is not clear if it is required for parathyroid maintenance once they are established.

2.5 The Thymus-Parathyroid Connection

2.5.1 Do the Thymus and Parathyroids Have Overlapping Functions?

The primary functions of the thymus and parathyroid glands are quite distinct, with the thymus playing a critical role in producing T cells and

parathyroids controlling calcium physiology through the production of PTH. However, the physical connection between the thymus and parathyroid organs during early organogenesis has led to reports that these organs may indeed have overlapping functions.

The original report of the *Gcm2* null mutant phenotype received attention not only because it was the first gene to specifically be required only for parathyroid organogenesis but also because of the conclusion that the thymus could act as a secondary source of PTH [12]. This conclusion was based on survival of a significant proportion of *Gcm2* null mutants, even in the absence of parathyroid glands, their report of low levels of serum PTH in the absence of parathyroids, and on the observation that removing the thyroid and parathyroids together from wild-type mice did not cause lethality, which removing the thymus as well caused rapid death (presumably due to lack of PTH). As the parathyroids had been thought to be the sole source of physiological PTH, this was considered a significant finding with potential implications for human health [30]. A more recent study, based on this conclusion, reported the ability to generate and isolate parathyroid-like cells from thymic epithelial cells, as an initial effort to produce parathyroid cells for transplant [31].

While this report was consistent with the common origin of the thymus and parathyroids in the 3rd pp, work from the author's lab showed that this conclusion was not entirely accurate [2]. Instead, the PTH thought to be produced by the thymus was produced by authentic parathyroid cells that remain attached to the thymus during normal organogenesis. This study showed that the process of thymus-parathyroid separation is inefficient and "messy," leading to small clusters of parathyroid cells remaining associated with the thymus and numerous small clusters of parathyroid cells throughout the neck region in addition to the primary parathyroid glands. These "ectopic" thymus-associated parathyroid cells are the likely source of PTH in the original *Gcm2* null paper and also call into question the identity of the parathyroid cells that were thought to have been generated from thymus cells in the 2011 study [31], as these could have been parathyroid cells already present in the thymus.

While the thymus does not have true parathyroid-like function, the parathyroid domain during initial organogenesis does have a transient thymus-related function. At E11.5, prior to the separation of the two organs, the parathyroid domain expresses *Ccl21*, a chemokine that contributes to initial immigration of lymphoid progenitors to the thymus, which is important in early thymus organogenesis [32, 33]. Therefore, while the thymus doesn't appear to have any parathyroid function, the parathyroid domain does help recruit lymphoid cells to the thymus, at least during initial organogenesis.

2.5.2 Stability of Parathyroid Cell Fate

The presence of small clusters of parathyroid cells throughout the neck in both mice and humans, as a consequence of normal development, also has another unusual consequence. In about half of mice and in a substantial percentage of humans, these remnants of the organ separation process can downregulate the parathyroid program and transdifferentiate in a thymus fate, forming small cervical thymi [34, 35]. In addition, the author's lab has recently shown that about 25 % of these cervical thymi have previously differentiated as parathyroid, including prior expression of *Pth* [36]. These parathyroid-derived cervical thymi (pCT) generate T cells with a specific functional phenotype that could have implications for the function of the immune system in individuals with pCT [36]. While the mechanisms by which this cell fate switch occurs are unknown, parathyroid fate appears to stabilize at about the newborn stage, after which the frequency of cervical thymi remains constant. This "window of opportunity" for parathyroid cells to downregulate the parathyroid program and transdifferentiate to a thymus fate suggests that there is an underlying instability in parathyroid fate during a specific temporal window during the late fetal stage.

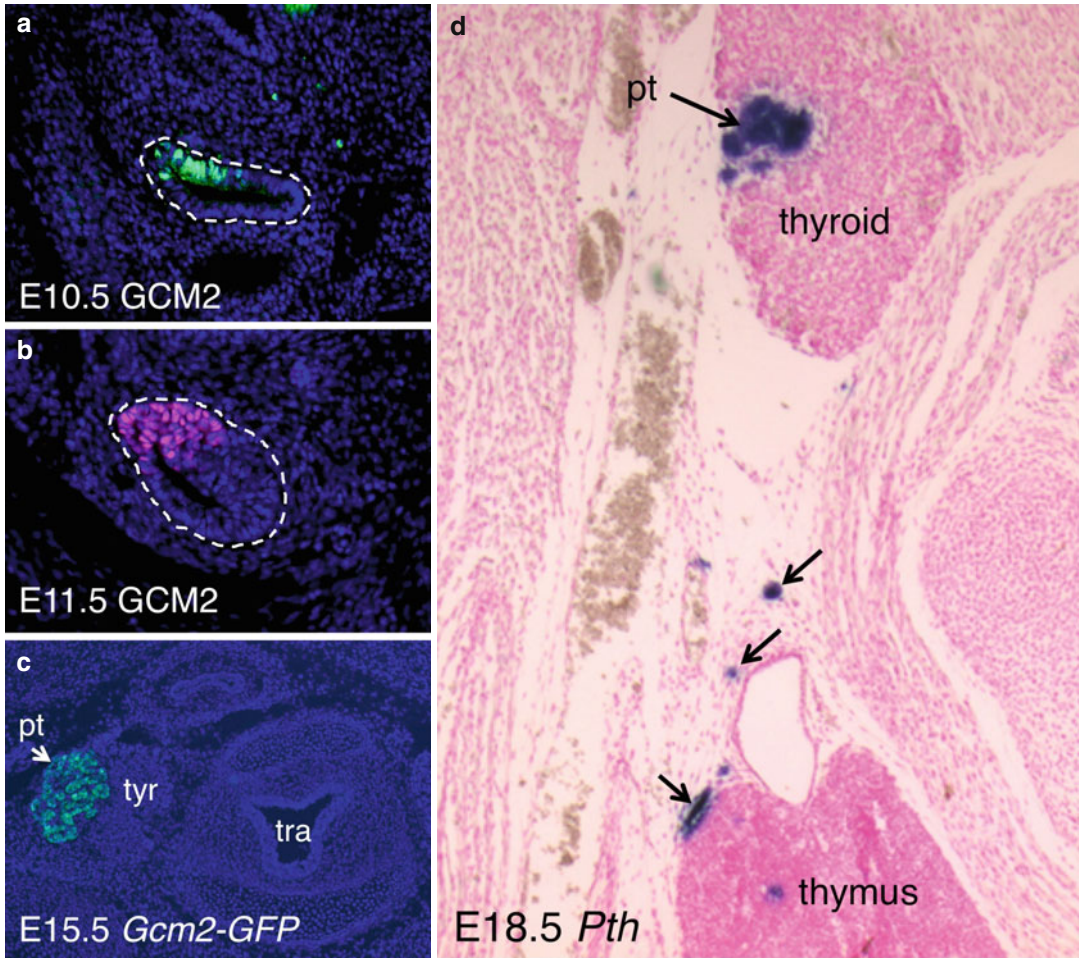

Fig. 2.1 Parathyroid organogenesis in the mouse embryo. (**a**, **b**) Saggital sections of mouse E10.5 (**a**) and E11.5 (**b**) embryos stained with an antibody recognizing GCM2. At these stages, GCM2 (*pink* or *green*) marks the dorsal-anterior domain of the 3rd pharyngeal pouch-derived organ primordium (*outlined* in *white dashed line*); the remainder of the pouch becomes thymus. (**c**) By E15.5, the parathyroid (*pt*) has separated from the thymus and is usually located near the lateral aspects of the thyroid lobes (*tyr*). In this panel, tra, trachea. *Gcm2* expression is shown using a GCM2-EGFP transgene. (**d**) At E18.5 and after birth, the main parathyroid gland (*pt*) is usually located at or within the thyroid gland, here identified by in situ hybridization with a probe for *Pth*. However, small clusters of parathyroid cells are present throughout the neck between the main parathyroid and the thymus gland (*arrows*), remnants of the process of organ separation and migration

This phenomenon is not just an oddity of development that may affect the immune system. Understanding how cell fate is stabilized is important to the issue of therapeutic stem cell-based interventions in general and to the generation of parathyroid cells for transplant in particular. Parathyroid cells are excellent targets for generation of differentiated cells for transplant from ES or iPS cells. Further investigation of this apparently inherent but transient instability, and how it is resolved during development, could provide important keys to future efforts to generate parathyroid cells for transplant.

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References

1. Gilmour J (1937) The embryology of the parathyroid glands, the thymus, and certain associated rudiments. J Pathol 45:507–522
2. Liu Z, Farley A, Chen L, Kirby BJ, Kovacs CS, Blackburn CC et al (2010) Thymus-associated parathyroid hormone has two cellular origins with distinct endocrine and immunological functions. PLoS Genet 6(12):e1001251
3. Okabe M, Graham A (2004) The origin of the parathyroid gland. Proc Natl Acad Sci U S A 101(51): 17716–17719
4. Neves H, Dupin E, Parreira L, Le Douarin NM (2012) Modulation of Bmp4 signalling in the epithelial-mesenchymal interactions that take place in early thymus and parathyroid development in avian embryos. Dev Biol [Research Support, Non-US Gov't] 361(2):208–219
5. Gordon J, Manley NR (2011) Mechanisms of thymus organogenesis and morphogenesis. Development 138(18):3865–3878
6. Kim J, Jones BW, Zock C, Chen Z, Wang H, Goodman CS et al (1998) Isolation and characterization of mammalian homologs of the Drosophila gene glial cells missing. Proc Natl Acad Sci U S A 95(21): 12364–12369
7. Gardiner JR, Jackson AL, Gordon J, Lickert H, Manley NR, Basson MA (2012) Localised inhibition of FGF signalling in the third pharyngeal pouch is required for normal thymus and parathyroid organogenesis. Development 139(18):3456–3466
8. Gordon J, Wilson VA, Blair NF, Sheridan J, Farley A, Wilson L et al (2004) Functional evidence for a single endodermal origin for the thymic epithelium. Nat Immunol 5(5):546–553
9. Gordon J, Patel SR, Mishina Y, Manley NR (2010) Evidence for an early role for BMP4 signaling in thymus and parathyroid morphogenesis. Dev Biol 339(1):141–154
10. Foster KE, Gordon J, Cardenas K, Veiga-Fernandes H, Makinen T, Grigorieva E et al (2010) EphB-ephrin-B2 interactions are required for thymus migration during organogenesis. Proc Natl Acad Sci U S A 107(30):13414–13419
11. Hashemolhosseini S, Wegner M (2004) Impacts of a new transcription factor family: mammalian GCM proteins in health and disease. J Cell Biol [Research Support, Non-US Gov't Review] 166(6): 765–768
12. Gunther T, Chen ZF, Kim J, Priemel M, Rueger JM, Amling M et al (2000) Genetic ablation of parathyroid glands reveals another source of parathyroid hormone. Nature 406(6792):199–203
13. Liu Z, Yu S, Manley NR (2007) Gcm2 is required for the differentiation and survival of parathyroid precursor cells in the parathyroid/thymus primordia. Dev Biol 305(1):333–346
14. Chisaka O, Capecchi MR (1991) Regionally restricted developmental defects resulting from targeted disruption of the mouse homeobox gene *hox-1.5*. Nature 350:473–479
15. Manley NR, Condie BG (2010) Transcriptional regulation of thymus organogenesis and thymic epithelial cell differentiation. Prog Mol Biol Transl Sci 92:103–120
16. Chen L, Zhao P, Wells L, Amemiya CT, Condie BG, Manley NR (2010) Mouse and zebrafish Hoxa3 orthologues have nonequivalent in vivo protein function. Proc Natl Acad Sci U S A 107(23):10555–10560
17. Chojnowski J, Trau H, Masuda K, Manley N (2013) Complex tissue specific roles for HOXA3 during thymus and parathyroid development. Paper presented at the international society for developmental biology conference, Cancun, June 2013
18. Su D, Ellis S, Napier A, Lee K, Manley NR (2001) Hoxa3 and pax1 regulate epithelial cell death and proliferation during thymus and parathyroid organogenesis. Dev Biol 236(2):316–329
19. Manley N, Bain V, Gordon J, Gutierrez K, Cardenas K, Richie E (2012) Regulation of thymus and parathyroid organ fate specification by Shh and Tbx1. Paper presented at the mouse molecular genetics conference, Asilomar, Sept 2012
20. Jerome LA, Papaioannou VE (2001) DiGeorge syndrome phenotype in mice mutant for the T-box gene, Tbx1. Nat Genet 27(3):286–291
21. Grigorieva IV, Mirczuk S, Gaynor KU, Nesbit MA, Grigorieva EF, Wei Q et al (2010) Gata3-deficient mice develop parathyroid abnormalities due to dysregulation of the parathyroid-specific transcription factor Gcm2. J Clin Invest 120(6):2144–2155
22. Bowl MR, Nesbit MA, Harding B, Levy E, Jefferson A, Volpi E et al (2005) An interstitial deletion-insertion involving chromosomes 2p25.3 and Xq27.1, near SOX3, causes X-linked recessive hypoparathyroidism. J Clin Invest 115(10): 2822–2831
23. Griffith AV, Cardenas K, Carter C, Gordon J, Iberg A, Engleka K et al (2009) Increased thymus- and decreased parathyroid-fated organ domains in Splotch mutant embryos. Dev Biol 327(1):216–227
24. Moore-Scott BA, Manley NR (2005) Differential expression of Sonic hedgehog along the anterior-posterior axis regulates patterning of pharyngeal pouch endoderm and pharyngeal endoderm-derived organs. Dev Biol 278(2):323–335
25. Grevellec A, Graham A, Tucker AS (2011) Shh signalling restricts the expression of Gcm2 and controls the position of the developing parathyroids. Dev Biol [Research Support, Non-US Gov't] 353(2):194–205
26. Garg V, Yamagishi C, Hu T, Kathiriya IS, Yamagishi H, Srivastava D (2001) Tbx1, a DiGeorge syndrome candidate gene, is regulated by sonic hedgehog during pharyngeal arch development. Dev Biol 235(1):62–73

27. Mannstadt M, Bertrand G, Muresan M, Weryha G, Leheup B, Pulusani SR et al (2008) Dominant-negative GCMB mutations cause an autosomal dominant form of hypoparathyroidism. J Clin Endocrinol Metabol [Case Reports Research Support, NIH, Extramural Research Support, Non-US Gov't] 93(9):3568–3576
28. Ding C, Buckingham B, Levine MA (2001) Familial isolated hypoparathyroidism caused by a mutation in the gene for the transcription factor GCMB. J Clin Invest 108(8):1215–1220
29. Kamitani-Kawamoto A, Hamada M, Moriguchi T, Miyai M, Saji F, Hatamura I et al (2011) MafB interacts with Gcm2 and regulates parathyroid hormone expression and parathyroid development. J Bone Miner Res [Research Support, Non-US Gov't] 26(10):2463–2472
30. Balling R, Erben RG (2000) From parathyroid to thymus, via glial cells. Nat Med [News] 6(8):860–861
31. Woods Ignatoski KM, Bingham EL, Frome LK, Doherty GM (2011) Directed trans-differentiation of thymus cells into parathyroid-like cells without genetic manipulation. Tissue Eng Part C Methods 17(11):1051–1059
32. Liu C, Saito F, Liu Z, Lei Y, Uehara S, Love P et al (2006) Coordination between CCR7- and CCR9-mediated chemokine signals in prevascular fetal thymus colonization. Blood 108(8):2531–2539
33. Liu C, Ueno T, Kuse S, Saito F, Nitta T, Piali L et al (2005) The role of CCL21 in recruitment of T-precursor cells to fetal thymi. Blood 105(1):31–39
34. Dooley J, Erickson M, Gillard GO, Farr AG (2006) Cervical thymus in the mouse. J Immunol 176(11):6484–6490
35. Terszowski G, Muller SM, Bleul CC, Blum C, Schirmbeck R, Reimann J et al (2006) Evidence for a functional second thymus in mice. Science 312(5771):284–287
36. Li J, Liu Z, Xiao S, Manley NR (2013) Transdifferentiation of parathyroid cells into cervical thymi promotes atypical T-cell development. Nat Commun [Research Support, NIH, Extramural] 4:2959

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