ABSTRACT

The identification of mechanisms leading to the restriction of lineage potential and cell fate specification of multipotential progenitor cells falls within the purview of the developmental biologist. In specific, neural crest (NC) cell differentiation has long been a favored model process to examine how environmental cues cooperate with cell intrinsic factors to specify the birth of multiple cell lineages, including sympathetic and adrenal chromaffin (SA) cells. Over the years, a handful of genes (MASH-1, Phox2a/b, Hand2, GATA-2/3) have been identified that, when their expression patterns are perturbed, lead to a variable degree of disruption in SA cell development, function and tissue-specific gene expression profiles. These genes have historically been thought to act in a monotonous, linear fashion (e.g. gene product A regulates gene B, whose product in turn regulates gene C). Recent genetic studies in mice and other model organisms provide substantial evidence to indicate that these regulatory effectors may interact in a non-linear, self-sustaining feedback network. This review summarizes our current knowledge of the five principal players that partake in the transcriptional regulatory circuitry that is employed during SA cell development.

Keywords: neural crest, sympathetic and adrenal chromaffin cell, transcription factors, MASH-1, Phox2a/b, Hand2, GATA-2/3, TH, DBH

SYMPATHETIC AND ADRENAL CHROMAFFIN CELL DEVELOPMENT: LINEAGE SPECIFICATION

During early embryogenesis, NC cells delaminate from the dorsal surface of the neural tube beginning at about the 6-somite stage in mice (e8.0–8.5) or around HH stage 9 (e2.0) in chick embryos (Gammill et al. 2006). The NC cells migrate ventrally or dorsolaterally to arrive at diverse final destinations within the embryo where they differentiate into cell lineages that include sympathetic neurons, sensory neurons, melanocytes, parafollicular cells and adrenal chromaffin cells as well as much of the bone, cartilage and connective tissue of the head and neck (Le Douarin 1982). To date, we have only an incomplete mechanistic understanding of how multipotential NC cells are eventually induced toward a given lineage commitment decision and their choice of migration paths, but it is widely accepted that the combinatorial effects of extrinsic environmental cues encountered by migrating NC cells, together with their cell intrinsic programs, determine their final cell fate decisions (for details, see Harris and Erickson 2007).

In order to pattern SA cell lineages, trunk-derived NC cells migrate ventrally, passing through the anterior somitic mesoderm of the developing embryo to arrive in the vicinity of the dorsal aorta (DA) at around e10 in the mouse or at e2.5 in the chick (Fig. 1; Loring and Erickson 1987; Goridis and Rohrer 2002). Bone morphogenetic proteins (BMPs) secreted from the wall of the DA have been shown to be essential for the specification of SA cell lineages. Definitive evidence demonstrating that BMPs can augment sympathetic neuronal differentiation comes from experiments showing that administration of exogenous BMP (2, 4 or 7), or forcible expression of a constitutively active BMP type I receptor, increases the number of tyrosine hydroxylase (TH) expressing cells within a NC cell population (Varley et al. 1995; Reissmann et al. 1996; Shah et al. 1996; Varley et al. 1996, 1998; Schneider et al. 1999; Bilo-deau et al. 2001). Furthermore, in ovo forced expression of BMP-4 in the vicinity of the developing sympathetic ganglia results in the generation of ectopic TH-positive cells (Reissmann et al. 1996). Several reports have documented that the mRNAs encoding BMP-4/7 and their receptors (BMPR-IA and BMPR-IB) accumulate in the DA wall and in NC cells that aggregated nearby, respectively (Reissmann et al. 1996; Shah et al. 1996; McPherson et al. 2000). Finally, it has been shown that after physically implanting beads that release noggin, a potent and specific inhibitor of BMP-4/7, adjacent to the DA, the expression of noradrenergic and neuronal markers in NC cells that had coalesced nearby is abolished (Schneider et al. 1999).
BMPs bind to heterodimeric complexes that consist of type I (BMPR-IA, BMPR-IB and ALK2) and type II (BMPR-II, ActR-II and ActR-IIB) serine/threonine kinase receptors (reviewed in Kawabata et al. 1998). While conventional germ line mutagenesis of all six receptors has been performed, only disruption of the BMPR-IA, ALK2 and BMPR-II genes results in embryonic lethality between e6.5 and e9.5 (Mishina et al. 1995; Gu et al. 1999; Mishina et al. 1999; Beppu et al. 2000). Thus, a definitive test for the role of BMPs and their receptors in SA cell commitment and differentiation in vivo must await the generation and analyses of conditional gene-targeted alleles.

In response to BMP signals emanating from the DA wall, NC cells undergo differentiation to form the primary sympathetic ganglia and express transcription factors MASH-1 (Mammalian Achaete-Scute Homolog 1)/CASH-1 (the chick homologue of MASH-1), Phox2a/b, Hand2 (heart and neural-crest derivatives-expressed 2) and GATA-2/3, which are known to impact SA cell differentiation in zebrafish, chick and mouse studies (Guillemot et al. 1993a, 1993b; Pattyn et al. 1997, 1999; Howard et al. 2000; Lim et al. 2000; Tsarovina et al. 2004; Lucas et al. 2006; Moriguchi et al. 2006; Pattyn et al. 2006). Secondarily, these SA cell precursors then adopt neuronal and catecholaminergic characteristics, which are typified by the expression of neurofilament, SCG10, neuron-specific tubulin, TH and dopamine β-hydroxylase (DBH) (Fig. 2; Cochard et al. 1978; Cochard and Paulin 1984; Groves et al. 1995; Sommer et al. 1995; Ernsberger et al. 1995; Schneider et al. 1999; Ernsberger et al. 2000; Flatmark 2000). These differentiated SA cell precursors then embark on a second migratory passage from the vicinity of the DA to their final destinations where they generate sympathetic ganglia, adrenal chromaffin cells or extra-sympathoadrenal lineage derivatives such as the transient embryonic organ of Zukerkandl (Fig. 1; Anderson and Axel 1986; Anderson et al. 1991). While sympathetic neurons and adrenal chromaffin cells have historically been postulated to share a common SA cell precursor (Anderson and Axel 1986; Anderson et al. 1991), the observation that there exist subtle differences in the effects attributed to gene-ablative mutations in the sympathetic neurons or the adrenomedullary chromaffin cells has lead many in the field to speculate that perhaps there are alternates, distinct NC progenitor cells that are committed exclusively to either one or the other lineage (Unsicker et al. 2005; Huber 2006).

However, genetic proof for BMP involvement in vivo in SA cell development is lacking since homozygous mutant embryos carrying ablative mutations in the genes encoding BMP-2 and BMP-4 die early during gestation, between e6.5 and e10.5 (Winnier et al. 1995; Zhang and Bradley 1996). bmp7 homozygous mutants expire perinatally with evidence of skeletal, renal and eye defects but with no reported SA cell deficiency (Luo et al. 1995; Dudley et al. 1995). The...
SYMPATHETIC AND ADRENAL CHROMAFFIN CELL DEVELOPMENT: A PARADIGMATIC TRANSCRIPTION FACTOR REGULATORY NETWORK?

Much of our understanding of the role of transcription factors in SA cell specification and function derives from loss- and gain-of-function experiments in cell-based or organismal model systems that the expression levels of individual genes has been altered. The interpretation of the observed SA cell developmental deficiencies following these experimental manipulations relies principally on the expression analysis of putative downstream target genes using in situ hybridization or immunocytochemical localization techniques. There are a number of potential limitations in such studies, as the precise expression levels of target genes in the regulation of developmental events cannot be easily evaluated using either of these qualitative assays. Another theoretical shortcoming in the application of these techniques or their interpretation is that reduction of a putative downstream gene expression in a given mouse/chick/zebrafish mutant does not always indicate that it is directly regulated by the upstream regulator, as the gene ablation might autonomously or non-autonomously affect the survival and/or organization of cell populations expressing the gene under study (Boyle and de Caestecker 2006). To circumvent some of these issues, we enriched adrenal chromaffin cells by flow cytometry to quantitatively examine gene expression levels in pure SA cell populations (Moriguchi et al. 2006).

In avian primary sympathetic ganglia, the basic helix-loop-helix (bHLH) transcription factor CASH-1 (the chick homologue of MASH-1) is expressed immediately prior to the paired/homeodomain transcription factor Phox2b (at the 29/32-somite stage), which is then followed by expression of the bHLH transcription factor Hand2 and Phox2a (at the 31/32-somite stage) and the zinc finger protein GATA-2 (the functional counterpart of mouse GATA-3 in the developing chick SA system at the 33/34-somite stage). Finally at the end of this temporal gene expression cascade, TH and DBH, both of which are required for noradrenergic anabolic production, can be detected in 35-somite chick embryos (Ernsberger et al. 1995, 2000; Howard et al. 2000; Tsarovina et al. 2004). Through the analyses of gene loss- and gain-of-function studies in model organisms, our current understanding is that SA cell differentiation is governed by this handful of key transcription factors that are (directly or indirectly) activated by BMPs. Loss-of-function mutations in any of these five transcription factors in the mouse leads to embryonic lethality or phenotypic abnormalities, which include variable deficits in SA and non-SA tissue development (Guillomet et al. 1993a; Pattyn et al. 1999; Lim et al. 2000; Tsarovina et al. 2004; Moriguchi et al. 2006). For simplicity, we will restrict this discussion to deficiencies in SA cell lineages.

MASH-1 is induced by the administration of BMPs to primary NC cells in culture (Lin et al. 1998). In mouse embryos, NC cells begin to express MASH-1 when they first aggregate near the DA to form the primary sympathetic chain (Huber et al. 2002; Morikawa et al. 2005). MASH-1 expression in the sympathetic ganglia remains high until e13, followed by rapid down-regulation from e14.5 (Morikawa et al. 2005). In adrenal chromaffin cells, MASH-1 expression seems to be down-regulated two days later at e16.5 (Huber et al. 2002). The biological significance of MASH-1 in downstream gene expression in these cells is unknown, although our recent data are consistent with the possibility that GATA-3 may play a role in the silencing of MASH-1 (Moriguchi et al. 2006).

Early studies indicated that MASH-1 was essential in vivo for the development of the autonomic nervous system lineages, including SA cells. MASH-1-deficient NC cells arrived normally at the DA of e10.5 embryos to form the primary sympathetic ganglia and could express some (e.g. neurofilament 68 and 160, neuron-specific tubulin, Phox2b and c-Ret), but not other (e.g. Phox2a, TH and DBH) SA cell markers before ensuing atrophy (Guillomet et al. 1993a; Sommer et al. 1995; Hirsch et al. 1998; Huber et al. 2002). However, a more recent study indicated that in MASH-1 homozygous mutant embryos, a complete SA cell differentiation program lagged behind that of wild-type animals by 1-2 days (Pattyn et al. 2006). From these observations, one can only conclude that MASH-1 is not essential for migrating NC cells to acquire a SA cell type, and that perhaps together with other partner regulatory molecules, it co-operatively promotes the differentiation and survival of SA cell precursors.

SA cells also express Phox2a, a homeodomain transcription factor closely related to Phox2b (Valarche et al. 1993; Morin et al. 1997; Pattyn et al. 1997). Gain-of-function experiments have indicated that Phox2a is sufficient to promote autonomous noradrenergic differentiation by its expression in the absence of MASH-1 (Moriguchi et al. 1993a; Sommer et al. 1995; Hirsch et al. 1998; Huber et al. 2002). Nevertheless, loss of Phox2a function did not significantly impair SA cell development (Morin et al. 1997).

The homeodomain transcription factor Phox2b is expressed in all noradrenergic neurons of the central and the peripheral nervous system (Pattyn et al. 2002; Morikawa et al. 1998). In murine embryos, Phox2b is induced by the administration of BMPs to NC cells that assemble at the DA at e10.5 and colonize the sympathetic chain (Huber et al. 2005). These data are consistent with the interpretation that Phox2b plays a proximal and vital role in SA cell differentiation. The Dbh promoter has been shown to be directly regulated by Phox2. Both Phox2a and Phox2b bind to regulatory elements in, and stimulate transcription from, the Dbh promoter in conjunction with cyclic-AMP pathway activation (Yang et al. 1998; Kim et al. 1998; Swanson et al. 2000; Patanis et al. 2000; Huber et al. 2002). Phox2b can also trans-activate the Th promoter (at -175/-158 bp) via direct DNA binding (Zellmer et al. 1995). The bHLH transcription factor Hand2 (aka dHand) is expressed in the sympathetic ganglion primordium, and promotes noradrenergic differentiation of NC cells in vitro and in vivo. Hand2 cooperates with Phox2a in activating transcription of Dbh promoter constructs in cell-based co-transfection assays (McFadden et al. 2002; Firulli et al. 2003; Rychlik et al. 2003; Xu et al. 2003). Hand2 transcrip-
tion, which can be induced by BMPs, is initiated after CASH-1 and Phox2b, but before Phox2a, GATA-2, TH, and DBH in chick embryos (Howard et al. 2000; Tsarovina et al. 2004). In several independent studies, Hand2 expression in sympathetic ganglia has consistently been shown to depend on Phox2b activation, but is independent of MASH-1 (Howard et al. 2000; Huber et al. 2002, 2005; Morikawa et al. 2005), suggesting an epistatic regulatory relationship between Phox2b and Hand2 for cell differentiation. Thus, it was probably surprising and unexpected that forced expression of Hand2 would lead to reciprocal induction of Phox2b expression, as well as to the expression of noradrenergic and pan-neuronal markers, in NC and P19 embryonal carcinoma cells (Howard et al. 2000; Morikawa et al. 2005).

Constitutive Hand2 germ line mutation leads to early embryonic lethality (Srivastava et al. 1997). A recent analysis of the Hand2 conditional deletion mutation specifically in neural crest descendents, achieved by the use of a Wnt1/Cre-expressing transgene, indicated that, except for TH and DBH, Hand2 is dispensable for the expression of the usual protein repertoire characteristic of SA cells (Morikawa et al. 2007). Similar gene expression effects were also detected in the zebrafish Hand2 deletion mutant, hands off, in which sympathetic precursor cells aggregated to form sympathetic ganglia (Phox2a/b and Hand2 expression in the zebrafish Hands off mutant, a subset of Mash1), while GATA-2, TH and DBH levels were strongly reduced (Lucas et al. 2006). Given the plethora of in vitro and in vivo data that implicate Hand2 as a key player in SA cell differentiation, these recent observations are indeed surprising and perhaps hint at broader than anticipated genetic redundancy amongst bHLH proneural genes in sympathetic neuronal development (Howard et al. 2000; Morikawa et al. 2005, 2007).

The zinc finger transcription factors GATA-2 and GATA-3 are both expressed in SA cell lineage of mouse embryos, while only GATA-2 is expressed in the chick (George et al. 1994; Groves et al. 1995; Lim et al. 2000; Tsarovina et al. 2004). GATA-2 expression in chick embryos may also be modulated by BMPs since it was strongly suppressed by the BMP antagonist, noggin (Tsarovina et al. 2004). Gain-of-function studies in chick embryos revealed that, unlike Phox2a/b and Hand2, forced expression of GATA-2 induced ectopic neurons lacking noradrenergic traits in chick peripheral nerve precursors (Gordis and Rohrer 2002; Tsarovina et al. 2004). However, transgenic GATA-3 complementation of GATA-3-deficient SA cells significantly restored a population of highly TH-positive sympathetic neurons, suggesting that the effect on noradrenergic cell induction by GATA-2/3 depends on the cellular context (Moriguchi et al. 2006). Interestingly, GATA-3 deficiency results in loss of GATA-2 expression in e10.5 primary sympathetic ganglion cells (Tsarovina et al. 2004) and in chromaffin cells (Moriguchi, unpublished data), suggesting that GATA-2 expression in SA tissues depends on GATA-3.

Gata3 constitutively mutant mice expire of noradrenergic deficiency by e10.5, and can be rescued either pharmacologically or by complementation with a SA cell lineage-specific GATA-3 transgene (Lim et al. 2000; Moriguchi et al. 2006). Inactivation of Gata3 in mice leads to a significant loss of TH and DBH expression, as well as to a general deficiency in SA cell development, both in sympathetic neurons and adrenal chromaffin cells (Lim et al. 2000; Tsarovina et al. 2004; Moriguchi et al. 2006). Although the primary sympathetic ganglia form normally in e10.5 Gata3 mutant embryos, at later embryonic stages, enhanced apoptosis is evident such that by e18.5, Gata3 null mutants develop abnormally small thoracic paravertebral sympathetic ganglia (35% smaller in size compared to wild-type littermates) with reduced number of neurons (Tsarovina et al. 2004; Moriguchi et al. 2006). Similarly, adrenomedullary chromaffin cells in e18.5 mice lacking GATA-3 also amounted to only 30% of controls, and these cells lack TH and DBH expression (Moriguchi et al. 2006). Furthermore, Phox2b (which hitherto had been thought to act upstream of GATA-3) and Hand2 expression were both found to be significantly reduced, implicating GATA-3 as a positive regulator for the maintenance of Phox2b and Hand2 transcription at least in the remaining GATA-3-deficient chromaffin cells (Moriguchi et al. 2006). Curiously, MASH-1 was not appropriately down-regulated during differentiation of the remaining GATA-3-deficient chromaffin cells in e18.5 Gata3 mutants. Thus, it appears that GATA-3 may be a negative regulator of MASH-1 expression during late embryogenesis (Moriguchi et al. 2006). Insofar as terminally differentiated target gene regulation is concerned, GATA-3 has been reported to activate the Th promoter, but remarkably without any requirement for its DNA binding activity as it apparently acts by tethering to the CREB protein bound to a CRE site in the Th promoter (Hong et al. 2006).

SYMPATHETIC AND ADRENAL CHROMAFFIN CELL DEVELOPMENT: ENIGMATIC CROSS-REGULATORY GENE INTERACTIONS

Taken together, although some of the transcription factors discussed here seem to function sequenntially in what could be considered to be a classical linear developmental hierarchy, the data are actually more consistent with the possibility that SA cell differentiation is controlled by mutually reinforcing feedback transcriptional interactions between GATA-3, MASH-1, Hand2, Phox2a and Phox2b (Fig. 3). Unfortunately, the current literature sheds little additional light on whether any of these transcription factors are mutually (directly or indirectly) regulated by one another. The Phox2a and Phox2b promoters have been characterized, but without specific reference to any SA cell lineage-restricted activity (Flora et al. 2001; Hong et al. 2001; Samad et al. 2004). Thus, the data published to date characterizing Phox2a and Phox2b expression provide an inadequate foundation on which to base further regulatory analysis. Our Gata3 cis-regulation studies have revealed that even a 662 kbp Gata3 YAC, containing approximately 451 kbp and 211 kbp of 5’ and 3’ flanking sequence information, respectively, is missing the regulatory element(s) that confers expression in SA system organs (Lakshmanan et al. 1999; Hasegawa et al. 2007). Hence, (at least to date) any formal proof supporting a hierarchy proposed based upon gene expression would be considered to be a classical linear developmental hierarchy, the data are actually more consistent with the possibility that SA cell differentiation is controlled by mutually reinforcing feedback transcriptional interactions between GATA-3, MASH-1, Hand2, Phox2a and Phox2b (Fig. 3). Unfortunately, the current literature sheds little additional light on whether any of these transcription factors are mutually (directly or indirectly) regulated by one another. The Phox2a and Phox2b promoters have been characterized, but without specific reference to any SA cell lineage-restricted activity (Flora et al. 2001; Hong et al. 2001; Samad et al. 2004). Thus, the data published to date characterizing Phox2a and Phox2b expression provide an inadequate foundation on which to base further regulatory analysis. Our Gata3 cis-regulation studies have revealed that even a 662 kbp Gata3 YAC, containing approximately 451 kbp and 211 kbp of 5’ and 3’ flanking sequence information, respectively, is missing the regulatory element(s) that confers expression in SA system organs (Lakshmanan et al. 1999; Hasegawa et al. 2007). Hence, (at least to date) any formal proof supporting a hierarchy proposed based upon gene expression.
pression analyses in Mash1, Phox2, dHand or Gata3-abla-
tive mutant animals remains absent (Fig. 3). Until the regu-
ulatory elements governing the SA tissue specificity of each
of these transcription factors are identified, how and which
transcription factors directly regulate which of the multiple
regulatory genes discussed here is a major question that re-
 mains outstanding.

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