Transcriptional and Epigenetic Regulation of Neural Crest Induction during Neurulation

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Epigenetics · Chromatin remodeling · Folic acid · Gene regulation · microRNA · Neural crest · Neural stem cell · Neural tube · Neurulation

Abstract
Neurulation is one of the many important events in mammalian development. It is the stage of organogenesis in vertebrate embryos during which the neural tube is transformed into the primitive structures that will later develop into the central nervous system. Recent transcriptome analysis during neurulation and early organogenesis in humans and mice has identified the global dynamics of gene expression changes across developmental time. This has revealed a richer understanding of gene regulation and provides hints at the transcriptional regulatory networks that underlie these processes. Similarly, epigenome analysis, which collectively constitutes histone modifications, transcription factor binding, and other structural features associated with gene regulation, has given a renewed appreciation to the subtle mechanisms involving the process of neurulation. More specifically, the histone demethylases KDM4A and KDM6B have recently been shown to be key histone H3K4 and H3K27 modifiers that regulate neural crest specification and neural tube closure. Additionally, miRNAs have recently been shown to influence transcription of genes directly or by altering the levels of epigenetic modifiers and thus regulate gene expression. This mini review briefly summarizes the literature, highlighting the transcriptional and epigenetic regulation of key genes involved in neural crest induction and neural crest specification by transcription factors and miRNAs. Understanding how these mechanisms work individually and in clusters will shed light on pathways in the context of diseases associated with neural crest cell derivatives such as melanoma, cardiovascular defects and neuronal craniofacial defects.

Introduction
In vertebrates, the neural tube is the embryo’s precursor to the central nervous system, which comprises the brain and spinal cord. Neurulation is the stage of organogenesis in vertebrate embryos during which the neural tube is transformed into the primitive structures that will later develop into the central nervous system [1]. This stage consists of primary and secondary neurulation. Primary neurulation divides the ectoderm into the following cell types: (a) the neural tube (internally located); (b) the epidermis (externally located), and (c) neural crest cells
NCCs develop in the region between the neural tube and epidermis, and as development progresses migrate to new locations. Primary neurulation begins after the neural plate forms. The edges of the neural plate start to thicken and lift upward, forming the neural folds. The center of the neural plate remains grounded, allowing a U-shaped neural groove to form. This neural groove sets the boundary between the right and left sides of the embryo. The neural folds pinch in towards the midline of the embryo and fuse together to form the neural tube [2]. Figure 1 depicts all the processes and some of the important genes/proteins involved at different stages of the induction of neural crest (NC). In secondary neurulation, the cells of the neural plate form a cord-like structure that migrates inside the embryo and hollows to form the tube. Neural tubes in mammals close in the head in the opposite order than they close in the trunk. In the head (a) NCCs migrate; (b) the neural tube closes, and (c) the overlying ectoderm closes. In the trunk (a) the overlying ectoderm closes; (b) the neural tube closes, and (c) NCCs migrate [2].

The notochord plays an integral role in the development of the neural tube. The notochord induces the neural tube to form in the overlying ectoderm. This is known as primary induction. Once the ectoderm is induced to become neural ectoderm, it can also induce its neighbors to become neural ectoderm. This is called planar induction. The ectoderm is divided into three major domains: the surface ectoderm, which generates primarily epidermis; the neural tube, which generates brain and spinal cord, and the NC generating peripheral neurons, pigment and facial cartilage [2, 3]. The dorsal neural tube creates the NC, which migrate away following an epithelial-to-mesenchymal conversion to give rise to a diverse set of cell types. These include peripheral nervous system, adrenal medulla, melanocytes, facial cartilage and dentine of teeth. The peripheral nervous system consists of Schwann cells, neuroglial cells, sympathetic nervous system and parasympathetic nervous system, sympathetic ganglia, dorsal root sensory ganglia and melanocytes of the skin [4]. Neurulation creates the outer ectodermal layer, which covers over the neural tube once it is created. The ectodermal layer gives rise to epidermis, hair, nails, sebaceous glands, olfactory epithelium, mouth epithelium, lens and cornea. The mouth epithelium gives rise to anterior pituitary, tooth enamel and cheek epithelium [5]. At the end of crest emigration, the midline of the dorsal neural tube becomes the roof plate. This serves as a signaling center for the organization of dorsal neuronal cell types [6].

In mammals, miRNAs, noncoding RNAs approximately 22 nucleotides in length, play critical roles in various physiological processes by acting as posttranscriptional regulators to reduce translation of target genes by either destabilizing mRNAs or blocking their translation [7, 8]. miRNAs are central regulators of NC development [9–11].

In the NC, repression of targets by regional and spatiotemporal biogenesis of miRNAs elicits critical changes in gene expression programs that regulate gene regulatory networks crucial to NC development [12]. Knowledge of miRNA expression profiles during NCC differentiation into distinct lineages introduces the possibility of producing adult NC stem cells (NCSCs) for regenerative purposes. This mini review briefly summarizes the literature, highlighting the transcriptional and epigenetic regulation of key genes involved in NC induction and NC specification. This understanding will shed light on pathways linked to neurocristopathies or diseases associated with NCC derivatives such as melanoma, cardiovascular defects and neuronal craniofacial defects.
NC Induction: Transcriptional Regulation of Genes

NCCs arise in the neural folds at the border between neural and non-neural ectoderm in early embryos [13]. Neural induction is defined as the step when ectodermal cells become specified as neural stem or precursor cells. Later in development, these specified cells will no longer respond to signals that induce alternative fates, and have thus committed to a neural fate. Ultimately, these cells will differentiate into neurons and other neural cell derivatives [14]. NC induction occurs via signaling between these tissues and appears to be mediated by the Wnt and BMP signaling pathways [15, 16]. NC induction at the plate border is mediated by mesodermal signals which include fibroblast growth factor (FGF) and mesodermal and adjacent non-neural ectodermal Wnt signaling. One or both of these signals induce expression of individual neural plate border specifier genes, such as Pax3, Zic1, Gbx2, Dlx3/5 and Msx1/2. Pax3 and Zic1 in the presence of Wnt upregulate Snail and FoxD3 expression, respectively. MiRNAs that regulate other genes or are regulated by gene products are listed in the red boxes. The → denote activation and ⊥ denote suppression. MiRNAs are listed in boxes with red frames (black frames in the print version); genes are designated by squares or ovals.

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NC specification is defined by the expression of NC specifier genes in premigratory and NC progenitors. NC specification involves three important events: (1) delamination; (2) epithelial-to-mesenchymal transformation (EMT), and (3) NC cell fate determination and differentiation (fig. 3).

Delamination

NCCs separate from neighboring neuroepithelial cells by delamination, which involves a partial or complete EMT [19]. At delamination, the tissue splits into separate populations. Delamination is triggered by a Bmp/canonical Wnt cascade involving Bmp4, Wnt1, Msx1 and c-Myb [20, 21], which promotes EMT via activation of Snail2, Foxd3 and members of the SoxE family [22]. Snail2, Foxd3, Sox9 and Sox10 activate β1-integrin [22], participate in switching cadherin profiles from N-cadherin to cadherin 6B to cadherin 7 and 11 [23], and modulate RhoB expression [24]. The switch from strong cell adhesion (mediated by N-cadherin) required for maintaining epithelial integrity to weak cell-cell adhesion...
Fig. 3. A summary of gene regulatory networks and miRNAs in NC specification. 

- a NC specification involves processes that give the neural plate border progenitor characteristics of the bona fide NC. These cells undergo EMT, cell cycle arrest followed by delamination, extensive migration and different events of terminal differentiation. MiRNAs that regulate other genes or are regulated by gene products that are involved in cell cycle/delamination, EMT and NCC differentiation are shown. The → denote activation and ⊥ denote suppression. miRNAs are listed in boxes with red frames (thick black frames in the print version); genes are designated by squares or ovals.
(supported by cadherin 6B and cadherin 7) promoting separation from the epithelium and allowing cell migration may be a general step during NC development. The BMP4/Wnt1 cascade is also essential for the G1/S transition of NC precursors located in the dorsal neural tube [20], to maintain NC identity [22]. Activation of the BMP/Wnt cascade is linked to somite maturation and noggin inhibition which leads to early departure of NC cells, while maintenance of noggin blocks NC delamination [25]. Differentiating somites appear to release a factor that blocks noggin expression in the dorsal neural tube [26]. This unidentified factor in turn initiates the BMP/Wnt cascade. Taken together, these data indicate that a combination of factors, including ligands and transcription factors, is required to promote NCC delamination.

**Epithelial-to-Mesenchymal Transformation**

EMT is a series of events at the molecular level orchestrating a change from an epithelial to a mesenchymal phenotype [27]. EMT is brought about by the integration of extracellular signals, which include extracellular matrix components such as collagen or hyaluronic acid, and secreted ligands, such as members of the TGFβ and FGF families. These receptor-mediated signaling events [28] in turn upregulate the expression of Snail1, Snail2 and FoxD3 that orchestrates cellular changes by directly mediating transitions in cell-junction assembly, motility and adhesion occurring during EMT [29, 30].

For EMT to occur, premigratory NCCs which exist within a fully polarized epithelial layer, adjoined by adherens junctions and tight junctions, have to lose their apical-basal cell polarity and dissolve tight junctions. These events are accompanied by changes in cytoskeletal organization and a switch in adhesive properties so that cells can separate from the neuroepithelium and emigrate [28]. Cadherins play a major role in EMT. Type I cadherins, associated with stable cell assemblies, are replaced by mesenchymal cell type II cadherins, with lower adhesive- ness, allowing NC cells to increase their motility [31]. NC specifies FoxD3 and Snail downregulate expression of N-Cad and E-Cad (or Cad6B in chick and mouse), respectively, while upregulating mesenchymal migratory proteins, such as Cad7. Similarly, Snail downregulates tight junction claudins/occludins and upregulates the gap junction protein connexin-43α1 (Cx43α1) [18].

**NCC Fate Determination/Differentiation**

After separating from surrounding tissue, NCCs migrate extensively throughout the embryo. To arrive at their target region, NCCs must interpret multiple environmental signals that directly influence where they go and settle to differentiate [32, 33]. SoxE transcription factors Sox9 and Sox10 are major players in this process. These transcription factors regulate effector genes that give derivative cells their terminal characteristics. Sox9 is first expressed during NC specification in premigratory NCCs and Sox10 during early delaminating and migrating NCCs. These transcription factors later control the differentiation of NC-derived cartilage by directly binding the collagen type II α1 (Col2α1) promoter [34]. Sox10 expression persists in neurons and melanocytes, regulating multiple downstream effectors [35]. Sox10 (1) regulates [36, 37] and also acts synergistically with MITF to control the expression of dopachrome tautomerase (Dct/TRP2) [36], essential for melanin synthesis during melanocyte differentiation; (2) controls the expression of both Mash1 and Phox2b, two key transcription factors responsible for sympathetic neuron fate [38]; (3) regulates neuro-rogenin-1 (Neurog1) [35] and therefore regulates sensory neuron fate specification also; (4) in the enteric nervous system, Sox10 controls the glial-cell-derived neurotrophic factor (GDNF)-Ret pathway by physically interacting with PAX3 to synergistically activate the c-Ret receptor tyrosine kinase that transduces GDNF signals [39, 40] in the enteric nervous system; (5) during gliogenesis, SOX10 directly regulates Schwann cell-specific myelin genes such as protein zero (P0), myelin basic protein (MBP), proteolipid protein [41], connexin-32, connexin-47 and peripheral NS myelin [42], and (6) coordinates normal enteric NS development in collaboration with endothelin-3 [43].

**Epigenetic Regulation of Genes Involved in NC Induction**

*MicroRNAs in Caudal Neural Tube*

There has been minimal work done on the role of miRNAs in caudal neural tube development. miRNAs act as modulators of the epigenetic landscape in NCSCs [44]. MicroRNAs regulate molecules that change histone marks during NC development. MicroRNA genes can be epigenetically regulated and miRNAs can in turn repress key enzymes that drive epigenetic remodeling. Ichi et al. [45], using a folate-responsive mouse model of neural tube defect, *Splotch*, showed that in heterozygous mouse embryos, levels of miRNAs such as miR-138, miR-148a, miR-185 and miR-339-5p were upregulated. These miRNAs target KDM6B, a histone H3K27 demethylase, thus decreasing KDM6B expression and increasing
H3K27 methylation. This in turn altered methylation patterns on Hes1 promoter, associated with stem cell maintenance and proliferation, and Neurog2 promoter, associated with sensory differentiation, compared to wild-type embryos. Methylated H3K27 associates with the Hes1 promoter and methylation results in decreased Hes1 expression and lowered stem cell proliferation. Simultaneously, low association between methylated H3K27 and the Neurog2 promoter, but high association between acetylated H3K9 and H3K18 and the Neurog2 promoter, results in premature neurogenesis. Folic acid-mediated rescue of the caudal neural tube phenotype in Splotch could be due to reversible downregulation of KDM6B targeting miRNAs, resulting in upregulation of KDM6B and subsequent lowering of H3K27 methylation [45]. Demethylated H3K27 showed decreased binding with Hes1 promoter and increased binding with Neurog2 promoter, resulting in increased stem cell proliferation/maintenance and normal neurogenesis instead of premature neurogenesis [39]. The reason why this happens is not clear. Demethylated H3K27 could possibly render the chromatin more open for normal neurogenesis. Demethylated H3K27 occupancy with Neurog2 promoter could make the acetylated histone such as H3K9 or H3K18 more accessible to the Neurog2 promoter, resulting in normal neurogenesis. In short, folic acid can regulate expression of these miRNAs and therefore modulate the epigenetic landscape of Hes1 and Neurog2 during neural tube closure [45]. Other miRNAs that regulate epigenetic targets such as EZH2, HDAC1/4 and DNMT1 are shown in table 1.

MicroRNAs in Cranial NC

Cranial NCCs make an integral contribution to the elaborate program of craniofacial development [46]. Disruption of Shh signaling or platelet-derived growth factor (Pdgf) pathways causes craniofacial abnormalities, including cleft palate [9]. miR-140 negatively regulates Pdgf signaling during palatal development and provides a mechanism for disruption of Pdgf signaling causing palatal clefting. MiR-140 loss of function elevates Pdgfrα protein levels, alters palatal shape and causes NCCs to accumulate around the optic stalk, a source of the ligand Pdgfa [47]. MiR-140 disconnects palatal precursor cell migration from Pdgfrα signaling [47]. miR-140 modulates Pdgfrα-mediated attraction of cranial NCCs to the oral ectoderm, where crest-derived signals are necessary for oral ectodermal gene expression. These results suggest that the conserved regulatory interactions of miR-140 and pdgfrα define a mechanism of palatogenesis, and they provide candidate genes for cleft palate.

The TGF-β signaling pathway mediated by Smad2 and Snail is also essential for normal palate development [48, 49]. Molecular interactions exist between miR-200b and TGF-β-mediated Smad2, Snail and E-cadherin during palatogenesis [50]. miR-200b (1) modulates the expression of E-cadherin, apoptosis and proliferation in the midline epithelial seam region by regulating Smad2 and Snail, implying an important cellular control mechanism in the precise morphogenesis of the secondary palate; (2) affects migration and palatal fusion through regulation of the Zeb family, Zeb1 and Zeb2, of zinc finger transcription factors [50, 51], and (3) induces E-cadherin expression and reduces Zeb1 and Zeb2 expression [52, 53].

MicroRNAs in Cardiac NCC Patterning

Dicer and miRNAs are essential for NCC survival, migration and patterning in craniofacial and cardiovascular development [10, 54]. Targeted deletion of Dicer in NCCs leads to severe craniofacial and cardiovascular defects, which are similar to human congenital neuro-craniofacial-cardiac defects [55]. Dicer loss of function is at least in part mediated by miR-21 and miR-181a, which in turn repress the protein level of Sprouty2, an inhibitor of Erk1/2 signaling [55]. Studies suggest that the NC gives rise to cells that will be part of the cardiovascular system [56]. Cardiac NCCs in the caudal pharynx support development of the persisting aortic arch arteries into the great arteries of the thorax and form their smooth muscle tunics. Mutants of DGCR8, a double-stranded RNA-binding protein that interacts with the RNase III enzyme Drosha and forms a micro-complex in the nucleus to process primary microRNA (pri-miRNA) into precursor miRNA (pre-miRNA) [57, 58], display a wide spectrum of malformations, such as persistent truncus arteriosus and ventricular septal defect. Loss of Dgcr8 causes a significant portion of cardiac NCCs to undergo apoptosis, decreasing the pool of progenitors required for cardiac OFT (outflow tract) remodeling, thus suggesting a new role of Dgcr8 in controlling cardiac NCC survival during cardiovascular morphogenesis [59].

Conclusion, Challenges and Future Directions

Neurocristopathy refers to a diverse class of pathologies that may arise from defects in the development of tissues containing cells derived from the embryonic NCC lineage [60]. Examples (reviewed in [61]) include, but are not restricted to: Waardenburg syndrome, Hirschsprung...
Table 1. The functions of miRNAs during different stages of neural crest specification

<table>
<thead>
<tr>
<th>Gene</th>
<th>miRNA</th>
<th>Function</th>
<th>Cell type</th>
<th>Developmental stage</th>
<th>Exp/in silico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sox9</td>
<td>miR-145</td>
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<td></td>
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<td>chondrocytes</td>
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<td>exp</td>
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<tr>
<td></td>
<td>miR-140</td>
<td>chondrocyte initiation, cartilage-specific</td>
<td>chondrocytes</td>
<td></td>
<td>exp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regulation [77, 78]</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>cartilage regulator [73]</td>
<td></td>
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<tr>
<td></td>
<td>miR-124</td>
<td>spinal cord neurogenesis [79]</td>
<td>neuroepithelial stem cells</td>
<td>spinal cord</td>
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<tr>
<td></td>
<td></td>
<td>embryonic growth [80]</td>
<td></td>
<td>E7.5 embryos</td>
<td>exp</td>
</tr>
<tr>
<td></td>
<td>miR-101</td>
<td>chondrocyte ECM degradation [81]</td>
<td>chondrocytes</td>
<td></td>
<td>exp</td>
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<tr>
<td>Snail/Slug</td>
<td>miR-124</td>
<td>inhibits EMT [82]</td>
<td>breast cancer</td>
<td></td>
<td>exp</td>
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<tr>
<td></td>
<td>miR-124a</td>
<td>maintains stemness [83]</td>
<td>human ESC</td>
<td>gastrulation</td>
<td>exp</td>
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<tr>
<td></td>
<td>miR-1</td>
<td>inhibits EMT [84]</td>
<td>prostate adenocarcinoma</td>
<td></td>
<td>exp</td>
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<tr>
<td></td>
<td>miR-200</td>
<td>inhibits EMT [84]</td>
<td>prostate adenocarcinoma</td>
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<td>exp</td>
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<tr>
<td></td>
<td>miR-34</td>
<td>inhibits EMT [84, 85]</td>
<td>colorectal cancer cell line HCT116</td>
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<td>exp</td>
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<tr>
<td>c-Myc</td>
<td>miR-33b</td>
<td>reduced cell proliferation [86]</td>
<td>medulloblastoma</td>
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<tr>
<td>Id</td>
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<td>proliferation and invasiveness [87]</td>
<td>breast cancer cells</td>
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<td>exp</td>
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<tr>
<td>Twist</td>
<td>† miR-199a</td>
<td>development of neural cell population in cerebellum [88]</td>
<td>murine molar tooth germ cells</td>
<td>exp</td>
<td></td>
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<tr>
<td></td>
<td>† miR-214</td>
<td>midbrain, nasal processes and fore and hind limb buds [89]</td>
<td>midbrain, nasal processes and fore and hind limbs</td>
<td>exp</td>
<td></td>
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<tr>
<td></td>
<td>† miR-1</td>
<td>musculature [90]</td>
<td>Drosophila muscles during larval growth</td>
<td>exp</td>
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<td>Sox10</td>
<td>† miR-106a</td>
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<td>Schwann cells</td>
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<td></td>
<td>† miR-338</td>
<td>sympathetic/parasympathetic nervous system [91]</td>
<td>Schwann cells</td>
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<td>† miR-92b</td>
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<td>Schwann cells</td>
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<td>† miR-350</td>
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<td>Schwann cells</td>
<td>exp</td>
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<tr>
<td></td>
<td>† miR-17</td>
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<td>Schwann cells</td>
<td>exp</td>
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<tr>
<td></td>
<td>† miR-340</td>
<td>Schwann cells [91]</td>
<td>Schwann cells</td>
<td>exp</td>
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<tr>
<td></td>
<td>† miR-363</td>
<td>Schwann cells [91]</td>
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<td>† miR-19b</td>
<td>Schwann cells [91]</td>
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<td></td>
<td>† miR-20b</td>
<td>Schwann cells [91]</td>
<td>Schwann cells</td>
<td>exp</td>
<td></td>
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<tr>
<td>MITF</td>
<td>† miR-204</td>
<td>differentiation of retinal pigment cell [92]</td>
<td>retinal pigment cell</td>
<td>exp</td>
<td></td>
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<tr>
<td></td>
<td>† miR-211</td>
<td>melanocyte development [93]</td>
<td>melanocytes</td>
<td>exp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>† miR-17–19 cluster</td>
<td>melanocyte development [94]</td>
<td>melanocytes</td>
<td>exp</td>
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<tr>
<td></td>
<td>miR-148</td>
<td>melanogenesis [94]</td>
<td>melanocytes</td>
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<td></td>
<td>miR-137</td>
<td>melanogenesis, melanocyte survival and function [92, 95, 96]</td>
<td>melanocytes</td>
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<td>miR-25</td>
<td>melanogenesis/pigmentation [97]</td>
<td>melanocytes</td>
<td>exp</td>
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The miRNAs negatively regulate the genes necessary for NC specification, except in case of arrows where the gene products down- or upregulate the miRNA expressions. ECM = Extracellular matrix; Exp = experimental.
### Table 1 (continued)

#### b miRNAs affecting and affected by NC-inducing signals

<table>
<thead>
<tr>
<th>Inducing signals</th>
<th>miRNA</th>
<th>Function</th>
<th>Cell type</th>
<th>Developmental stage</th>
<th>Exp/in silico</th>
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<tr>
<td>BMP signaling</td>
<td>miR-26a</td>
<td>inhibition of Smad1/4 [98]</td>
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<tr>
<td></td>
<td>miR-320–367</td>
<td>inhibition of type II BMP receptors [98]</td>
<td>skeletal muscle</td>
<td>exp</td>
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<tr>
<td>Wnt</td>
<td>miR-142-3p</td>
<td>osteoblast differentiation [99]</td>
<td>osteoblast</td>
<td>exp</td>
<td></td>
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<tr>
<td></td>
<td>miR-452</td>
<td>EMT [100]</td>
<td>NCC</td>
<td>first pharyngeal arch</td>
<td>exp</td>
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<tr>
<td>FGF</td>
<td>Dgcr8 KO</td>
<td>decreases ERK/FGF signaling [59]</td>
<td>cardiac and skeletal muscle</td>
<td>exp</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>precursor cells</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>cardiovascular morphogenesis [59]</td>
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</tbody>
</table>

The miRNAs negatively regulate the NC-inducing signals except in the case of arrows, where the inducing signals are involved in down- or up-regulating the expressions of these miRNAs. Exp = Experimental.

#### c miRNAs affecting neural plate border specifier genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>miRNAs</th>
<th>Function</th>
<th>Cell type</th>
<th>Developmental stage</th>
<th>Exp/in silico</th>
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<td>Msx1/2</td>
<td>miR-181a</td>
<td>osteoblastic differentiation [101]</td>
<td>osteoblasts</td>
<td></td>
<td>exp</td>
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<tr>
<td>Pax3</td>
<td>miR-128a</td>
<td>regulate muscle cell differentiation [102]</td>
<td>muscle cells</td>
<td></td>
<td>exp</td>
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<tr>
<td></td>
<td>miR-206</td>
<td>regulate myogenesis [103]</td>
<td>muscle cells</td>
<td></td>
<td>exp</td>
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<tr>
<td>Zic 1</td>
<td>miR-101</td>
<td>deregulation of β-catenin [104]</td>
<td>human fibroblasts</td>
<td></td>
<td>exp</td>
</tr>
</tbody>
</table>

These miRNAs negatively regulate the neural plate border specifier genes. Exp = Experimental.

#### d miRNAs regulating epigenetic targets

<table>
<thead>
<tr>
<th>Targets</th>
<th>miRNA</th>
<th>Activation or repression</th>
<th>Epigenetic regulation</th>
<th>Cell type</th>
<th>Dev stage</th>
<th>Exp/in silico</th>
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</thead>
<tbody>
<tr>
<td>HDAC4</td>
<td>miR-1</td>
<td>repression [105]</td>
<td>CpG methylation</td>
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<td>exp</td>
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<td>EZH2</td>
<td>miR-26a</td>
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<td>DNMT3A/B</td>
<td>miR-29</td>
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<td></td>
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<td></td>
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<tr>
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<td>miR-101</td>
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<td></td>
<td>lung cancer cells</td>
<td>exp</td>
<td></td>
</tr>
<tr>
<td>p300, MeCp2</td>
<td>miR-132</td>
<td>activation [109]</td>
<td>CpG methylation</td>
<td>cultured rat neurons</td>
<td></td>
<td>exp</td>
</tr>
<tr>
<td>KDM6B</td>
<td>miR-138</td>
<td>repression [45]</td>
<td>histone modification</td>
<td>NCSCs</td>
<td>E9.5</td>
<td>exp</td>
</tr>
<tr>
<td>DNMT1, 3B</td>
<td>miR-148a</td>
<td>repression [110]</td>
<td>CpG methylation</td>
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<td>exp</td>
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<td>miR-148a</td>
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<td>histone modification</td>
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<td>miR-339-5p</td>
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<td>histone modification</td>
<td>prostate cancer cells</td>
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</tbody>
</table>

The expression of epigenetic targets such as HDAC1, HDAC4, EZH2, p300, MeCp2, DNMT1, 3A/3B and KDM6B is regulated by miRNAs. Dev = Developmental; Exp = Experimental.
Transcriptional and Epigenetic Regulation of NC Induction

References


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Transcriptional and Epigenetic Regulation of NC Induction


