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Review

Epigenetic regulation in neural crest development

Na Hu [a,1], Pablo H. Strobl-Mazzulla [b,*,1], Marianne E. Bronner [a]

[a] Division of Biology and Biological Engineering, 139-74, California Institute of Technology, Pasadena, CA 91125, USA
[b] Laboratory of Developmental Biology, Instituto de Investigaciones Biotecnológicas—Instituto Tecnológico de Chascomús (CONICET-UNSAM), Chascomús, Argentina

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ABSTRACT

The neural crest is a migratory and multipotent cell population that plays a crucial role in many aspects of embryonic development. In all vertebrate embryos, these cells emerge from the dorsal neural tube then migrate long distances to different regions of the body, where they contribute to formation of many cell types and structures. These include much of the peripheral nervous system, craniofacial skeleton, smooth muscle, and pigmentation of the skin. The best-studied regulatory events guiding neural crest development are mediated by transcription factors and signaling molecules. In recent years, however, growing evidence supports an important role for epigenetic regulation as an additional mechanism for controlling the timing and level of gene expression at different stages of neural crest development. Here, we summarize the process of neural crest formation, with focus on the role of epigenetic regulation in neural crest specification, migration, and differentiation as well as in neural crest related birth defects and diseases.

Introduction

Neural crest cells are a population of multipotent stem/progenitor cells that are induced during gastrulation at the neural plate border, between the neural and non-neural ectoderm. By neurulation, definitive neural crest cells are specified as premigratory cells within the dorsal neural tube and initiate expression of typical neural crest markers like *FoxD3* and *Sox10*. They then emerge from the neural tube by undergoing an epithelial to mesenchymal transition (EMT) whereby they delaminate from the neuroepithelium, assume a mesenchymal morphology and migrate extensively to different parts of the body. After migration, they differentiate into numerous derivatives including neurons and glia of the peripheral nervous system, melanocytes, portions of the cardiac outflow tract, craniofacial bone and cartilage, and smooth muscle of major blood vessels (Bronner and LaBonne, 2012; Sauka-Spengler and Bronner-Fraser, 2008; Sauka-Spengler and Bronner, 2010). Understanding neural crest development is important because these cells are involved in a variety of birth defects, diseases and cancers, including cleft lip and palate, heart defects, Hirschprung's disease, melanoma and neurofibromatosis.

There is good evidence that transcriptional events are critical for many aspects of neural crest development. A neural crest gene regulatory network (GRN) (Meulemans and Bronner-Fraser, 2004) comprised of transcriptional and signaling events has been proposed to function in a feed-forward series of regulatory circuits (Betancur et al., 2010; Sauka-Spengler and Bronner-Fraser, 2006). This neural crest GRN appears to be highly conserved throughout vertebrates, including basal agnathans (Sauka-Spengler et al., 2007), suggesting that these regulatory mechanisms were in place before the divergence of jawed and jawless vertebrates, likely to the base of the origin of vertebrates at 550 million years ago.

In addition to transcriptional regulation, there is growing evidence to support roles for epigenetic regulation as critical for many aspects of neural crest development, most notably in controlling the timing of gene expression at different developmental stages. Here we discuss the critical role of epigenetic regulation during neural crest development and disease and some examples of how it impinges upon the neural crest GRN.

Overview of epigenetic regulation

Epigenetic modifications are defined as mechanisms that regulate gene expression without altering the underlying sequence of DNA (Bernstein et al., 2007). However, recent changes in the usage of the term have led to the suggestion that the requirement of heritability be dropped and that epigenetic events might better be defined as "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states" (Bird, 2007).

* Corresponding author at: Instituto de Investigaciones Biotecnológicas—Instituto Tecnológico de Chascomús, Intendente Marino Km 8, 2, Chascomús 7130, Argentina.
E-mail address: strobl@intech.gov.ar (P.H. Strobl-Mazzulla).
[1] These authors contributed equally to this work.

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Epigenetic modifiers can alter chromatin structure and genome function through different processes such as DNA modifications, histone modifications and variants, or can work as a complex to regulate higher-level chromatin conformation in an ATP-dependent manner. Depending on the specific type of regulator, the outcome can either lead to gene activation, in which the chromatin is relaxed and DNA is accessible to transcription factors, or to gene repression, where chromatin is tightly packed and inaccessible to transcriptional regulators.

Epigenetic modifiers, including "writers" and "erasers" that establish the epigenetic code (Fig. 1), are key regulators of developmental events and also aberrant marks associated with many types of cancers, and disease states (Portela and Esteller, 2010). Here, we focus on various epigenetic regulators that have been shown to play a role in neural crest development and neural crest related diseases (Table 1). The epigenetic machinery falls into the following groups: DNA methylation, histone methylation, histone acetylation, Polycomb repressive complex, ATP-dependent chromatin remodeling complex, and other regulators that work with the epigenetic machinery to regulate neural crest development. Different types of DNA and histone modifications and family members of chromatin remodeling complexes have been reviewed recently in (Liu and Xiao, 2011).

Neural crest induction and specification

The process of neural crest formation is initiated by signaling events, mediated by ligands including BMPs, WNTs and FGFs that are secreted from neighboring tissues such as the neural and non-neural ectoderm as well as the underlying mesoderm. During gastrulation, these signals establish the neural plate border region and initiate neural crest induction (Basch and Bronner-Fraser, 2006; Heeg-Truesdell and LaBonne, 2004; Steventon et al., 2005; Stuhlmiller and Garcia-Castro, 2012). The neural plate border region has the competence to form not only neural crest cells but also other cell types such as placode cells and some central nervous system (CNS) cells. Signaling inputs in this region up-regulate a group of transcription factors called 'neural plate border specifier genes' including *Msx1/2*, *Pax3/7*, *Dlx5*, *AP2A*, *Gbx2* and *Zic1*. The collective and overlapping expression of these genes confers upon the neural plate border region the unique ability to form neural crest cells. However, among all the neural plate border specifiers, the *Pax3/7* genes, when combined to *Zic1*, are sufficient to activate a bona fide neural crest specification program (Basch et al., 2006; Hong and Saint-Jeannet, 2007; Milet et al., 2013; Monsoro-Burq et al., 2005; Sato et al., 2005).

During neurulation, neural plate border circuitry activates a set of transcription factors called the 'neural crest specifier genes' in the dorsal neural tube. These include genes like *AP2*, *n-Myc*, *Id*, *Snail2*, *FoxD3*, *Ets-1*, *Sox8/9/10*, with some differences in the timing of their initial expression (Khudyakov and Bronner-Fraser, 2009). These factors function to maintain multipotency, promote their epithelial-to-mesenchymal transition (EMT), initiate delamination and migration, while also affecting cell proliferation and survival. A bona fide neural crest cell is first recognizable by the expression of transcription factors such as *FoxD3, Sox9, Snail2,* and *Sox10*, which are expressed in the dorsal neural tube and/or newly delaminated neural crest cells, depending upon the species. These genes regulate downstream effector genes to promote EMT and migration, at which point the neural crest cells become an identifiable population of multipotent-migratory stem-like cells (Barembaum and Bronner-Fraser, 2005; Gammill and Bronner-Fraser, 2003; Sauka-Spengler and Bronner-Fraser, 2008).

Neural crest EMT and migration

During the epithelial to mesenchymal transition process, neural crest cells alter cell junctions, adhesive properties and morphology to acquire cell motility, which enables them to migrate long distances to their final destinations. For example, they switch from expression of cadherins characteristic of epithelial cells to cadherins of more mesenchymal character and lose tight junctions while establishing gap junctions. Neural crest specifier genes like *Snail2* and *FoxD3* regulate downstream genes to facilitate this process. As a result, N-Cad and Cad6B are down-regulated and Cad7 is up-regulated, along with an N-cad to E-cad switch and modulation of gap junction proteins and integrins (Kerosuo and Bronner-Fraser, 2012; Strobl-Mazzulla and Bronner, 2012; Rogers et al., 2013). At this point, neural crest cells become a distinct group of mesenchymal cells that delaminate from the neuroepithelium and migrate out of the dorsal neural tube.

During their migration, neural crest cells interact with each other and with their environment via signaling receptors such as

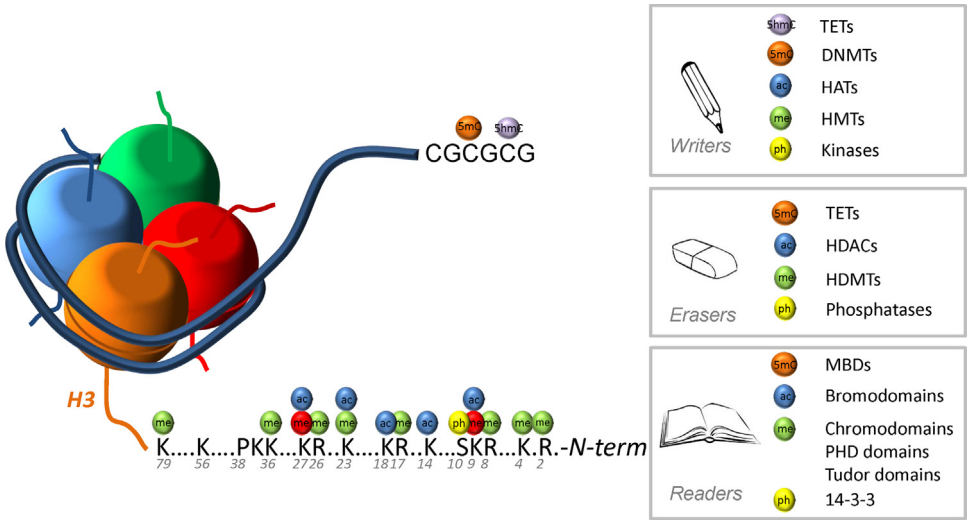

Fig. 1. Schematic diagram of the different epigenetic marks identified on histone H3 and DNA and their respective "writer", "eraser" and "reader" proteins. Histone methylations on red and green are associated with transcriptional repression and activation, respectively. TETs, Ten-Eleven translocation enzymes; DNMTs, DNA methyltransferases; HATs, histone acetyltransferases; HDACs, histone deacetylases; HMTs, histone methyltransferases; and HDMTs, histone demethylases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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