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Review

Epithelial to mesenchymal transition: New and old insights from the classical neural crest model

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ABSTRACT

The epithelial-to-mesenchymal transition (EMT) is an important event converting compact and ordered epithelial cells into migratory mesenchymal cells. Given the molecular and cellular similarities between pathological and developmental EMTs, studying this event during neural crest development offers and excellent in vivo model for understanding the mechanisms underlying this process. Here, we review new and old insight into neural crest EMT in search of commonalities with cancer progression that might aid in the design of specific therapeutic prevention.

1. Introduction

The neural crest (NC) is a transient embryonic cell population characterized by its multipotency and migratory ability. Induced at the boundary between neural and non-neural ectoderm, the NC is specified via a well-orchestrated transcriptional program, now referred to "gene regulatory network" [1–6]. As neurulation proceeds, NC precursors are restricted to the dorsal aspect of the neural fold and neural tube, where they can be distinguished by the expression of "neural crest specifier genes". Subsequently, they undergo an epithelial-to-mesenchymal transition (EMT) to become migratory NC cells that migrate extensively to diverse locations. At their destinations, some undergo a reaggregation process via a mesenchymal-to-epithelial transition (MET) and further differentiate into many types of cells, ranging from neurons and glia of sensory, autonomic and enteric ganglia, to adrenomedullary secretory cells, smooth muscle cells, melanocytes, and bone and cartilage cells.

NC cells have attracted the attention of embryologists for over a century as a model for studying embryonic induction, specification, migratory potential and differentiation. In fact, perturbation experiments yield very different anomalies depending upon the phase of NC cell development that is disrupted (e.g., migration versus differentiation), with disruption in NC EMT generally causing the most severe phenotypes. Interestingly, common signaling pathways appear to occur during NC EMT as in other developmental EMTs such as those occurring during gastrulation in the primitive streak, somite decondensation, cardiac valve formation, etc. [7]. Notably, malignant cells also appear to use the same mechanisms to delaminate from an epithelial tumor as those used by embryonic epithelial cells to delaminate and migrate during development. This highlights the importance of understanding the normal mechanisms of NC EMT as these might provide important clues regarding the mistakes that lead to abnormal development or loss of the differentiated state.

In this review, we focus on new and old insights into NC formation as one of the best studied developmental examples of EMT, highlighting their importance during embryogenesis as well as a model for understanding cancer cells and tumor progression.

2. The EMT process in NC cells

A variety of in vivo and in vitro analyses in chick and Xenopus along with genetic studies in the mouse and zebrafish have identified some of the cellular and molecular mechanisms underlying EMT during NC cell delamination as well as some of the signaling cascades that trigger these events (Fig. 1). After their specification, premigratory NC precursors from the dorsal neural tube undergo an EMT process that can be parsed into several, sometimes overlapping, steps that ultimately allow the precursors to leave the neural tube, becoming bona fide NC cells that migrate through the extracellular matrix. The process of NC EMT events requires: (i) the coordinated activity of transcription factors and molecular signaling pathways, (ii) changes in cell junctions and polarity, (iii) changes in adhesion properties, and (iv) changes in the extracellular matrix.

After EMT, the migratory ability of NC cells starts either prior to or soon after fusion of the neural folds depending upon the

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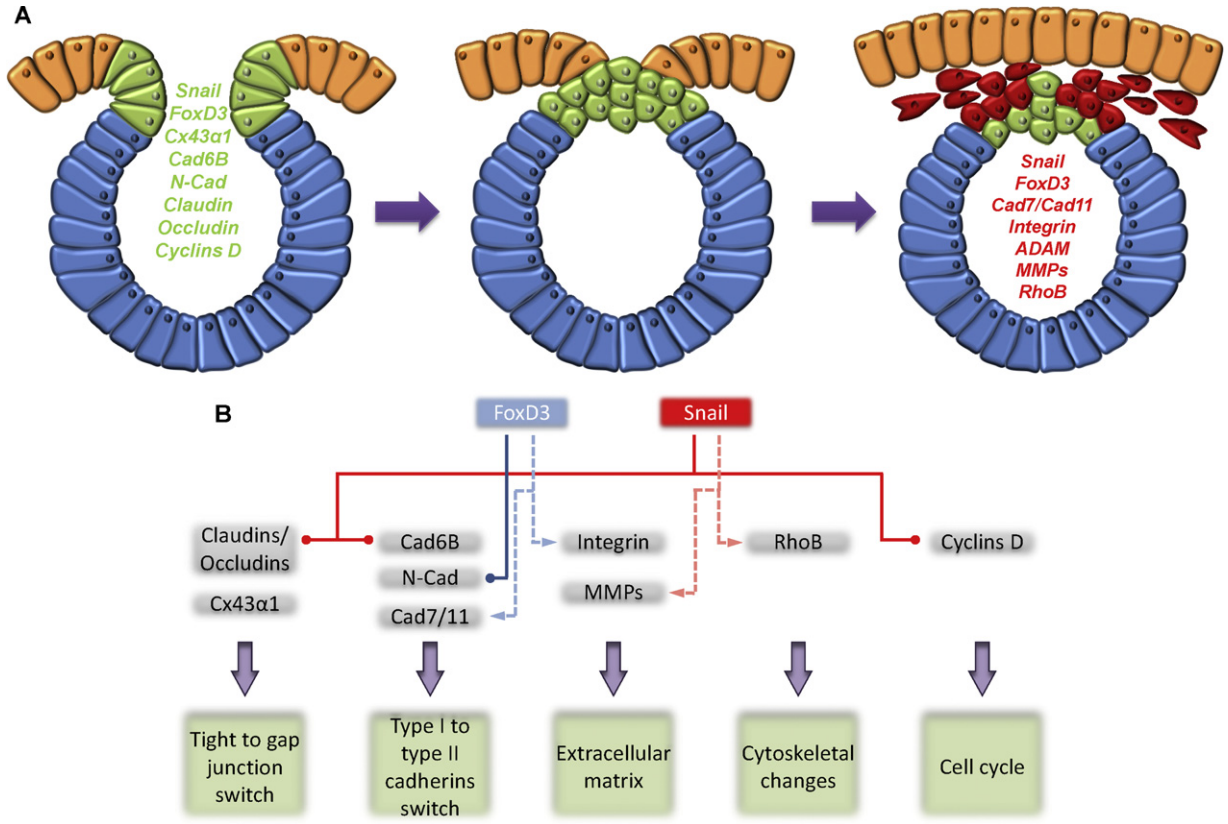

Fig. 1. (A) Schematic representation of the genes expressed on neural crest cells prior (green) and after (red) undergoes epithelial-to-mesenchymal transition. (B) Neural crest epithelial-to-mesenchymal transition regulation. NC specifiers, FoxD3 and Snail down-regulate expression of molecules that are associated with epithelial static cell populations, such as N-Cad and E-Cad (or Cad6B in chick and mouse), respectively, to give place to the up-regulation of mesenchymal migratory proteins, such as Cad7. Similarly, Snail down-regulates tight junction claudins/occludins to permit the up-regulation of gap junction protein connexin-43α1 (Cx43α1), which may also depend on Snail expression. Gene regulation in which the repressors Snail or FoxD3 up-regulate the expression of matrix metalloproteases (MMPs), integrins, Cad7 or RhoB may denote indirect regulatory interactions, possibly mediated by other repressors (represented by dotted lines).

vertebrate species [8]. Concomitantly, NC cells acquire mesenchymal characteristics, as they express the intermediate filament vimentin and possess a flattened morphology with filopodia and lamellipodia, facilitating their spreading [9–11]. Migratory NC cells follow stereotypical pathways depending upon their axial level of origin. Cranial NC cells invade the surrounding cranial mesenchyme and ultimately condense to contribute to various cranial ganglia and craniofacial cartilage and bones. Migratory NC cells in the trunk that follow the ventral pathway differentiate into components of the peripheral nervous system, while those migrating dorsolaterally become melanocytes [8].

2.1. Transcription factors

The signaling pathways utilized during EMT in the NC are similar to those that are active in other developmental EMT process. Indeed, NC EMT is triggered by the integration of extracellular signals, which include components of the extracellular matrix as well as a number of secreted ligands including members of TGFβ, Wnt and FGF families. This initial event is necessary to convert neuroepithelial precursors into migratory NC cells through activation of a number of transcriptional regulators, including the zinc finger transcription factors, Snail1 and Snail2 (formerly known as Slug), and the winged-helix transcription factor FoxD3, which are critical factors that coordinate the cellular changes occurring during EMT [5].

Snail: Snail promotes NC EMT by directly mediating transitions in cell-junction assembly, motility and adhesion [5]. In chicks, NC cells express Snail2 whereas Snail1 is expressed in the mouse and both factors coexist in Xenopus [12–14]. Loss of function experiments in chick and Xenopus result in a strong abrogation of cranial NC cell migration [12,15,16]. Conversely, gain-of-function experiments reveal that Snail1 in Xenopus and Snail2 in chick are sufficient to induce expansion of the cranial NC territory and production of a greater number of migrating NC cells. However, numerous observations suggest that Snail genes may be neither sufficient nor necessary for NC cell specification and delamination, and may play different roles at different axial level [12,17,18]. These results indicated that Snail-expressing cells must either receive additional inputs or express other transcriptional regulators at different axial levels to achieve specification and execute the EMT program.

Until recently, it was not possible to discriminate whether Snail genes functioned during specification, delamination or both. However, several recent studies indicate that Snail can regulate target genes, such as E-cadherin [19], as well as genes encoding structural proteins that constitute the junction's backbone such as claudin-3, claudin-4, claudin-7, and occludin [20], by directly binding to E-box sequences within their promoters. In mouse and chick embryos, a non-overlapping complementary mRNA expression pattern between Snail1/E-Cadherin and Snail2/Cadherin-6B, respectively, has been observed at the boundary of the ectoderm and the neural tube in the head region [19,21]. Moreover, it has been demonstrated in chick that Snail2 directly binds to Cad6B regulatory sequence and represses it expression to allow NC cell delamination [21]. Conversely, Cad6B expression persists in migrating NC in mouse and the trunk of chick embryos after cessation of NC cell delamination [22–24]. Taken together, these