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Review

Nodal signalling in embryogenesis and tumourigenesis

Daniela F. Quail, Gabrielle M. Siegers, Michael Jewer, Lynne-Marie Postovit*

Department of Anatomy and Cell Biology, University of Western Ontario and Robarts Research Institute, London, ON, Canada

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ABSTRACT

With few exceptions, most cells in adult organisms have lost the expression of stem cell-associated proteins and are instead characterized by tissue-specific gene expression and function. This cell fate specification is dictated spatially and temporally during embryogenesis. It has become increasingly apparent that the elegant and complicated process of cell specification is "undone" in cancer. This may be because cancer cells respond to their microenvironment and mutations by acquiring a more permissive, plastic epigenome, or because cancer cells arise from mutated stem cells. Regardless, these advanced cancer cells must use stem cell-associated proteins to sustain their phenotype. One such protein is Nodal, an embryonic morphogen belonging to the transforming growth factor-β (TGF-β) superfamily. First described in early developmental models, Nodal orchestrates embryogenesis by regulating a myriad of processes, including mesendoderm induction, left–right asymmetry and embryo implantation. Nodal is relatively restricted to embryonic and reproductive cell types and is thus absent from most normal adult tissues. However, recent studies focusing on a variety of malignancies have demonstrated that Nodal expression re-emerges during cancer progression. Moreover, in almost every cancer studied thus far, the acquisition of Nodal expression is associated with increased tumourigenesis, invasion and metastasis. As the list of cancers that express Nodal grows, it is essential that the scientific and medical communities fully understand how this morphogen is regulated in both normal and neoplastic conditions. Herein, we review the literature relating to normal and pathological Nodal signalling. In particular, we emphasize the role that this secreted protein plays during morphogenic events and how it signals to support stem cell maintenance and tumour progression.

Contents

Abbreviations: ALDHhi, high expression of aldehyde dehydrogenase; ALK, activin-like kinase receptor; AP, anterior–posterior; AVE, anterior visceral endoderm; BMPs, bone morphogenic proteins; CER1, Cerberus; CFC, conserved cysteine-rich domain; CSCs, cancer stem cells; dpc, days postcoitum; DVE, distal visceral endoderm; EBAF, endometrial bleeding-associated factor; EGF-CFC, epidermal growth factor-cripto FRL1 cryptic; EMT, epithelial-to-mesenchymal-transition; EpiSC, epiblast embryonic stem cell; ERK, extracellular regulated kinase; ER/PR, oestrogen and progesterone receptor; FOXH1, forkhead box HI; GBM, glioblastoma multiforme; GDF1, growth differentiation factor 1; GPI, glycosyl-phosphatidylinositol; *Gsc*, *Goosecoid*; H3K9me3, methylated histone H3 at lysine 9; H3K18ac, acetylated histone H3 at lysine 18; hESCs, human embryonic stem cells; HIF, hypoxia-inducible factor; hPSCs, human pluripotent stem cells; LR, left–right; MAPK, mitogen activated protein kinase; mESC, mouse embryonic stem cells; miRNA, microRNA; NCBI, National Centre for Biotechnology Information; PD, proximal-distal; PE, pre-eclampsia; PEE, proximal epiblast enhancer; rNodal, recombinant Nodal; SARA, SMAD anchor for receptor activation; SMAD, mothers against decapentaplegic; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor; Xnr, Xenopus Nodal-related.

* Corresponding author at: Department of Anatomy and Cell Biology, Schulich School of Medicine & Dentistry, University of Western Ontario, Medical Sciences Building, Room 438, London, ON, Canada N6A 5C1.
E-mail address: Lynne.Postovit@schulich.uwo.ca (L.-M. Postovit).

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1. Introduction

Embryonic development is characterized by the spatial and temporal differentiation of stem cells, leading to the generation of tissue diversity. This process of differentiation is dictated by microenvironmental mediators such as morphogen gradients and oxygen availability (Quail et al., 2012a). The instructive cues of the embryonic programme culminate in an organism made of tissues and cell types that maintain homeostatic balance concomitant with exquisite structure–function relationships. In cancer, the embryonic programme is disrupted resulting in the manifestation of stem cell-like characteristics (Fig. 1) (Hendrix et al., 2007). Alternatively, some cancers may arise from resident stem cell populations (Chen et al., 2012; Driessens et al., 2012; Gilbertson and Graham, 2012; Visvader and Lindeman, 2006). This stem-cell-like nature of cancer is correlated with metastatic progression, resistance to therapy and a poor clinical prognosis. Hence, understanding and targeting molecules that sustain stem cell-like phenotypes could be of tremendous therapeutic value.

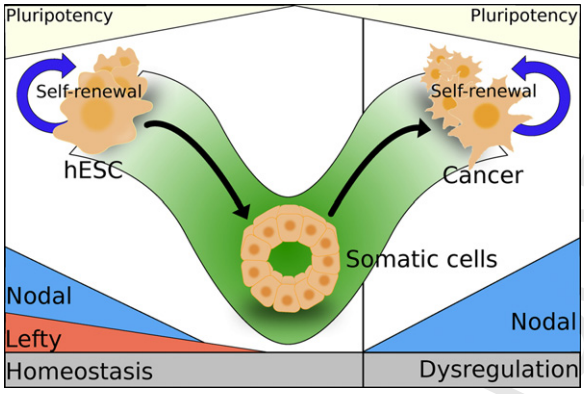

Fig. 1. Nodal signalling is a developmental phenomenon that is "re-awakened" during cancer progression: tumour progression is characterized by a loss of tissue structure and by the acquisition of a more stem cell-like phenotype. In many ways this process represents an "undoing" of the differentiation that occurs during development and mimics certain aspects of induced pluripotency. The mechanism by which cancer cells aberrantly acquire the expression of Nodal likely involves epigenetic alterations facilitated by microenvironmental mediators such as oxygen availability. Normal embryonic stem cells maintain a balance of activators and inhibitors of self-renewal in order to facilitate differentiation in response to specific cues. Here we highlight Nodal and its inhibitor Lefty. In contrast, cancer cells hijack these elegant signalling pathways in a manner that favours uncontrolled growth in the absence of normal differentiation. In this example, the cancer cells express Nodal in the absence of Lefty.

A number of proteins have been shown to regulate both normal and neoplastic stem cell populations. One example is Nodal. Nodal is a member of the transforming growth factor-β (TGF-β) superfamily, which includes TGF-βs, activins, growth/differentiation factors (GDFs), and bone morphogenic proteins (BMPs) (Quail et al., 2012a; Schier, 2009). Originally discovered in mouse, Nodal homologues have been characterized in humans, *Xenopus* (frogs), and zebrafish, amongst other model organisms (Schier, 2009). As is the case for mouse Nodal, there is currently only one annotated isoform for human Nodal mRNA in the National Centre for Biotechnology Information (NCBI) Entrez Gene database (http://www.ncbi.nlm.nih.gov:80/sites/entrez) corresponding to one Nodal ligand. Human Nodal is found on chromosome 10 and consists of three protein-coding exon regions that are translated into a 347 amino acid pro-protein. Nodal is further processed into a mature form (amino acids 238–347) with a C-terminus that might be important for interactions with other proteins such as co-receptor Cripto (Schier, 2009). Unlike mammals, zebrafish have three Nodal orthologues (cyclops, squint, and southpaw), whilst frogs have six "Xenopus Nodal-related" members (Xnr1-6), although only 5 of these (Xnr1,2,4–6) have canonical Nodal functions (Schier, 2009). Regardless of the species, in chordates Nodal proteins are essential for the induction of mesoderm and endoderm, and left–right patterning during embryogenesis (Hendrix et al., 2007; Schier, 2009; Shen, 2007).

Nodal is relatively restricted to embryonic and reproductive cell types and is not detectable in most normal adult tissues (Hendrix et al., 2007; Hooijkaas et al., 2011). However, recent studies have demonstrated that Nodal expression re-emerges during cancer progression (Lawrence et al., 2011; Lee et al., 2010; Lonardo et al., 2011; Strizzi et al., 2012; Topczewska et al., 2006). Moreover, in almost every cancer studied thus far, the acquisition of Nodal expression is associated with increased tumourigenesis, invasion and metastasis (Table 1) (De et al., 2012; Lawrence et al., 2011; Lee et al., 2010; Lonardo et al., 2011; Papageorgiou et al., 2009; Quail et al., 2012a, 2012b, in press; Strizzi et al., 2012; Topczewska et al., 2006). As more cancers expressing Nodal are added to the list, it is becoming increasingly important that we understand the mechanisms by which this morphogen is regulated. Here we

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