Developmental Biology 433 (2018) 177–189

Contents lists available at ScienceDirect

Developmental Biology

journal homepage: www.elsevier.com/locate/developmentalbiology

Review article

Bioelectric signaling in regeneration: Mechanisms of ionic controls of growth and form

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ARTICLE INFO

Keywords:
Bioelectricity
Ion channel
Resting potential
Voltage
Patterning

ABSTRACT

The ability to control pattern formation is critical for the both the embryonic development of complex structures as well as for the regeneration/repair of damaged or missing tissues and organs. In addition to chemical gradients and gene regulatory networks, endogenous ion flows are key regulators of cell behavior. Not only do bioelectric cues provide information needed for the initial development of structures, they also enable the robust restoration of normal pattern after injury. In order to expand our basic understanding of morphogenetic processes responsible for the repair of complex anatomy, we need to identify the roles of endogenous voltage gradients, ion flows, and electric fields. In complement to the current focus on molecular genetics, decoding the information transduced by bioelectric cues enhances our knowledge of the dynamic control of growth and pattern formation. Recent advances in science and technology place us in an exciting time to elucidate the interplay between molecular-genetic inputs and important biophysical cues that direct the creation of tissues and organs. Moving forward, these new insights enable additional approaches to direct cell behavior and may result in profound advances in augmentation of regenerative capacity.

1. Introduction

A critical goal of regenerative biology and medicine is to understand and control the mechanisms underlying the processes directing growth and patterning. Alongside conventionally-studied transcriptional networks and chemical cues, additional inputs enable cells to cooperate and make decisions necessary for the repair and remodeling of complex anatomical structures. Endogenous ion flows serve as important regulators of cell behavior, coordinating cell activity during pattern homeostasis. Located within cell membranes, ion channels, pores, and pumps create a complex language of bioelectric signals that is tightly integrated with gene regulatory networks to direct cell behavior toward the creation and maintenance of functional tissues and organs. Here we discuss the known roles of ion-based physiological processes in directing cell behavior during pattern formation and regeneration. Specifically excluded in this review are the fast-acting action potentials associated with neurons and muscle cells, externally-applied electromagnetic fields and radiation, and ultra-weak photon emission.

2. What is developmental bioelectricity?

All cells drive and respond to changes in transmembrane voltage potential (V_{mem}). Unlike fast-spiking currents normally associated with nerve and muscle cell activity, ion pumps, channels, and pores distribute specific ion species across cellular plasma membranes to produce slowly-changing spatial patterns of resting potential (Fig. 1). In addition, groups of cells can be electrically connected via the diffusion of small molecules between cells through electrical synapses known as gap junctions (Fitzharris and Baltz, 2006; Mathews and Levin, 2017). These transmembrane potentials, fluxes of individual ions, and iso-electric cell compartments established by gap junctions, convey information to target cells, their neighbors, and in some instances, to distant locations. This signaling modality is used to process and transmit information about regenerative parameters such as cell type, tissue size, positional information, axial polarity, and organ identity (Levin, 2014; Levin et al., 2017; Pitcairn and McLaughlin, 2016). Importantly, these signals (unlike the familiar mRNA and protein signals) can only be characterized in the living state. Furthermore, the ability of channels and gap junctions to open and close post-translationally means that bioelectric cell states are a complex function of a given cell's microenvironment history, impinging physiological signals, and expression levels of electrogenic machinery.

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http://dx.doi.org/10.1016/j.ydbio.2017.08.032
Received 1 June 2017; Received in revised form 23 August 2017; Accepted 28 August 2017
Available online 25 December 2017

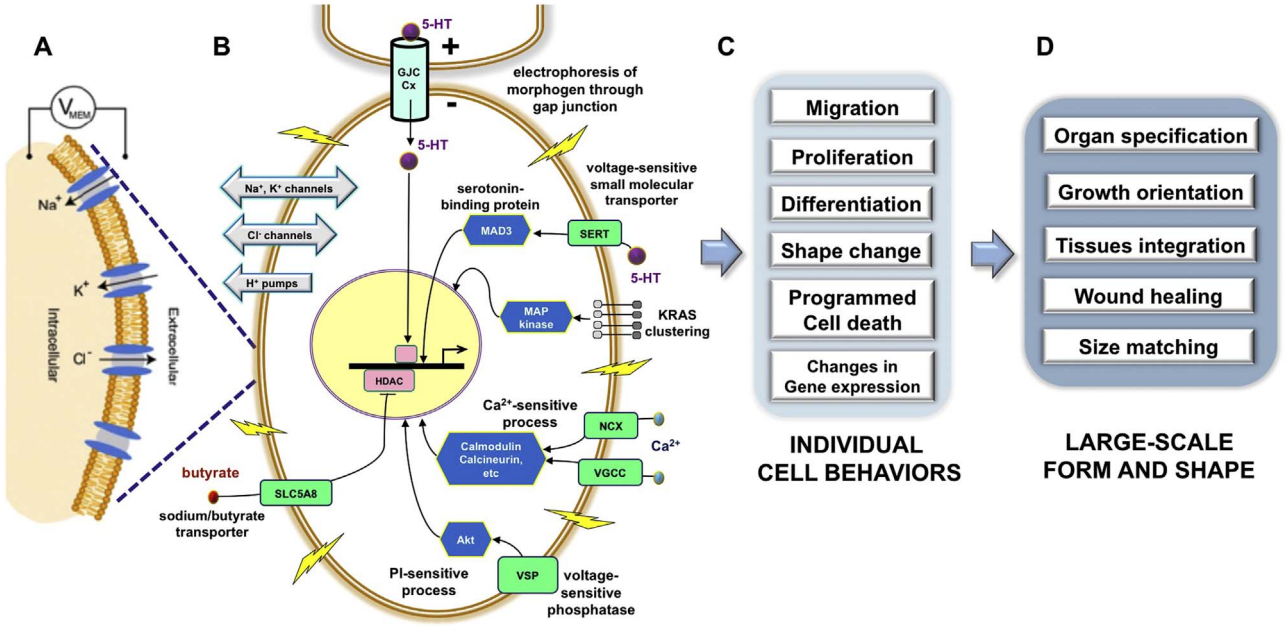

Fig. 1. Bioelectrical signaling drives pattern formation at the level of the cell, tissue, and organism. (A) Changes in transmembrane voltage are transduced (B) by a set of membrane mechanisms (voltage-powered transporters of serotonin and butyrate, voltage-gated calcium channels, voltage-regulated phosphatases, and others) into second-messenger cascades that regulate gene expression, thus directing cell behavior (C) such as, migration, proliferation, cell death, differentiation, gene expression, and shape changes. (D) In turn, these changes in cell behavior enable the creation of complex structures. Abbreviations: 5-HT, 5-hydroxytryptamine, also known as serotonin; HDAC, histone deacetylase; MAD3, Max-interacting transcriptional repressor; Akt, serine/threonine-specific protein kinase; GJC, gap junction communication; NCX, Na^+/Ca^{2+} exchanger; VGCC, voltage-gated calcium channel; Cx, connexin; MAP kinase, mitogen-activated protein kinase. Lightning bolts represent changes in resting membrane potential. Panels A and B modified with permission (Levin, 2007b).

3. Over a century of observations in developmental bioelectricity - a historical perspective

The “electrical properties of living tissues” have been discussed by scientists for over a century (Mathews, 1903); prescient workers such as Burr and Northrop (1935) and Lund (1947) characterized bioelectrical gradients in developing and regenerative systems, and used applied voltages to show that bioelectric signals were not merely epiphenomena of housekeeping physiology but were instructive for specific changes in growth and patterning in a range of fungal, plant, invertebrate, and vertebrate species. Marsh and Beams spearheaded some of the useful studies supporting an instructive role for bioelectric signaling during tissue patterning. By applying external electric fields to worm fragments, they demonstrated the ability to specifically alter the anterior-posterior polarity of regenerating fragments of planaria (Marsh and Beams, 1947, 1952). Subsequent instrumental work by several researchers including Lionel Jaffe, Richard Nuccitelli, Richard Borgens, Colin McCaig, and Ken Robinson, found that the electrical properties of single cells, neural tissues, epithelia, and entire appendages, were able to direct growth, morphology, and tissue polarity during regeneration of a wide range of model species (Borgens, 1982, 1983, 1986, 1989; Jaffe, 1980, 1981, 1982; Jaffe et al., 1974; McCaig et al., 2005; Nuccitelli and Jaffe, 1974, 1976; Robinson, 1983).

With the advent of modern molecular, cellular, and genomic methodologies, more recently researchers have built upon these early studies to characterize proteins responsible for generating the bioelectric signals, transduction machinery that converts voltage change into second-messenger cascades, the gene regulatory networks downstream of bioelectric signaling, and ultimately the underlying mechanisms that direct cell behavior. The development of molecular-resolution genetic and pharmacological tools to investigate and manipulate ion flow has revealed that changes in resting potential can control individual cell behaviors including: proliferation, cell death, migration, and differentiation, in of a wide variety of cells types (Fig. 1). In addition, recent data implicate endogenous spatiotemporal patterns of V_{mem} in regulating processes during embryonic development, regeneration, and patterning, that when altered, are responsible for a wide range of channelopathies and birth defects (Matusik, 2017; Persson and Bondke Persson, 2016).

4. Cell-level control of behavior by ion-mediated processes

During the creation of organized tissues, the ability to control cell behavior is critical for the formation of properly patterned structures. Large-scale morphogenesis necessitates the coordination of individual cells whose function is regulated via the integration of molecular cues and endogenous bioelectrical signals (as outlined in Fig. 1). Both the creation of functional organs during development and regeneration of missing structures post-injury, require careful regulation of cell movement and positioning. Examples of cell migration events include the movement of progenitor cells towards the injury site observed in: planaria (Salo and Baguna, 1985), zebrafish (brains, hearts, fins) (Salo and Baguna, 1985; Tahara et al., 2016; Zupanc, 2006), and stem cell homing (Chute, 2006). Over half a century ago, several groups reported that electric fields could be used to direct cell behavior to orient cells either parallel or perpendicular to the field line, extend cell processes, or direct migration relative to the positioning of an anode or cathode (Anderson, 1951; Hyman and Bellamy, 1922). Although there is some debate over which cell types respond to physiologically relevant electric fields (Robinson and Cormie, 2008), subsequent work has shown numerous embryonic and somatic cell types exhibit galvanotaxis in electric fields *in vivo* (Pullar and Isseroff, 2005; Stump and Robinson, 1983; Yao et al., 2008; Zhao et al., 1997). It has been postulated that during embryogenesis these electric fields serve to both polarize the early vertebrate embryos as well as provide important positional cues that direct cell movements necessary for morphogenesis and pattern formation (Pitcairn et al., 2017; Shi and Borgens, 1995). This is especially relevant for guiding innervation and the movement of epithelial cells to close wounds – key components of regenerative response (Cao et al., 2013; Reid et al., 2005; Yamashita et al., 2013).