

Bioelectric Signaling Networks through Tissue Regeneration in Human Disease

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Abstract

The article explores bioelectric signaling as an information system that helps coordinate tissue patterning and regeneration. Membrane potentials generated by ion channels, pumps, and transporters can influence proliferation, migration, differentiation, gene expression, and multicellular organization. Gap junctions allow neighboring cells to share electrical and chemical information, creating tissue-level voltage patterns that can guide anatomy in regenerative models. The article emphasizes that these physiological signals interact with genetic and biochemical pathways rather than replacing them. Single-cell transcriptomic and epigenomic approaches can identify regulatory programs associated with particular voltage states, while CRISPR perturbation can test which genes generate or respond to those states. Dose-response and threshold behavior are important because small electrical changes may have no effect while larger changes can reorganize patterning. Translational work should distinguish organized regeneration from nonspecific cell growth. Overall, bioelectric networks are presented as an additional control layer linking rapid physiology to later transcription and tissue form.



Cells must solve a positional problem in order to regenerate tissue. New cells not only have to determine their fate but also where they fit in a head, a limb, a nerve, or an organ boundary. Both genes and chemical gradients carry some of that information, but experiments with highly regenerative animals indicate that signals from the membrane voltage and ion flow also contain instructive information. Physiology is part of the information system which controls anatomy, and can organize the growth of many cells through bioelectric networks.

All living cells have a membrane potential which is maintained by ion channels, pumps and transporters. For nonexcitable tissues, these voltages are sometimes regarded as a "background physiology" but developmental and regenerative research indicates that stable voltage patterns can affect the proliferation, migration, differentiation and gene expression. Adjacent cells can exchange electrical and chemical information through Gap Junctions, forming multicellular circuits.

Planarian regeneration is very striking evidence. If it is a small fragment, it can regenerate full animals with the proper head tail polarity. The voltage pattern may be manipulated in the first hours after amputation to alter which structures regenerate by manipulating proton pumps or ion channels. A short early insult may therefore alter the course of an anatomical process which takes days to develop.

In one set of experiments, it was found that the process of early depolarization affects the anterior/ posterior identities before the large transcriptional differences are apparent. The

changes in membrane potential performed within a narrow window post injury altered the expression of later genes and may result in the production of double headed animals. The conclusion is that bioelectric state comes before part of the gene regulatory cascade, not as a late effect of tissue differentiation.

When dealing with scale, bioelectric signaling also has an impact. An ion pump can be manipulated to change the size of the head and of the organs in planaria without just increasing or decreasing the amount of tissue that is growing. It has been found that the phenotype is associated with remodeling and apoptosis, implying that voltage patterns contribute to the determination of the suitable proportion of the regenerated structures.

The network can have memory. Temporary disruption of gap junction communication has resulted in the regeneration of planaria with altered body plans even after the original treatment has been removed. A hidden residual risk exists in some morphologically normal descendants to develop abnormal anatomy following another amputation. Such discoveries indicate that the pattern information is stored in stable bioelectric states without DNA sequence variations.

This doesn't mean that genes are unimportant. Genes encode ion channels and pumps and voltage changes modify transcription via Ca^{2+} , neurotransmitter and second messenger pathways. The key concept is reciprocal control: The electrical apparatus is built by the gene regulatory networks, and the electrical states, in turn, control the gene expression. Regeneration is a dynamic process that arises out of the interaction of molecular and physiological information.

Single cell 'Epigenomics' can help bridge these scales. The chromatin accessibility and transcription factor activity can be profiled in cells in different voltage states. Based on bioelectric perturbation, researchers can ask which regulatory elements are opened or closed prior to morphology changes to affect the developmental decision. The electrical state can then be perturbed using CRISPR technology to determine if specific genes are required for the electrical state.

Functional rescue is particularly useful. If there is a channel knockout that prevents regeneration, it can be followed up with channel restoration, changing the membrane voltage by another channel, or turning on a channel downstream. Rescue can be used to determine what is the critical variable, whether that is the specific protein, ionic current, membrane potential or the downstream signal, in this case calcium.

The regeneration of human tissues is less extensive than the regeneration of planarians

and caution must be taken to ensure that the mechanism can be translated directly into human tissue. Fibrosis, immune response, vascularisation and limited stem cell populations are all tissues involved in mammalian wound healing and organ repair. Bioelectric control is shown to work in a flatworm, but it doesn't mean that it will work in regenerating a human organ. The utility of this approach is that conserved principles are identified that can be tested in mammalian tissues.

There is an intermediate system, engineered tissues. Cell behavior can be monitored on organoids, cell sheets, and wound models, with controlled electrical or pharmacologic perturbations imposed on these. Electrical states can be mapped using voltage sensitive reporters and gene expression can be used to identify downstream programs. They enable causal experiments without prematurely claiming clinical regeneration.

One of the main factors is safety as ion channels affect heart, nerve, and muscle function. A drug that alters the membrane potential in general can have a profound off target effect. If it were to be used in regenerative applications, tissue-specific delivery, exposure for a short period, or molecular targets that are limited to the repair site would be required. Mechanistic precision is thus crucial before bioelectric control can be considered as a therapeutic approach.

The network can be made visible using voltage sensitive dyes and genetically encoded reporters. Such tools can provide a map of depolarized and hyperpolarized areas before the anatomical changes. Repeated imaging can identify if a perturbation is capable of altering a transient wound signal or a stable body wide pattern. Also quantitative maps can be directly compared to gene expression domains.

The gap junction connectivity is a measurement that should be made separately due to the different implications of the same cell voltage if the cells are tightly coupled or loosely coupled. Blocking junctions can separate electrical compartments and change the long range pattern coordination. The expression of connexin or innexin along with voltage can provide clues to whether the failure of regeneration is due to lack of a signal or inability to propagate.

Bioelectric state can be influenced by mechanical forces. Ion channels are affected by wound tension, stiffness of the extracellular matrix and cell shape, and voltage affects the behavior of the cytoskeleton. Regeneration is thus a mixture of electrical, chemical and mechanical information. Multifactor experiments can be used to determine if voltage is informative when mechanical conditions are also fixed.

It is important for translation to be dose responsive. Depending on the network stability, small voltage changes may produce no visible change, changes or abrupt anatomical changes. If those thresholds can be mapped, a therapeutic window can be found and the behaviour of pattern control can be determined as a continuous regulator or a switch.

Function should be included for long term follow up. Correct anatomy can be accompanied by aberrant innervation, contractility or sensor functions. Restoring integrated physiology is the key to success in restoration. Hence, bioelectric interventions should be assessed following the visible repair phase, not at the time when it seems the morphology is normal.

Computational control theory can be used in bioelectric research. A tissue network could be modeled as a set of interacting voltage states, having feedback, and candidate interventions could then be simulated prior to experimentation. The model must be able to predict intermediate voltage pattern as well as the final anatomy. Fitting both to the level is more powerful than fitting morphology only.

Conserved motifs can be identified across species by regeneration. The conserved variable might not be the channel itself but voltage, if different organisms go through different channels to depolarize a wound. If convergence of such would occur, then state of physiology would be a more transferable target than one species specific protein.

Another approach to local control is biomaterial design. Electrical environments can be sculpted with conductive scaffolds or patterned electrodes and can additionally promote tissue growth. Their utility lies in proving that they can alter the electrical signal to cause regeneration of the programme, not just contraction or proliferation.

Reversibility is a way of assessing regenerative control. If an abnormal pattern is generated by an altered voltage state, then switching back to the original state should fix regeneration in future events when the network is still plastic. Bidirectional control shows that electrical pattern is an instructive variable and not a one way injury marker.

The key will be to see if the controlled voltage manipulation is having an effect on organized repair – not just cell growth.

Michael Levin's research interests span the areas of bioelectric signaling, regeneration, and developmental biology, all of which involve a systems approach to tissue patterning. In addition to genes and soluble morphogens, cells regulate each other's anatomy. Rapid spatial information in the form of voltage gradients, ion flows, and gap junction networks can influence later transcription and form. By reading and manipulating those

physiological networks, regenerative medicine can get a new control layer, without losing sight of the powerful results obtained in model organisms, which are now accepted, useful and valid for human therapies.