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Meeting Report

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"Bioelectricity in Development, Regeneration, and Cancers" Cell Bio 2023: A Joint Meeting of the American Society of Cell Biology and European Molecular Biology Organization December 2–6, 2023, in Boston, MA, USA

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Abstract

Cell Bio conferences—organized jointly by the American Society of Cell Biology (ASCB) and European Molecular Biology Organization (EMBO)—showcase a diverse global community of the brightest researchers in Cell Biology and in emerging interdisciplinary topics, including bioelectricity. In this report, we briefly overview the Cell Bio 2023 subgroup meeting ''Bioelectricity in Development, Regeneration, and Cancers.'' This subgroup meeting featured 12 talks (7 Principal Investigators and 5 junior scientists) exploring the role of bioelectricity in endogenous and diseased states in model systems ranging from cells in culture to single-cell organisms such as yeast all the way to mammalian systems (including tools and technology developed for exploring bioelectricity and electrotaxis in cells and tissues). The subgroup meeting concluded with a discussion on the current challenges and opportunities for the field of bioelectricity.

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Morphological Patterning

The subgroup meeting was kicked off by a very interesting talk by Laura Borodinsky from the University of California–Davis on neural cell primary cilia and Sonic Hedgehog (Shh) signal in neural tube using *Xenopus laevis* embryonic development as a model system. Her laboratory identified calcium (Ca^{2+}) spikes in the neural tube distributed in a dorsoventral asymmetric manner, and these Ca^{2+} signals operate independently in the cytosol versus primary cilia. Evidence was shown for noncanonical Shh signal acting through the TRPC3 channel regulating Ca^{2+} in the primary cilia, which then acts on SOX2 and other neuronal markers to cause neural stem cells to differentiate into neurons.

This study is an excellent example of the integration of bioelectric signals with morphogen signals and gene-regulatory networks during embryonic development, which is a research area that remains largely unexplored and primed for experimental investigation to generate models of how these networks of signals orchestrate morphogenetic processes during embryonic development.

Along similar lines, Emily Bates from the University of Colorado talked about depolarization regulating Ca^{2+}-dependent bone morphogen protein (BMP) release in the developing palate of the mouse. She showed that Anderson–Tawil syndrome, which although mainly causes neurological defects, also leads to a lot of craniofacial morphology defects. Mouse KCNJ2 channel knockout in neural crest cells led to similar craniofacial defects.

Evidence was shown that BMP signal was disrupted in these loss-of-function animals, although all BMP signal components were expressed and present. KCNJ2-mediated membrane voltage (V_{mem}) depolarization leads to Ca^{2+} transients, which are critical for BMP release from vesicles,

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and in KCNJ2 knockout mice, there was no depolarization, no Ca^{2+} transients, and no BMP release, which might be the cause of craniofacial morphology defects.

Mikaela Follmer from Emily Bates' laboratory at the University of Colorado discussed unraveling the interplay between Ca^{2+} signal and soluble *N*-ethylmaleimide-sensitive factor attachment proteins receptors (SNARE) proteins in morphogenesis. She used *Drosophila* wing development as a model for limb development and the roles of BMP/Dpp in limb/wing patterning. She showed evidence for the importance of Ca^{2+} oscillations controlled by Stim and SERCA along with SNARE complex proteins for proper release of BMP/Dpp from wing discs, showing their importance for proper wing patterning.

The SNARE complex proteins can act in opposing manners, allowing tight BMP/Dpp release regulation. These sets of talks suggest that V_{mem} and Ca^{2+}-mediated regulation of morphogen release could be a conserved mechanism across various tissues that might work in tandem with various morphogens in regulating multiple aspects of embryonic development and patterning.

GuangJun Zhang from Purdue University talked about bioelectric regulation in zebrafish embryos and fin patterning. Using a genetically encoded voltage reporter accelerated sensor of action potentials 1 (ASAP1) line, he showed direct evidence for V_{mem} dynamics during the cleavage furrow, and this V_{mem} dynamics then exhibits as cellular transients during gastrulation and can become tissue/organ level events during segmentation stages.

In addition, he showed zebrafish mutants with all elongated fins were caused by transient and ectopic expression of *kcnj13/Kir7.1* and *kcnj10a* within 1–2 days postfertilization. Ectopic expression of another five different K^+ channels could induce different morphological aspects of the fins, suggesting that bioelectricity, not a specific channel, is the key for zebrafish fin size and pattern determination.

Regeneration and Cellular Reprogramming

Samatha Hack from Wendy Beane's laboratory at Western Michigan University talked about the relationship between bioelectric signals and reactive oxygen species (ROS) during adult tissue repair using the Planaria regeneration model system. ROS is crucial for wound closure and regeneration. She beautifully showed that injury-mediated V_{mem} depolarization may be responsible for triggering Ca^{2+} signal, which in turn is crucial for generating ROS, which triggers wound repair gene transcription. These findings also serve as an example of a possible relationship between bioelectricity and metabolism, as ROS are key components of cellular metabolism.

Cell Migration (Electrotaxis/Galvanotaxis) and Cancers

Daniel Cohen from Princeton University gave a fascinating presentation on the bioelectric reprogramming of collective cell behaviors. He talked about tissues as living communities and his groups successful attempts at developing tools for interactive control of tissues, which has broad applicability, for example, in expediting wound healing. Using these tools (SCHEEPDOG), he showed express control of skin cell movement (both immature and mature) using electric fields. He did raise caution about using these tools as they can override some of the natural safeguards, such as contact inhibition, and hence applications need to be carefully designed.

These tools were also used on 3D spherical cultures to control internal lumen pressure by causing the movement of ions and resulting in osmotic changes. This can be generalized for control of all organ systems that have cavities or lumen. A fascinating observation shared was electrotaxis-mediated symmetry breaking in the 3D spherical cultures. These tools that allow electrotaxis-mediated express control of cell and tissue collective behavior are extremely valuable tools for the bioelectricity field, allowing the investigation of many different biological processes and the role of bioelectricity in them.

Chrystian Junqueira Alves from Mount Sinai talked about mechano-electrical regulation of glioblastoma (a deadly brain cancer with little available treatments) stem cell migration through confined spaces. Using a custom-built microfluidic setup, he showed evidence that glioma stem cells really like constricted space migration, and confined migration enhances their invasiveness. He showed that endocytosis (essentially membrane recycling) of cell membranes on one end of the cell is important for confined cell migration.

Interestingly Plexins (classically known as axon guidance cues) are crucial for this endocytosis since CRISPR/Cas9-mediated Plexin-B2 knockout reduced membrane tension, decreased endocytosis of anionic phospholipids, and in turn caused a major hyperpolarization of cell membrane surface charges, which disrupted Ca^{2+} backflow necessary for confined migration of glioblastoma cells. This was a great example of connecting biochemical, bioelectric, and mechanical signals in controlling cell behavior. Also, the tools they developed could be highly useful for studying bioelectricity and its role in cell migration in various contexts.

Zhuoxu Ge from Sean Sun laboratory at John Hopkins University talked about the interplay of V_{mem} and cytoskeleton directing cell migration. Using a genetically encoded voltage reporter, CyoFP1-JEDI, they observed the role of V_{mem} in cell cycle progression, proliferation, and migration in nonexcitable cells. They found that Na^+/H^+ exchanger (NHE) is important for cell migration. The cytoskeleton through NHE depolarized the leading protrusions of cells, which is essential for migration. This was an excellent example of a direct connection between the cytoskeleton and ion channels and V_{mem}. Using the tool developed, they also showed dynamic changes in V_{mem} associated with cell division and shape changes.

There were two very interesting talks from members of Julie Theriot's laboratory at University of Washington on investigating electrotaxis/galvanotaxis. Nathan Belliveau talked about identifying the genes that support neutrophil galvanotaxis. Inspired by a small-scale screen in Dictyostelium that identified signaling components that contribute to galvanotaxis, he showed results of a genome-wide unbiased genetic screen for loss of galvanotaxis in HL60 neutrophil-like cells where gene expression was perturbed using CRISPRi.

Cells that perform galvanotaxis were separated from those that were defective in galvanotaxis, and their small guide RNAs were compared and analyzed. Out of 400 shortlisted knockdown perturbations, only a few exclusively affected

galvanotaxis and did not affect regular migration. They identified TMEM154, a plasma membrane protein that is predicted to have its extracellular domain glycosylated and an intracellular domain containing phosphorylation motifs. TMEM154 (now called Galvanin) immediately localizes to the anodic (trailing/back) of the cells and appears to inhibit actin polymerization there.

This could be one of the electric sensors in mammalian cells that is the fundamental mechanism behind the perception of electric fields by cells. Along similar lines, Mugdha Sathe talked about zebrafish T cell migration away from wounds due to endogenous electric fields. First, using a zebrafish skin explant system, she showed that neutrophils migrate toward the cathode at the same rate as the surrounding epidermal tissue, which also migrates to the cathode.

In contrast, T cells migrate toward the anode in the opposite direction to the surrounding tissue and neutrophils. She confirmed this *in vivo* in zebrafish using a laceration model and showed that endogenous electric and osmotic cues are essential in curating the cell population at the wound site that is conducive for wound healing.

Calcium Signaling and Bioelectricity

A major thread running through many of the talks was the involvement of Ca^{2+} signaling. Ca^{2+} was shown to be involved in a plethora of biological processes, from cell division, neural cell differentiation, cell migration, to morphogen secretion. This coincides with Ca^{2+} being a node of a bowtie network where there are a multitude of signal inputs into Ca^{2+} and a multitude of signaling outputs from Ca^{2+}.

How Ca^{2+} can relay a specific input to a specific output is a complete mystery and a primed area of investigation. Perhaps looking at spatiotemporal dynamics and frequency modulation of Ca^{2+} signals might be key to understanding how Ca^{2+} is involved in many different signals and biological processes.

Cuming Duan from the University of Michigan Ann Arbor gave a talk on Ca^{2+} channel TRPV6 regulation of epithelial cell renewal by reprograming growth factor signaling and mitochondrial metabolism. Using skin ionocytes (quiescent and differentiated cells), he showed evidence for TRPV6/Ca^{2+}-mediated reactivation of these cells. Sustained and elevated mitochondrial V_{mem} and mitochondrial metabolism (including the electron transport chain) are essential for cell reactivation.

Increased mitochondrial metabolism leads to increased ROS-induced serum glucocorticoid-regulated kinase 1 and increased ATP production, which is responsible for ionocyte plasticity. This is a wonderful example of mitochondrial bioelectric signaling affecting cell plasticity and couples bioelectric signaling with mitochondrial metabolism. This relation between bioelectricity and mitochondria is a completely unexplored area, and it is exciting to see research push boundaries in this area.

Qian Chen from the University of Toledo talked about Ca^{2+} transients during cell division requiring a mechanosensitive polycystin-2 channel, Pkd2. Using the fission yeast as the model system, they showed evidence for Ca^{2+} spike during the cleavage furrow ingression and cell separation during cytokinesis, and the Pkd2 channel that is localized to the cleavage furrow regulates these Ca^{2+} spikes.

The Pkd2 channel, in turn, is activated by membrane tension and promotes Ca^{2+} transients during cell division. This same mechanism operates in cell division in vertebrate embryos, indicating the evolutionarily conserved nature of this mechanism, which could be helpful in understanding human autosomal dominant polycistronic kidney diseases.

End of Session Discussion

At the end of the session's discussion, it was acknowledged unanimously that the bioelectricity field has come a long way from its beginning, and topics important for the advancement and dissemination of the field of bioelectricity were discussed. Although the start of the bioelectricity field can be traced back to several centuries ago, bioelectricity is still an emerging research area, lagging behind other fields in terms of broad awareness among the biology and bioengineering communities. Areas such as molecular biology and genetics are further ahead in part because they depend on data that can be obtained from dead and fractionated cells.

Bioelectricity is fundamentally a wholistic property of living cells and tissues, and cannot be resolved in fixed material or reduced to individual ion channel genes or proteins. Moreover, advances in bioelectricity often require the researcher to have a multidisciplinary background, including physics, physiology, evolutionary biology, and neuroscience. These barriers, and the resulting relatively limited appreciation and familiarity with the extant achievements in our fields, still affect aspects such as the publication of rigorous scientific research in this field in high-impact journals.

At the meeting, a need was identified to address a misperception of bioelectricity, a vague epiphenomenal or housekeeping parameter, rather than as an instructive signaling modality. This needs to be done proactively and energetically through good and extensive science outreach and communication not only among scientists (writing extensive reviews and articles addressing the issues and its history in good journals) but also among student curricula and the general public (educational materials, textbooks, books, and other avenues of public exposure to this field) about the incredible power, tractability, and usefulness of bioelectricity in biological processes.

We know this is possible because biomechanics field has taken a similar journey, moving from a niche topic to a well-accepted mainstream discipline recognized and studied by undergraduate and graduate students. This was mainly due to the development of powerful new *in vivo* techniques rendering biophysical parameters tractable and linking them to the key advances in the molecular cell biology field. Bioelectricity stands ready to take its place as a key lynchpin at the intersection of physical, genetic, and informational processes in living systems.

Another issue raised was fractionation in the bioelectricity field and the isolation of these fractions. Particularly, much research is going on in the field of Material Research Society where there are useful biocompatible tools such as genetically encoded biosensors and techniques being developed by researchers, but they do not know or have heard about (and hence do not talk to) folks working on uncovering role of bioelectricity in organismal systems, which could hugely benefit from them and *vice versa* for tool and technology applications.

Similar is the issue with ion channel researchers who are part of the American Physiological Society who have not heard or are aware of the other two fractions. The field needs efforts to integrate these fractions so that we know about each other's work and collaborate and use each other's knowhow to further the field and be a cohesive unit.

One possible way mentioned to achieve this was through holding a regular conference or meeting that incorporates researchers from all these fractions of the bioelectricity field together. Tangentially, a need was also identified for efforts to integrate the Bioelectricity field into mainstream science by having a delegate of bioelectricity field researchers go to more general science conferences and gatherings to expose to the broader scientific community the usefulness and importance of this field.

Along similar lines, even in the research happening within the sphere of uncovering bioelectricity roles in biology, most researchers are working in isolation with customized tools and technologies built to serve their model system and the questions they are asking. These same tools could be extremely useful for other researchers in the bioelectricity field, and such exposure and cross-talk are needed, perhaps through the development of tutorials with nuances and details about how the customized technique works and in which model system.

These tutorials could be updated when they are tested by another group on a different system as to whether they worked or not. Such a repository of custom tools, techniques, and knowhow about the field of bioelectricity would be an extremely valuable resource for everyone working in the field and would reduce the barrier of entry into the field for young researchers. This could also be facilitated by having a virtual gathering on a semi-regular basis, perhaps as a retreat to talk about tools and techniques and progress in the field.

Conclusion

Altogether, this meeting clearly revealed the excitement, opportunity, and energy around the field of bioelectricity. Owing to the time limitation, some of the prospects of bioelectricity, such as biosensors and voltage manipulating tools, such as chemogenetics and optogenetics, were not included this time. We hope future bioelectricity meetings will have these topics.

Forty percent of the participants were early-career scientists, and the number of laboratories in this interdisciplinary effort is growing steadily. We envision subsequent meetings to continue the momentum. For example, The Cell Bio 2024 will be held in San Diego, CA, December 14–18, 2024. To make more young scientists aware of bioelectricity, we hope to have a subgroup meeting or mini-symposium in this kind of traditional society meeting.

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