JEM Journal of Experimental Medicine

VIEWPOINT

Molecular memory of cell fate: A missing dimension of neural implant biocompatibility

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Neural implants are limited by the foreign body response, a protective but often unresolved reaction culminating in reactive gliosis and signal instability. We propose that long-term implant instability arises from progressive erosion of lineage-defining regulatory programs, uncoupling cellular compensation from tissue needs.

Neural implants and the persistent challenge of the foreign body response

Although once considered an immune-privileged site, the central nervous system (CNS) is characterized by a well-regulated immunological environment in which glial cells, particularly microglia and astrocytes, coordinate neuroprotective surveillance and homeostatic control. Neural implants, including microelectrode arrays, deep brain stimulators, and regenerative scaffolds, disrupt this equilibrium and trigger a defense response known as the foreign body response (FBR). Although protective in principle, chronic FBR at the neural implant remains a major barrier to long-term bioelectronic device stability (Luttikhuizen et al., 2006). Classically, FBR begins with implantation-induced tissue injury and protein adsorption onto the material surface, followed by innate immune recruitment and macrophage adhesion. When the material is too large or nondegradable, as with most neural implants, the response becomes chronic. In peripheral tissues, chronic FBR often leads to fibrotic encapsulation. In the CNS, the dominant response is reactive gliosis, where microglia and astrocytes form a glial scar that isolates the device but disrupts neuronal connectivity, local signaling, and reliable stimulation (O'Shea et al., 2020). Although strategies targeting surface chemistry, stiffness, and drug release can reduce early immune activation, even tissue-integrating and mechanically adaptive materials may lose effectiveness over time. This suggests that CNS FBR cannot be explained by acute injury or material properties alone but reflects a sustained implant tissue interaction that may drive long-term reprogramming beyond the initial inflammatory phase.

Immune memory at the neural implant: Beyond acute inflammation

Placing a neural implant in the brain is not only a materials challenge, but also a surgical and immunological event. Implantation causes tissue injury, vascular disruption, and potential infection risk, activating innate immune pathways before chronic device–related forces emerge. Innate immune cells are not passive responders—they encode biological information through epigenetic and metabolic reprogramming, generating memory states that range from transient priming to longer lasting trained immunity (Ter Steeg et al., 2021; Netea et al., 2020). In the CNS, long-lived microglia integrate signals from infection, systemic inflammation, injury, and aging (Wendeln et al., 2018; Tiwari et al., 2024). Yet, such experience-dependent encoding builds on a more fundamental regulatory layer—the lineage-determining transcriptional scaffolding that establishes and maintains cellular identity (Heinz et al., 2010). Neural implants therefore raise a distinct question: not simply whether prior exposure alters future immune responses, but whether persistent implant-associated stress progressively destabilizes the lineage-specific regulatory architecture that sustains coordinated tissue function—driving the transition from acute inflammation to chronic dysfunction.

From compensation to maladaptation: Regulatory drift and loss of coordination

Emerging hybrid bioelectronic systems, including immune cell–associated "circulatronics," challenge the classical concept of the implant as a purely physical object (Yadav et al., 2025). Although such approaches may mitigate some aspects of foreign body recognition, they also raise a deeper question: how does a cell respond to a stimulus that is neither biological nor transient, but sustained, mechanical, and integrated into its own circuitry? We propose that the nature of the stimulus—biological, synthetic, or hybrid—may shape not only the immediate response, but also how cellular memory is organized over time. In this context, epigenetic memory refers to the stable transmission of regulatory states over time, without changes in DNA sequence

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(Kim and Costello, 2017). Under physiological conditions, such memory supports adaptation by allowing stimulus-induced programs to be layered onto existing regulatory scaffolds. However, when stimuli are continuous, repetitive, or poorly resolved, these same mechanisms may become maladaptive—driving cells toward transcriptional entropy and features of dysdifferentiation associated with aging-related loss of identity (Zs-Nagy et al., 1988; Kane and Sinclair, 2019). Mechanical forces may further contribute to this process—physical cues transmitted through the cytoskeleton and nuclear architecture can remodel chromatin organization, including heterochromatin structure and DNA methylation in a cell type–specific manner (Song et al., 2022). Sustained perturbation may reshape regulatory architecture through coupled effects on nuclear mechanics and 3D chromatin organization—progressively weakening lineage-associated enhancer–promoter contacts while reinforcing stress-associated regulatory hubs. In the brain, such changes are unlikely to remain cell-autonomous: as stress-responsive programs become uncoupled from network-level coordination, inflammatory responses may exceed adaptive needs, and tissue coherence is lost. Implant failure may therefore reflect not only excessive inflammation, but also a broader destabilization of coordinated tissue function (Fig. 1).

Beyond tolerance: Toward a framework for adaptive biocompatibility

From a biomaterial standpoint, an implant is usually considered biocompatible if the body tolerates it and the device performs its intended function for the required period. Yet, even highly biocompatible materials trigger a FBR, which is part of normal defense and wound healing. Although devices undergo rigorous in vitro, animal, and ISO 10993–based testing, many still lose function over time (Williams, 2008). Classical biocompatibility therefore tells us whether a material is initially tolerated, but not whether surrounding tissue can maintain long-term stability.

Cells constantly face internal fluctuations, external stress, and molecular noise. Homeostasis is therefore not passive, but an active buffering process. This is especially relevant for neural implants, where periimplant tissue may initially adapt to injury, and altered mechanical forces through reparative responses. However, when these pressures persist, compensation can shift from repair toward reinforcement of maladaptive cellular states. One way to understand this is through chromatin, which shapes how cells interpret and remember stress over time. DNA methylation provides a durable regulatory layer that can preserve lineage programs over long timescales and, in dividing cells, across generations. Histone modifications add another layer of control. Repressive marks such as H3K9me3 and H3K27me3 help stabilize cell state, while their loss has been linked to aging, chromatin instability, and cellular stress. Unlike DNA methylation, however, these marks are not directly copied during replication; they must be actively restored after cell division (Alabert et al., 2015). This distinction matters in the CNS, where different cell types maintain stability through different mechanisms. Neurons are largely postmitotic and may accumulate environmental cues over a lifetime without division. Microglia are long-lived and divide slowly, so their regulatory state may be partly retained and partly remodeled (Réu et al., 2017). Oligodendrocyte precursor cells, in contrast, continue to proliferate and differentiate throughout adulthood, meaning their cellular state must be repeatedly reestablished.

Under chronic implant–associated stress, we consider the possibility that cells may undergo functional realignment, in which core lineage-defining activities are gradually deprioritized to meet immediate environmental demands. For example, in chronic threat states, microglia may become less efficient at phagocytosis, lysosomal processing, and lipid handling. Astrocytes, in turn, may adopt standby phagocytic programs, upregulating receptors such as *Mertk* and *Axl*, when microglial clearance becomes inefficient (Konishi et al., 2020). Cell division adds another layer of complexity. In dividing cells, each round of division requires histone-based memory to be restored from a diluted signal. If the environment is continuously changing, each restoration event occurs under different instructive conditions. The cell is effectively rebuilding regulatory stability against a moving target, creating the possibility of biased restoration and cumulative drift. In nondividing or slowly dividing cells, regulatory memory is not diluted by replication, but chronic stress can still drive drift through chromatin remodeling, metabolic strain, and repeated inflammatory signaling. A key challenge in the CNS is that adaptive flexibility is unevenly distributed across cell types. Glial cells can reprogram gene expression, reenter the cell cycle, and scale compensatory functions in response to sustained threat; neurons have far less capacity to do so. As a result, glial adaptation may temporarily preserve local tissue integrity while gradually undermining circuit stability. These compensatory shifts could potentially adversely impact synaptic precision, metabolic support, and neuronal resilience. In this view, implant-associated failure reflects not only persistent inflammation, but also a sustained mismatch between flexible glial compensation and the limited ability of neurons to absorb equivalent functional drift. Neural implant stability may therefore depend not only on material tolerance, but also on how cells encode, preserve, and propagate the experience of the implant.

It is now possible to test this hypothesis using single-cell transcriptomics, epigenomics, spatially resolved transcriptomics and chromatin tracing assays. Single-nuclei assays providing simultaneous measurement of RNA levels and histone modifications enable not only definition of distinct transcriptional states, but also the activity states of upstream enhancers. Analysis of transcription factor motifs residing in enhancers perturbed by a device, as a function of time following implantation, enables inference of the driver transcription factors and upstream regulators. Single-cell analysis of DNA methylation in combination with chromatin conformation capture can reveal how these responses are encoded into durable molecular memory and the consequences with respect to enhancer–promoter interaction. Spatial transcriptomics and three-dimensional chromatin tracing assays performed in parallel would reveal how these processes unfold as a function of distance from the implant. In combination, these assays would enable a deeper understanding of the consequences of existing implant technology on glial cells and long-term function of the implant. Trajectory-based models built on

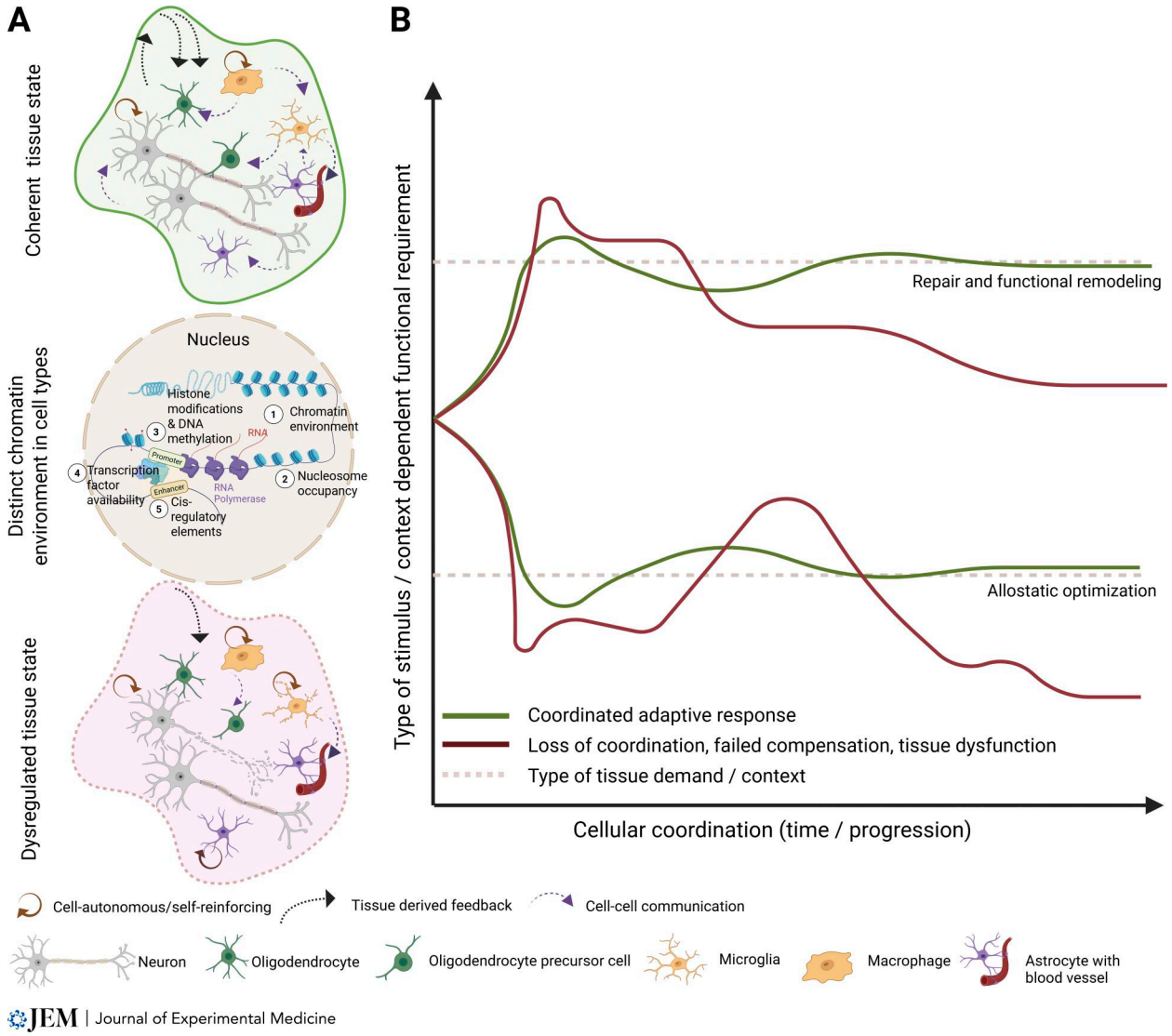

Figure 1. **Conceptual model of how chronic perturbation can rewire cellular memory from adaptive tissue coordination toward regulatory drift.** **(A)** In an adaptive peri-implant tissue state, cell-autonomous survival programs remain coordinated with multicellular communication and tissue-derived feedback. This coordination is regulated through epigenetic changes such as DNA methylation, histone modifications, transcription factor availability, chromatin accessibility, nucleosome positioning, and cis-regulatory elements. Together, these regulatory layers allow cells to respond to chronic perturbation while maintaining lineage fidelity and tissue coherence. In a dysregulated state, however, chronic stress can drive self-reinforcing cellular programs that become uncoupled from tissue-level feedback, leading to regulatory drift, altered communication, and loss of coordinated tissue function. **(B)** Response trajectories illustrate how cells continuously compensate for changing tissue demands over time. The dashed lines represent context-dependent functional requirements, not simply the amount of inflammation. Adaptive responses may involve repair, functional remodeling, or allostatic optimization depending on the tissue state. The green trajectory represents coordinated adaptation, where cellular responses remain aligned with tissue needs. The red trajectory represents failed compensation, where cellular programs become mismatched to context, leading to loss of coordination, chronic inflammatory signaling, and tissue dysfunction.

these data could then ask whether glial cells, neurons, and vascular-associated cells remain on coordinated adaptive paths or progressively diverge under chronic implant–associated pressure. This would give adaptive biocompatibility a measurable definition: the capacity of a neural implant to preserve coordinated regulatory trajectories across the peri-implant tissue. The success of a neural implant is therefore not simply whether the brain tolerates it, but whether the tissue around it remains itself.

Acknowledgments

This work was supported by the Alzheimer's Association and Cure Alzheimer's Fund. M.F.M. Xie and R.R. Tebak participated in this work through the Lumiere Foundation Research Mentorship Program. The figure was created using BioRender.com.

Author contributions: Ming Fa Michaelangelo Xie: visualization and writing—original draft, review, and editing. Rakshaan Rajeev Tebak: visualization and writing—original draft, review, and editing. Anagh Pathak: conceptualization and writing—original draft, review, and editing. Vini Tiwari: conceptualization, project administration, supervision, visualization, and writing—original draft, review, and editing. Christopher K. Glass: conceptualization,

funding acquisition, supervision, and writing—review and editing.

Disclosures: The authors declare no competing interests exist.

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