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Editorial

Cellular conversations at the crossroads of health and disease

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The Expanding Universe of Cell Signaling

The first issue of Cell Signaling in 2025 provides an interdisciplinary overview of cellular communication, covering topics ranging from neuronal and metabolic regulation to immune evolution and regenerative processes. The studies featured in this volume collectively demonstrate how signaling pathways govern the delicate, finely tuned balance between adaptation and dysfunction, and how their manipulation continues to inspire biotechnological and therapeutic innovation. This issue also exemplifies how contemporary signaling biology is evolving toward an integrative, multi-scale framework - uniting molecular precision with systemic understanding.

Introduction

In this issue [**Volume 3, Issue 1**], Cell Signaling brings together a variety of perspectives that converge on one of biology's most fundamental principles: communication. Signaling emerges as the currency of coordination and resilience across nervous, immune, and metabolic systems.

The many contributions deepen our understanding of how cells interpret, amplify and modulate molecular messages—processes that determine health and disease.

Neural and Cognitive Pathways: Memory, Neurogenesis, and Beyond

This issue opens with a comprehensive overview of PDE4 inhibition and cognitive function improvement by Graeme B. Bolger [1], which reaffirms the enzyme's role as a gatekeeper of cAMP-mediated learning and memory. Translating PDE4 biology into clinical trials is a significant step in the process of linking molecular neurochemistry with therapeutic development.

In a related vein, Jaehoon Song and Inhee Mook-Jung [2] revisit the dual actions of amyloid β on hippocampal neurogenesis, revealing how a single peptide can drive both pathology and plasticity.

Finally, Xiangyun Yao's team [3] has drawn attention to the neuroimmune interplay in traumatic and diabetic peripheral neuropathies, demonstrating that shifts in the immune phenotype dictate the success or failure of nerve regeneration.

There are also three brief commentaries: one by Taoli Liu, Shumin Cheng and Qingqing Zhu [4], which discusses Has-Circ-0105596/FTO signaling in Parkinson's disease and links circRNA regulation to dopaminergic neuron protection; one by Gal *et al.* [5], which reveals that the

chemokine-like molecule Orion may act as a signal that guides glial pruning during brain development and refines neural connections; and one by Liu *et al.* [6], which tells us that cognitive impairment in haemodialysis patients requires sufficient attention. They urge greater clinical attention and early assessment to protect neurological health, as cognitive decline is an often-overlooked complication in haemodialysis patients.

Together, these studies highlight the nervous system as a living interface where immune, metabolic and electrical processes converge. They also emphasize that neuronal signaling is inherently paradoxical, capable of fostering both cognition and degeneration depending on the cellular context.

Cell Fate Pathways: Apoptosis, Regeneration, and Oncogenic Resistance

Lucía Pronsato *et al.* [7] show that extracts from Nicotiana glauca trigger apoptosis in rhabdomyosarcoma cells, illustrating the therapeutic potential of plant-derived compounds and suggesting new phytochemical avenues in paediatric oncology.

Rukayat Aromokeye *et al.* [8] discussed the role of stress granules in heavy-metal-induced carcinogenesis, highlighting translational control under toxic stress.

Xingnan Zhang and Song Liu [9] extend this logic and recommend the synergistic inhibition of CDK1, a major regulator of cell cycle, and TSPO (Translocator protein), a protein located on the outer mitochondrial membrane, in malignant peripheral nerve sheath tumours (MPNSTs), suggesting that the combined targeting of mitochondrial and cell-cycle regulators could overcome therapeutic resistance.

Shirley K. Knauer and Roland H. Stauber [10] expand our understanding of chromosomal passenger proteins as guardians of genome stability under replication stress, potentially constituting new clinical targets in cancers.

At the epigenetic frontier, Ming Yang *et al.* [11] detail the importance of Methyltransferase-like (MTTL) proteins in epigenetic modifications (m6A) of RNA in head and neck cancers; Yu Wang *et al.* [12] explore PRDM16's methyltransferase activity and its methylation status in tumorigenesis.

Together, these articles demonstrate how cellular stress, chromatin remodeling, and RNA modification converge to define cancer resilience. In each case, cellular survival, proliferation, and differentiation are shown to hinge on intricate networks of molecular communication.

Metabolism and Aging: Signaling the Passage of Time

Dong I Lee and Dao-Fu Dai [13] examine the anti-aging effect of circulating α-Klotho in age-related cardiovascular diseases, through Sirt1-mediated pathways.

Libang Chen *et al.* [14] explore Sirt1-mediated deacetylation in Metabolic dysfunction-associated fatty liver disease (MAFLD), illuminating how epigenetic regulation fine-tunes hepatic metabolism and lipid homeostasis.

Dachuan Jin and Shunqin Jin [15] provide a meta-analysis on curcumin's effects in postmenopausal women, highlighting its antioxidant and anti-inflammatory mechanisms.

Moritz Schroll and Karima Djabali [16] discuss preclinical data from combined baricitinib and lonafarnib treatment in a mouse model of progeria, where dual inhibition of inflammatory and farnesylation pathways mitigates premature aging.

Byung-Joon Kim *et al.* [17] revisit insulin therapy in marginal β-cell deficiency, showing paradoxical effects on glycemic control.

These studies collectively emphasize that stress signaling is not inherently deleterious, but rather a versatile framework for adaptation and repair. Moreover, these studies view aging not as decline, but as a signaling imbalance — one that can be recalibrated.

Immunity, Inflammation and Inter-Species Perspectives

Chien Dinh Huynh [18] explores the interactions between gut microbiota and the immune system, emphasizing how diet, ethnicity and environment shape personalized immune responses.

Muchun He *et al.* [19] identified an NCAM1 homolog in oysters, with a potential immunosuppressive role in molluscs, revealing evolutionary differences with vertebrate NK-cells.

Simone de Araújo *et al.* [20] analyze Angiotensin-(1-7) as a pro-resolving modulator of macrophage function, advancing inflammation resolution research.

Deng *et al.* [21] uncover key gene and cell interactions driving early acne, offering insight for treatments that could prevent chronic inflammation and scarring.

Meanwhile, in a brief communication, Jiahui Tan *et al.* [22] recommended the use of a D2-like receptor agonist, ropinirole, a drug commonly used in Parkinson's disease, in periodontitis, as this D2 agonist shows anti-inflammatory potentials by inhibiting NAT10 in this pathological context.

These studies collectively frame immunity as a *restorative conversation* rather than a reactive war — one that echoes across species and ecosystems.

Frontiers in Biotechnology, Synthetic Systems, and Cellular Innovation

Anastasios Melis and Bharat Kumar Majhi [23] demonstrate that cyanobacteria can be used to produce human proteins as recombinant human interferon α-2, proposing a sustainable, light-driven bioproduction platform.

QiKai Han *et al.* [24] introduce $Ag_{135}Cu_{60}$ nanoclusters with a buckminsterfullerene topology, whose optical and structural properties bridge atomic-scale coordination with macroscopic function.

Qiang Yang *et al.* [25] highlight the role of the RSPO3–Wnt/β-Catenin axis in hepatic stellate cells as a key regulator of liver zonation and regeneration, redefining stellate cells as central coordinators of metabolic and reparative gatekeepers.

Juliane Da Graça and Etienne Morel [26] uncover how ER–endosome contacts initiate autophagy, redefining spatial signaling as a molecular determinant of survival. These findings highlight a central role for ER-endosome communication in the cellular response to nutritional stress and in the regulation of autophagy.

These works showcase how biological communication can now be *engineered, visualized, and reprogrammed* — from nano-scale particles to whole-organ architectures. They illustrate the expanding scope of "synthetic signal design", where biology and engineering converge.

Crosstalk and Convergence: The Stroke of Integration

Yifeng Zhang *et al.* [27] integrate endoplasmic reticulum stress and ferroptosis with the vitamin D signaling into a unified model of stroke pathophysiology, reinforcing the notion that survival under stress requires systemic coordination of intracellular defense modules.

Yanyun Shi and Qi Yao [28] discuss glutathione S-transferases in ferroptosis regulation, connecting NRF2/GSH/GST/RLIP76 and MRP1 signaling with anti-ferroptotic defense.

Both contributions exemplify a systems-signaling paradigm, where restoring the network balance replaces the older "single-target" model of intervention.

From PDE4 and cognition to RSPO3 and liver regeneration, and from the anti-aging role of α-Klotho to the structural cues of autophagy, Cell Signaling Volume 3 (1) sheds light on the unity of life's diverse messages.

Spanning 175 pages, signaling emerges as the connective tissue of biology, weaving molecular intent into physiological coherence. The cell, organ and organism are not separate entities, but rather chapters in a single conversation.

By 2025, signaling research will no longer focus on how signals travel, but on how meaning emerges from their interplay. The next frontier does not lie in discovering more messengers, but in learning how to listen to the dialogue they compose.

Signaling is not only the voice of the cell - it is the dialogue of the organism.

Conclusion

Overall, a shared message resonates across all contributions: '***Signaling is the universal language of life***'. From molecular oscillations to organ-level coordination, these studies have highlighted how communication within and between cells determines biological fate.

As Cell Signaling enters its third volume, this issue exemplifies the field's vibrancy and interdisciplinary scope, reaffirming that the study of cellular communication remains at the heart of biomedical science.

The diverse contributions collectively argue that signaling is not just a subject of biology; it is the language of biology. Every physiological process, from memory formation to hepatic regeneration and immune resolution to tumor resistance, is written in this molecular and messenger syntax. As researchers progress from deciphering individual components to constructing complete sentences in the language of signaling, the frontier of biomedical science expands to encompass a holistic, integrative and deeply interdisciplinary approach.

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