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EDITORIAL

Cellular signaling in immunity and disease

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Cellular signal transduction is the process by which cells respond to external stimuli, interpret the signals, and communicate with each other. The signal transduction pathways lie at the center of all biological functions. Recent findings have provided new insights into the mechanisms of signaling pathways, uncovering regulatory networks underlying various physiological processes. In this editorial, we highlight and comment on exciting research that will help deepen our understanding of signal transduction and its role in multiple biological processes, including diseases. Thus providing valuable insights for future research in this field.

Signaling in immunity: The ability of an organism to counter pathogenic assaults relies fundamentally on immune signaling networks. The pathogens are recognized at the surface of cells by receptors that recognize signature patterns in pathogens or pathogen-derived molecules [1,2]. This interaction results in the signaling responses as a first line of defense. The pathogens that enter the cells are intracellularly detected by the cytoplasmic receptors that recruit the downstream signaling components to eventually neutralize the pathogens or pathogenic agents [3]. Both plants and animals have evolved strategies to provide immunity against a broad range of pathogens. The recognition of pathogen-derived molecules at the surface or intracellularly results in local or global immune responses. Multiple lines of evidence show that plants, like animals, develop immune-based memories [4-6].

Animals have memory B cells for heightened immune responses to secondary infections. In plants, the memory of infection is believed to be transmitted as changes in the epigenetic landscape [7-9]. This ensures transcriptome reprogramming of defense-related genes. Unlike animals, the global immunity in plants requires the transport of mobile chemical signals from the infected tissue [10]. These signals are decoded in distal tissues by receptors or other sensors to elicit an immune response. Several proteins, including chromatin remodelers and Hybrid-proline-rich protein (HyPRP) family members, play important roles in mediating global immunity in plants [11-12]. The global signaling in plant immunity is mediated by mobile signals that transport via plant vasculature to systemic tissues [10]. Thus, the intricate interplay of signaling components helps both plants and animals ward off pathogens.
Signaling in development and disease: Cell signaling also plays an important role in development and disease. The development of complex multicellular organisms relies on mechanical and biochemical signaling events. Several molecular processes like actin-myosin contraction, microtubule dynamics, cytoskeletal rearrangements, mechanotransduction of ion channels, and extracellular matrix remodeling generate or transduce mechanical forces [13-17]. These forces can be transmitted through cell-cell interactions to affect tissue development or relayed to the brain via neurons. This mechanosensory system results in the induction of biochemical signals to affect the tissue fate or pathological state. The "mechanochemical feedback loops" essential for several key cellular processes in development and disease have been described [18-20]. Most of these mechanical responses work by protein conformational changes induced by mechanical forces. This modifies the biochemical properties of proteins and, consequently, their functions.

Mechanical properties of epithelial tissues are critical for tissue remodeling during wound healing [21,22]. The development of the heart in the developing embryos also relies on mechanical stimuli. In recent years, the role of mechanosensing in cardiac tissue development and disease has been assessed in some detail. In fact, the coordinated heartbeat may have originated primarily by mechanosensing rather than by electrochemical signaling [23,24]. Cardiomyocytes ought to be mechanically responsive to a variety of environmental stresses, including hemodynamic forces. In a healthy heart, cardiomyocytes are exposed to mechanical forces of the contractile apparatus of the heart [25]. In heart disease, however, the mechanical properties of cardiomyocytes are altered, leading to changes in cardiac load and output. Understanding the mechanosensory signaling of heart tissues will, therefore, be important to cure heart diseases.

Research in cancer immune signaling has led to discoveries that will help in understanding the complexity of cancer. GPCRs represent one of the largest family of receptors that have been implicated in several diseases. Although GPCRs have been investigated for drug designing, these receptors have remained largely underexplored in cancer immunology. Phosphorylation events initiated by receptor signaling, including GPCRs, regulate cellular integrity during various inflammatory conditions [26,27]. Recently, the use of large singe-cell RNA-sequencing datasets from various cancer types identified enrichment of GPCRs on $CD8^+$T cells. This research showed that GPCR signaling promotes $CD8^+$T cell dysfunction and immunotherapy failure [28]. Studying the GPCR repertoire of tumor-infiltrating $CD8^+$ T cells, combined with the synthetic biology approaches, will reveal immune-suppressive functions of GPCR signaling. This will, in turn, help improve cancer immunotherapies.

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Another signaling pathway widely implicated in cancers is Wnt/β-catenin signaling. The Wnt/β-catenin signaling pathway is often altered through a variety of genetic and epigenetic changes. Abnormal Wnt/β-catenin signaling can increase the prevalence and advancement of several cancers like colorectal, liver, lung, breast, and pancreatic cancers. Dysregulation of Wnt ligand expression, such as Wnt1, Wnt3a, and Wnt7a, and mutation of β-catenin can drive cell proliferation and inhibit apoptosis [29-31]. Mutations in receptors of the Wnt pathway, such as the Frizzled receptors, can also lead to constitutive activation of Wnt signaling and, consequently, cancers [32]. Wnt/β-catenin signaling can induce the expression of c-Myc, a potent oncogene involved in cell proliferation and tumor progression [33]. The binding of Wnts to frizzled (FZD) GPCRs drives the oligomerization of the effector protein Dishevelled (DVL) of the receptor complex. Multiple effector proteins form part of this complex that helps transduce downstream signaling. To understand how Wnt binding to FZD activates intracellular signaling and influences downstream response, Bowin C. F. et al. [34] investigated the dynamic interaction between FZD^5 and DVL2 elicited by Wnt family ligands. Using bioluminescence resonance energy transfer (BRET), Bowin C. F. et al. show that Wnt binding induces conformational changes in FZD^5-DVL2. These ligand-induced conformational changes at the receptor-transducer interface suggest the cooperative ligand-receptor-effector interplay.

Moreover, many non-canonical signaling routes have been discovered that expand the list of known signaling pathways [35,36]. These discoveries involve the identification of novel receptors, effectors, or other signaling components. Non-canonical Wnt signaling is associated with a wide range of pathologies, including vascular diseases. Advanced technologies have enabled the identification of the signal components at work, providing a sneak peek into the dynamics of signal transduction within cells. The use of advanced live-cell imaging techniques to visualize signaling events in real time has provided unprecedented insights into cell functions [37-39]. A recent study developed highly sensitive and tunable fluorescence resonance energy transfer (FRET)-based biosensors for $Ca2^+$, ATP, and NAD^+ with unprecedented dynamic ranges [40]. The spectral tunability of these biosensors enables the choice of spectral properties for multiplexing in fluorescence microscopy. Such findings emphasize the need to consider the complex interactions between signaling molecules for a comprehensive understanding of signal transduction processes. The integration of cutting-edge imaging techniques, such as super-resolution microscopy, single-cell imaging, and optogenetics, will help visualize dynamic signaling events with precision.

Additionally, computational modeling and simulation have significantly improved our understanding of complex signaling networks. Combining experimental data with computational modeling has tremendous potential in elucidating the dynamics of signaling pathways. The study of signaling pathways and their regulatory networks has opened new avenues for therapeutic interventions. This includes targeting specific signaling nodes or modulating the crosstalk between signaling pathways. As we continue to delve deeper into the field of signal transduction, we anticipate a series of breakthroughs in signal transduction research aided by highly advanced experimental and computational methodologies.

Disclosure statement

No potential conflict of interest was reported by the author.

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