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EVOLUTION OF CELL SIGNALING: FROM UNICELLULAR ORGANISMS TO HUMANS AND ITS IMPLICATIONS FOR MODERN MEDICINE

Rashidul Haque*

*Former Pro-Vice Chancellor, Varendra University, Rajshahi, Bangladesh; Former Professor, Emory University School of Medicine, Atlanta, USA, and Associate Professor, Department of Zoology, University of Rajshahi, Bangladesh. Prof R Haque, Atlanta, USA.

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***Corresponding Author**

Prof. Rashidul Haque
Former Pro-Vice Chancellor, Varendra University, Rajshahi, Bangladesh; Former Professor, Emory University School of Medicine, Atlanta, USA, and Associate Professor, Department of Zoology, University of Rajshahi, Bangladesh. Prof R Haque, Atlanta, USA.

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ABSTRACT

One of the fundamental characteristics of life is the ability to perceive environmental information and generate appropriate biological responses. The exchange and processing of such information occur through a process known as cell signaling. From unicellular bacteria to complex multicellular organisms such as humans, survival, growth, development, immunity, reproduction, and behavior all depend on effective signaling among cells and between cells and their environment. Throughout evolutionary history, cell-signaling systems have become increasingly sophisticated and specialized. A continuous evolutionary trajectory can be traced from the simple chemical sensitivity of primitive organisms to the highly integrated communication networks of the nervous, endocrine, and immune systems in modern animals. Recent research has further revealed that modern therapeutic interventions can impose evolutionary pressures on signaling pathways, contributing to the emergence of drug-resistant cancer cells, bacteria, and viruses. This article examines the origins and evolutionary development of cell-signaling systems and explores their relevance to contemporary medicine.

KEYWORDS: Cell signaling; evolution; receptors; signal transduction; multicellularity; drug resistance; cancer evolution.

INTRODUCTION

One of the most fundamental characteristics of life is the ability to respond to information. Organisms must detect and respond appropriately to the presence of food, the arrival of predators, environmental fluctuations, pathogen invasion, and opportunities for reproduction. The biological system that underlies the reception, processing, and execution of such responses is known as cell signaling. Cell signaling can be defined as the process by which cells detect chemical, electrical, or mechanical signals originating from their environment or from other cells and translate these signals into specific biological responses (Alberts et al., 2022). Without this process, higher levels of biological organization would be impossible. Cell division, embryonic development, tissue regeneration, immune defense, neural activity, learning, memory, and behavior all depend on cell signaling mechanisms.

From an evolutionary perspective, the history of cell signaling is inseparably linked to the history of life on Earth. A continuous evolutionary trajectory can be traced from the simple chemical sensitivity of early unicellular organisms to the highly sophisticated communication networks of the human nervous and endocrine systems. The emergence of multicellularity was particularly significant, as it was accompanied by a dramatic increase in signaling complexity. Coordinated function among diverse cell types required the evolution of increasingly advanced communication systems (King, 2004; Lim et al., 2014).

Over the past two decades, advances in genomics, molecular biology, and evolutionary biology have greatly expanded our understanding of the origin and evolution of cell-signaling systems. It is now evident that many major signaling pathways—including G protein-coupled receptor (GPCR), mitogen-activated protein kinase (MAPK), Wnt, Notch, and Hedgehog pathways—

originated early in evolutionary history and have subsequently been conserved, modified, and diversified across numerous lineages (Liebeskind et al., 2016; Pires-daSilva & Sommer, 2003).

At the same time, modern biomedical research has raised an important new question: can drugs influence the evolution of cell-signaling systems? The emergence of antibiotic resistance, the development of resistance to targeted cancer therapies, and the adaptive evolution of viruses all suggest that human-generated selective pressures are actively shaping the evolution of cellular signaling networks. Understanding these evolutionary dynamics is therefore essential not only for reconstructing the history of life but also for addressing some of the most pressing challenges in contemporary medicine (Palmer & Kishony, 2013; Holohan et al., 2013).

What is Cell Signaling?

Cell signaling is a fundamental biological process through which cells exchange chemical information with one another or with their external environment and generate specific physiological responses. In simple terms, it functions as the communication system of cells. This communication is essential for coordinating a wide range of biological activities, from metabolism and growth to development and immune defense.

Cell signaling generally occurs in four major steps:

1. **Signal generation** — A signaling molecule such as a hormone, neurotransmitter, cytokine, or growth factor is produced and released.
2. **Signal reception** — Specific receptor proteins located on the cell surface or within the cell detect and bind the signaling molecule.
3. **Signal transduction and amplification** — The activated receptor triggers a cascade of intracellular biochemical reactions, often involving multiple signaling proteins, which amplify the original signal.
4. **Cellular response** — The cell produces a specific response, such as changes in gene expression, protein synthesis, metabolic activity, cell division, or programmed cell death.

A classical example is **insulin signaling**. After food intake, the pancreas secretes insulin into the bloodstream. Insulin binds to its receptor on target cells and activates the PI3K–AKT signaling pathway. This leads to the translocation of the GLUT4 glucose transporter to the cell membrane, allowing glucose uptake into the cell and thereby reducing blood glucose levels.

Cell signaling is also central to the evolution of multicellular life. The emergence of complex multicellular organisms depended on the evolution of coordinated intercellular communication systems. Furthermore, modifications in signaling pathways play a critical role in evolutionary interactions between hosts and pathogens, shaping immune defenses and pathogenic strategies.

Evolutionary Origins of Cell Signaling

Most evolutionary biologists propose that cell signaling originated in ancient unicellular organisms approximately 3.5–4 billion years ago. Early life forms faced fundamental survival challenges, including locating nutrients, avoiding toxic substances, and adapting to fluctuating environmental conditions. Organisms capable of detecting and responding to environmental cues had a clear selective advantage, and natural selection gradually refined these chemical sensing systems.

Contrary to earlier assumptions that bacteria are structurally simple, modern research has revealed that they possess highly sophisticated signaling networks. One of the most primitive and widespread forms of cellular communication is **chemotaxis**, the directed movement of a cell or microorganism in response to chemical gradients. Chemotaxis is generally classified into two types:

- **Positive chemotaxis** — movement toward beneficial chemicals, such as nutrients or food sources
- **Negative chemotaxis** — movement away from harmful or toxic substances

This mechanism is not limited to bacteria. For example, human white blood cells utilize chemotaxis to migrate toward infection sites, where they help eliminate pathogens. Similarly, sperm cells in many animal species respond to chemical signals released by the egg or surrounding tissues, guiding them toward fertilization.

One of the most important and evolutionarily ancient bacterial signaling mechanisms is the **two-component system**, which plays a central role in environmental adaptation. This system consists of two core proteins:

1. Sensor histidine kinase — typically located in the bacterial cell membrane, it detects external environmental signals such as temperature changes, pH variation, or nutrient availability. Upon activation, it undergoes autophosphorylation.
2. Response regulator — receives the phosphate group from the sensor kinase and subsequently regulates the expression of specific genes, enabling adaptive physiological responses.

Through this system, bacteria can rapidly adjust to environmental stressors such as toxins, heat, or nutrient scarcity, thereby enhancing survival and reproductive success. Evolutionary processes such as gene duplication and horizontal gene transfer have further diversified these signaling networks.

Many researchers suggest that certain components of eukaryotic signaling pathways may have evolved from ancestral bacterial systems such as the two-component system (Capra & Laub, 2012).

The "Social Life" of Bacteria: Quorum Sensing Signals

An important milestone in the evolution of cellular communication is *quorum sensing*. Bacteria were once thought to function as entirely independent units; however, it is now well established that they communicate with one another through a sophisticated chemical language. Quorum sensing is a cell-to-cell communication system in bacteria that enables them to detect changes in population density and regulate gene expression accordingly. In simple terms, bacteria release small signaling molecules, known as autoinducers. When bacterial numbers are low, the concentration of these signals remains minimal and does not trigger a coordinated response. As the population increases, the concentration of signaling molecules also rises. Once a critical threshold is reached, this accumulated signal triggers a coordinated switch in gene expression, effectively turning specific genes on or off across the population.

Through quorum sensing, bacteria are able to coordinate complex group behaviors, including biofilm formation, activation of virulence genes, enhancement of antibiotic resistance, and adaptation to changing environmental conditions. This system represents a fundamental evolutionary step toward collective behavior, illustrating how even unicellular organisms exhibit sophisticated forms of social communication—an early parallel to the more complex communication systems observed in multicellular life.

The Expansion of Cell Signaling in Eukaryotes

The emergence of eukaryotic cells approximately two billion years ago marked a major turning point in the evolution of cellular signaling. As eukaryotic genomes expanded through gene duplication and diversification, numerous new receptors and signaling molecules evolved, giving rise to increasingly sophisticated signal transduction networks. Unlike the relatively simple signaling systems of prokaryotes, eukaryotes developed complex pathways involving G protein-coupled receptors (GPCRs), protein kinases, calcium signaling, and cyclic AMP (cAMP) signaling.

The evolution of multicellularity, tissue specialization, and physiological homeostasis created strong selective pressures for enhanced cellular communication. Large genomes, compartmentalized organelles such as the nucleus, mitochondria, and endoplasmic reticulum, and the need for precise environmental sensing all contributed to the development of intricate signaling networks. Consequently, cell signaling evolved from relatively simple linear pathways into highly integrated, multilayered regulatory systems.

Evolution of GPCRs: One of the Most Successful Molecular Innovations in Animals G protein-coupled receptors (GPCRs) constitute a highly diverse family of membrane receptors characterized by seven transmembrane helices, often referred to as seven-transmembrane receptors. Upon binding extracellular ligands—including hormones, neurotransmitters, odorants, and light-sensitive molecules—GPCRs activate associated G proteins, initiating intracellular signaling cascades. The diversification of GPCRs played a central role in the evolution of multicellular animals. They facilitated cell-to-cell communication, coordination among tissues and organs, nervous system development, hormonal regulation, behavior, and sensory functions such as vision and olfaction. For this reason, GPCRs are frequently regarded as one of evolution's greatest molecular success stories. Gene duplication was the primary driver of GPCR expansion. The human genome contains more than 800 GPCR genes, which collectively regulate smell, taste, vision, neural activity, and immune responses. Molecular phylogenetic analyses suggest that ancestral GPCR-like proteins were already present in unicellular eukaryotes and subsequently underwent extensive diversification during animal evolution (Krishnan et al., 2012). Because they translate a remarkable variety of external signals into cellular responses, GPCRs are often described as universal signal transducers.

Evolution of Receptor Tyrosine Kinases (RTKs)

Receptor tyrosine kinases (RTKs) are membrane-spanning signaling proteins that play essential roles in cell growth, development, and intercellular communication. They likely evolved from ancestral tyrosine kinase genes present in early eukaryotes and expanded through gene duplication and functional specialization. During animal evolution, RTKs diversified into multiple ligand-specific receptor families, including EGFR, PDGFR, and VEGFR. This diversification enabled increasingly precise communication between cells and contributed significantly to the evolution of complex tissues, organs, and multicellular organisms.

Evolution of the MAPK Signaling Pathway

The mitogen-activated protein kinase (MAPK) pathway is among the most ancient and evolutionarily conserved signaling systems in eukaryotes. It likely originated in unicellular ancestors, where it mediated responses to environmental stimuli. As multicellular organisms evolved, the pathway acquired additional functions in regulating cell proliferation, differentiation, development, stress responses, and immunity. Core components of the MAPK cascade are remarkably conserved across fungi, plants, invertebrates, and vertebrates, underscoring its fundamental biological importance. Dysregulation of MAPK signaling is implicated in cancer and numerous other diseases.

Evolution of the PI3K–AKT–mTOR Pathway

The PI3K–AKT–mTOR pathway is another highly conserved signaling network that regulates cell growth, metabolism, survival, and protein synthesis. Its origins can be traced to early unicellular eukaryotes, where it likely functioned in nutrient and energy sensing. During the evolution of multicellular animals, the pathway became integrated with hormonal, growth factor, and environmental signaling systems, enabling fine control of cell proliferation, tissue growth, and organismal development. The remarkable conservation of this pathway across eukaryotes highlights its critical role in survival and adaptation. However, aberrant activation of PI3K–AKT–mTOR signaling is also associated with cancer and a variety of other pathological conditions.

The Emergence of Multicellularity and the Revolution of Cell-to-Cell Communication

Approximately 600–800 million years ago, multicellularity evolved in the ancestors of animals, marking one of the most transformative events in the history of life. In unicellular organisms, a single cell performs all functions necessary for survival and reproduction. In multicellular organisms, however, different cells become specialized for distinct tasks and must operate in a highly coordinated manner. The greatest challenge of this new mode of life was the establishment of effective communication among cells. Without the ability to exchange information, the development of tissues, organs, and complex body structures would have been impossible.

Through evolution, several major mechanisms of cell-to-cell communication emerged:

1. Autocrine signaling – a cell produces signals that act upon itself.
2. Paracrine signaling – signals are exchanged between neighboring cells.
3. Endocrine signaling – signals are transported through the bloodstream to distant target cells.
4. Juxtacrine signaling – communication occurs through direct physical contact between adjacent cells.
5. Synaptic signaling – highly rapid signal transmission mediated by nerve cells.

The evolution of multicellularity was accompanied by a dramatic expansion in the genetic diversity of signaling networks. In particular, gene families encoding protein kinases, transcription factors, and cell-surface receptors underwent extensive diversification and expansion, enabling increasingly sophisticated forms of cellular communication and regulation (King et al., 2008). Many evolutionary biologists describe multicellular organisms as “cooperative societies of cells.” Within these societies, cell signaling serves not merely as a means of information transfer but also as a mechanism for maintaining cellular cooperation, coordination, and social order. From this perspective, cancer can be viewed as a breakdown of this cellular social contract, in which individual cells cease to follow the regulatory signals that normally govern growth, division, and cooperation with the organism as a whole.

Evolution of Signaling Pathways in Animal Embryonic Development

The evolution of signaling pathways in animal embryonic development represents the process through which complex multicellular organisms arose from unicellular ancestors over hundreds of millions of years. Among the most important developmental signaling systems are the Wnt, Notch, and Hedgehog pathways**.** One of the most remarkable discoveries in evolutionary developmental biology is that these core signaling mechanisms have remained highly conserved across diverse animal groups, including insects, mice, and humans. Although the signaling proteins themselves have changed little, their downstream gene networks have been repeatedly modified through evolutionary time. This process, known as network rewiring**,** allows the same signaling pathways to generate different structures in different organisms, such as human hands and bird wings. The addition of new genes and the refinement of regulatory networks have further expanded developmental complexity.

Wnt Signaling Pathway

The Wnt signaling pathway is a fundamental cellular communication system that regulates embryonic axis formation, cell proliferation, differentiation, tissue regeneration, and stem-cell maintenance. It functions throughout the life cycle, from early embryogenesis to adult tissue homeostasis. Core components of the pathway, including β-catenin and GSK3**,** originated before the emergence of multicellular animals. In unicellular organisms, these proteins primarily regulated intracellular metabolic processes. With the evolution of multicellularity in early animals such as sponges and hydra, they were co-opted for intercellular communication. This led to the emergence of the canonical Wnt/β-catenin pathway, which became central to body-axis specification and early developmental patterning. Subsequently, non-canonical Wnt pathways, including the Planar Cell Polarity (PCP) and Wnt/Ca^{2+} pathways**,** evolved. Despite extensive evolutionary diversification, the fundamental architecture and protein components of Wnt signaling have remained remarkably conserved (Santhanam, 2025).

Notch Signaling Pathway

The Notch signaling pathway is an ancient and highly conserved mechanism of direct cell-to-cell communication that plays crucial roles in embryonic development, cell-fate determination, and tissue formation. During development, genetically identical cells can differentiate into neurons, skin cells, blood cells, and other specialized cell types; Notch signaling is a key regulator of these decisions. The core components of the pathway were already present in the earliest multicellular animals (Metazoa). Evolutionary studies suggest that Notch receptors and ligands arose through exon shuffling and gene duplication in ancestral eukaryotes. As animals evolved from simple invertebrates to vertebrates, the Notch gene family expanded significantly. For example, while *Drosophila* possesses a single Notch receptor, mammals have four homologs **(**Notch1–Notch4**)** (Lv et al., 2024). Over evolutionary time, the pathway acquired additional functions beyond embryogenesis, including the regulation of adult stem-cell maintenance and neural plasticity (Zhou et al., 2022).

Hedgehog Signaling Pathway and the Evolution of Body Patterning

The Hedgehog (Hh) signaling pathway is another highly conserved developmental system that has played a central role in animal evolution. It is thought to have originated from ancient lipid- and sterol-regulatory mechanisms present in early prokaryotic ancestors. Two key pathway components, Patched (Ptch) and Smoothened (Smo)**,** are believed to have evolved from proteins involved in lipid transport and homeostasis. With the emergence of multicellular animals, this system was co-opted for developmental signaling. The Hedgehog gene was first identified in the fruit fly (*Drosophila*), where it regulates embryonic segmentation and wing development. During vertebrate evolution, the pathway expanded into three homologous ligands: Sonic hedgehog (Shh)**,** Indian hedgehog (Ihh), and Desert hedgehog (Dhh)**.** These molecules now regulate a wide range of developmental processes, from brain formation to limb and digit patterning in humans (Briscoe & Thérond, 2013). Evolutionary evidence suggests that the Hedgehog pathway emerged early in the evolution of bilaterian animals and subsequently became a central regulator of body-plan development (Ingham & McMahon, 2001).

Evolution of Immune Signaling

The evolution of immune signaling refers to the gradual development of increasingly sophisticated mechanisms by which immune cells detect pathogens and coordinate defensive responses over hundreds of millions of years. In the earliest unicellular organisms, simple chemical signaling systems evolved to sense and respond to environmental cues. With the emergence of invertebrates, such as insects, innate immunity became established. Cells of these organisms possess pattern-recognition receptors (PRRs) that detect conserved molecular signatures of pathogens and initiate defensive responses through intracellular signaling cascades (Shizuo A et al, 2006; Luke et al, 2013). One of the best-known examples of such receptors is the Toll-like receptor (TLR) family. Remarkably, the fundamental architecture of Toll-Toll-like receptor signaling is highly conserved between fruit flies and humans, providing compelling evidence of its deep evolutionary origins. In vertebrates, a diverse array of signaling molecules evolved, including cytokines such as chemokines, interleukins, and interferons. These small proteins and peptides function as intercellular messengers, enabling rapid communication among immune cells in response to infection, tissue damage, or other threats. In essence, they constitute a complex "chemical language" that coordinates and regulates immune activity throughout the body.

The evolution of adaptive immunity in jawed vertebrates marked a major milestone in immune signaling (Max et al, 2006). The activation and regulation of T lymphocytes and B lymphocytes required the emergence of highly intricate signaling networks, allowing the immune system to mount targeted and pathogen-specific responses (Martin et al, 2010). These signaling pathways enable immune cells to recognize particular antigens, proliferate, differentiate, and generate immunological memory. In modern mammals, numerous interconnected signaling pathways—including the NF-κB**,** JAK–STAT, and MAPK pathways—form a highly integrated and tightly regulated immune communication network. These pathways not only coordinate effective responses against invading pathogens but also help prevent excessive inflammation and immune-mediated tissue damage.

The continuous coevolutionary "arms race" between hosts and pathogens has been a major driving force behind the refinement of immune signaling mechanisms (Van Valen, 1973). As pathogens evolved strategies to evade or manipulate host defenses, immune systems responded by developing increasingly complex and efficient signaling networks. Consequently, the immune systems of contemporary animals are capable of mounting rapid, coordinated, and highly effective responses to a wide range of infectious challenges.

The Origin of the Nervous System: The Need for Rapid Signaling

During the early evolution of animals, unicellular organisms and simple multicellular life forms communicated primarily through cell-to-cell chemical signaling. However, as body size increased, the number of cells expanded, and active locomotion evolved, this relatively slow mode of communication became increasingly inadequate. Organisms faced growing selective pressures to capture prey, evade predators, respond rapidly to environmental changes, and coordinate the activities of different body regions. These challenges created a strong evolutionary demand for a faster and more reliable signaling system (Brunet & Arendt, 2016; Jékely et al., 2015). As a consequence, specialized signaling cells—neurons—evolved. Over time, these neurons became interconnected, forming nerve nets, ganglia, and eventually complex central nervous systems capable of transmitting information with remarkable speed through electrical and chemical signals (Arendt et al., 2016). Under these evolutionary pressures, certain cells acquired the ability to regulate membrane potentials through specialized ion channels, including sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) channels. This innovation enabled the generation and propagation of rapid electrical impulses, known as action potentials, along the cell membrane (Hille, 2001).

Although such electrical excitability initially appeared in isolated cells, it later became concentrated in specialized neurons capable of transmitting signals over long distances with high speed and precision. The evolution of electrical signaling laid the foundation for rapid behavioral responses, motor control, sensory information processing, and the development of increasingly sophisticated nervous systems. It represents one of the most important evolutionary innovations in the animal kingdom, facilitating the emergence of greater physiological and behavioral complexity (Arendt et al., 2016).

The earliest nervous systems are thought to have appeared approximately 600 million years ago among cnidarians, which possess diffuse nerve nets rather than centralized brains. Molecular studies further suggest that many of the ancestral forms of voltage-gated ion channels predated the evolution of animals and were already present in unicellular eukaryotes (Liebeskind et al., 2011). Thus, the nervous system was not an entirely novel invention but rather an evolutionary refinement and specialization of ancient cellular signaling mechanisms.

The Origin and Evolution of Synapses

Following the emergence of neurons, the need for rapid and regulated communication between them drove the evolution of synapses. The earliest neural systems may have relied primarily on direct electrical connections, analogous to modern gap junctions, for signal transmission. Subsequently, chemical synapses evolved, in which specialized molecules known as neurotransmitters carry signals from one neuron to another (Südhof, 2018). Unlike purely electrical transmission, chemical synapses allow signals to be amplified, inhibited, modulated, and integrated in diverse ways. These properties enabled the emergence of learning, memory, decision-making, and increasingly complex behaviors, thereby contributing significantly to the evolutionary success of animals (Kandel et al., 2021; Südhof, 2018). The human brain contains an estimated 10^{14}–10^{15} synaptic connections**,** forming one of the most intricate biological networks known (Kandel et al., 2021). Human memory, learning, language, and consciousness ultimately depend on the dynamic interactions occurring within these signaling networks, highlighting the profound evolutionary significance of synaptic communication.

Calcium Signaling: The Universal Language of Evolution

Calcium (Ca^{2+}) signaling is one of the most ancient and universally conserved mechanisms of cellular communication in the living world. It is found across virtually all forms of life, including bacteria, plants, fungi, and animals (Berridge et al, 2003; Clapham, 2007). Transient changes in intracellular calcium ion concentrations function as a form of “biological language,” enabling cells to detect environmental stimuli and generate appropriate physiological responses. Through evolution, this signaling system has become increasingly sophisticated, giving rise to complex regulatory networks that coordinate cellular activities across diverse organisms (Case et al., 2007). In modern animals, calcium signaling forms the foundation of numerous essential biological processes, including neuronal communication, muscle contraction, immune responses, embryonic development, gene regulation, learning, and memory formation (Berridge et al., 2003; Clapham, 2007). As a result, calcium signaling represents one of the most successful evolutionary innovations, persisting for billions of years and serving as a universal language of cellular communication across the tree of life (Carafoli & Krebs, 2016).

Evolution of Endocrine Signaling

The emergence of multicellular animals greatly increased the need for communication among cells. As animal bodies became larger and more complex, local signaling alone was insufficient to coordinate activities between distant tissues and organs. This challenge drove the evolution of endocrine signaling, a system of long-range communication in which specialized endocrine cells and glands secrete hormones into the bloodstream or body fluids to reach distant target cells (Alberts et al., 2022; Lodish et al., 2021). Hormones such as insulin, thyroid hormones, cortisol, testosterone and estrogen regulate growth, metabolism, reproduction, development, stress responses, and the maintenance of physiological homeostasis. Over evolutionary time, endocrine systems became increasingly sophisticated, enabling more precise coordination of complex bodily functions (Norris & Carr, 2021). Consequently, endocrine signaling is considered a key evolutionary innovation underlying the complexity, integration, and environmental adaptability of multicellular animals (West-Eberhard, 2003).

The endocrine and nervous systems are closely linked through the neuroendocrine system, with the hypothalamus and pituitary gland serving as major centers of integration (Bentley, 2015). This coordination allows animals to regulate seasonal reproduction, hunger and thirst, sleep–wake cycles, and responses to environmental change. The evolution of neuroendocrine regulation substantially enhanced the adaptability and physiological flexibility of complex organisms, contributing to their evolutionary success (Gilbert & Barresi, 2020; Norris & Carr, 2021).

Cancer: The Breakdown of Social Control in Cellular Signaling

Cell signaling pathways play a crucial role in the development and progression of cancer. From an evolutionary perspective, cancer has often been described as the “price of multicellularity” because multicellular organisms depend on the cooperation of individual cells for survival (Aktipis et al., 2015; Greaves & Maley, 2012). Under normal conditions, cells follow strict regulatory rules governing growth, division, differentiation, and programmed cell death (apoptosis). Cancer cells, however, break these rules: they proliferate excessively, evade death signals, exploit resources, and spread to other tissues. In this sense, cancer can be viewed as the evolution of “selfish cells” within the body.

The processes of cell growth, proliferation, differentiation, and apoptosis are regulated by several signaling pathways, including MAPK, EGFR, PI3K/AKT, Wnt, Notch, and p53 (Hanahan, 2022; Weinberg, 2014). Genetic mutations and epigenetic alterations can abnormally activate or disable these pathways, disrupting normal cellular control mechanisms (Vogelstein et al., 2013). As a result, cells may divide uncontrollably, resist apoptosis, stimulate angiogenesis (the formation of new blood vessels), and acquire the ability to invade distant organs through metastasis.

Cancer is therefore increasingly understood as a disease of dysregulated cellular signaling networks rather than simply uncontrolled cell proliferation. This insight has led to the development of targeted therapies that specifically inhibit abnormal signaling pathways, including EGFR, MAPK, and PI3K/AKT signaling components, thereby improving the precision and effectiveness of cancer treatment (Hanahan, 2022).

Do Drugs Influence the Evolution of Cell Signaling?

Drugs can significantly influence the evolution of cellular signaling systems by creating new forms of selection pressure. Cells, bacteria, or viruses that can evade a drug's effects are more likely to survive and reproduce, while susceptible organisms are eliminated. Over time, adaptive changes accumulate within signaling pathways, leading to the evolution of drug resistance and altered cellular responses (Greaves & Maley, 2012).

Antibiotics and the Evolution of Bacterial Signaling

The widespread use of antibiotics has imposed strong selective pressure on bacterial populations. Antibiotic-sensitive bacteria are killed, whereas bacteria carrying resistance-conferring mutations or genes survive and proliferate. As a result, resistant strains gradually become dominant within the population (Andersson & Hughes, 2010). A classic example is the emergence of penicillin-resistant ‘*Staphylococcus aureus*’ shortly after the introduction of penicillin. Many resistant strains evolved the ability to produce β-lactamase enzymes, which inactivate penicillin before it can disrupt bacterial cell-wall synthesis (Davies & Davies, 2010). This is a clear example of natural selection, with antibiotics acting as the selective force favoring resistant organisms.

Cancer Therapy and the Evolution of Signaling Pathways

Modern cancer therapies often target key signaling pathways that regulate tumor growth and survival, including EGFR, RAS–MAPK, and PI3K–AKT–mTOR pathways (Hanahan, 2022). For example, Imatinib transformed the treatment of Chronic Myeloid Leukemia by inhibiting BCR-ABL signaling, while Trastuzumab effectively targets HER2-positive breast cancers (Druker et al., 2001; Slamon et al., 2001). Cancer is increasingly viewed as an evolving population of cells subject to Darwinian selection (Greaves & Maley, 2012). Osimertinib, an EGFR-targeted therapy used for non-small-cell lung cancer, often produces dramatic initial tumor regression. However, genetic variation within tumors allows some cells to survive treatment through pre-existing or newly acquired resistance mutations (Mok et al., 2017).

These resistant cells gain a selective advantage and proliferate. In many cases, they activate alternative signaling pathways such as MET, HER2, or KRAS, enabling continued growth despite therapy (Leonetti et al., 2019). Consequently, drug-resistant clones emerge and tumors eventually recur. This process represents natural selection operating within a tumor population.

Viral Manipulation of Host Signaling

Viruses also target cellular signaling systems to enhance their survival. Many viruses alter cytokine signaling, suppress immune responses, and inhibit apoptosis. For example, HIV and several herpesviruses manipulate host immune signaling to establish long-term infections and evade immune surveillance (Finlay & McFadden, 2006; Gaglia & Munger, 2018). Thus, host–virus interactions represent an ongoing evolutionary arms race.

Drugs as Evolutionary Forces

Drugs generally do not create adaptive mutations directly; rather, they alter patterns of selection. In a drug-treated environment, susceptible cells are eliminated while resistant variants survive and spread. Over time, this process can reshape the structure and function of cellular signaling networks (Andersson & Hughes, 2010).

The Future: Evolutionary Medicine

The emerging field of evolutionary medicine applies evolutionary principles to understanding disease and improving treatment strategies. Because pathogens and cancer cells continuously evolve, effective therapies must account for the potential emergence of resistance. Consequently, approaches such as adaptive therapy, combination therapy, and signaling-network targeting are becoming increasingly important (Gatenby et al., 2009; Aktipis et al., 2013). As our understanding of evolutionary dynamics advances, future medicine will increasingly focus not only on eliminating disease but also on managing the evolutionary processes that shape resistance and treatment outcomes.

CONCLUSION

Cell signaling is one of the fundamental properties of life and has been closely linked to the evolution of biological complexity on Earth. From bacterial chemotaxis and quorum sensing to the nervous, immune, and endocrine systems of higher organisms, signaling mechanisms have played a central role at every level of biological organization. Evolutionary history shows that major biological innovations often arise through the modification and expansion of existing molecular components rather than the creation of entirely new ones. The remarkable conservation of signaling pathways such as GPCRs, RTKs, MAPK, and PI3K–AKT–mTOR reflects this continuity. At the same time, signaling networks remain dynamic and continue to evolve, as evidenced by antibiotic resistance, cancer adaptation, and virus–host coevolution. Thus, cell signaling should be regarded not merely as a mechanism of cellular communication but as a fundamental driver of biological complexity, adaptation, and evolution.

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