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Review

Autocrine Signaling and Quorum Sensing: Extreme Ends of a Common Spectrum

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'Secrete-and-sense cells' can communicate by secreting a signaling molecule while also producing a receptor that detects the molecule. The cell can potentially 'talk' to itself ('self-communication') or talk to neighboring cells with the same receptor ('neighbor communication'). The predominant forms of secrete-and-sense cells are self-communicating 'autocrine cells', which are largely found in animals, and neighbor-communicating 'quorum sensing cells', which are mostly associated with bacteria. While assumed to function independently of one another, recent studies have discovered quorum-sensing organs and autocrine-signaling microbes. Moreover, similar types of genetic circuit control many autocrine and quorum-sensing cells. Here, we outline these recent findings and explain how autocrine and quorum sensing are two sides of a many-sided 'dice' created by the versatile secrete-and-sense cell.

Secreting Signaling Molecules: A Fundamental Mode of Communication

Cells can communicate with each other by secreting signaling molecules that diffuse between them. Cells use a variety of receptors to detect the type and concentration of each extracellular signaling molecule. When the receptors bind to their cognate signaling molecules, they trigger cascades of intracellular signaling events that regulate diverse processes, such as the growth and death of cells [1–3], differentiation [4–8], and gene expression [9–20]. We usually categorize cells that secrete signaling molecules into two types: those that engage in 'autocrine signaling' and those that engage in 'paracrine signaling' (Figure 1). In autocrine signaling, a cell secretes a signaling molecule and simultaneously makes a receptor for that molecule. Paracrine signaling involves two types of cell. One type of cell secretes a molecule without making a receptor for it and the other type of cell makes a receptor for the molecule without secreting the molecule. Along with contact-mediated signaling, called 'juxtacrine signaling' [21], autocrine and paracrine signaling are responsible for almost all known cell–cell communications in multicellular systems [22]. These modes of signaling have primarily been studied in mammalian systems. However, recently, much progress has been made in studying paracrine signaling in populations of microbial cells, such as bacterial biofilms, and then extracting quantitative principles that apply to both mammalian systems (e.g., tissues) and microbial systems (e.g., biofilms) [23]. Nevertheless, many studies of autocrine signaling still mainly focus on mammalian systems and typically exclude discussions of microbial cells, notably how autocrine signaling may be related to quorum sensing. Quorum sensing, which allows the cells to 'measure' their population density to make collective decisions, is one of the most well-known and ubiquitous forms of microbial communication.

While autocrine signaling and quorum sensing both involve cells that secrete a signaling molecule and express its cognate receptors, they have long been thought to be two disparate

Trends

Cells often secrete and sense a signaling molecule to 'talk' to each other. Autocrine signaling is one of the main forms of such communication. 'Autocrine cell' refers to a cell that secretes a signaling molecule and makes its cognate receptor.

Recent studies have shown that an autocrine cell can communicate with itself (self-communication) and communicate with other cells (neighbor communication).

Quorum sensing involves autocrine cells determining their population density due to the cells engaging in neighbor communication without self-communication.

A ubiquitous genetic circuit, called the 'secrete-and-sense circuit', controls the ability of the autocrine cell to achieve self-communication, neighbor communication (including quorum sensing), and a mixture of the two.

Autocrine signaling and quorum sensing are two of many signaling modes enabled by the secrete-and-sense circuit.

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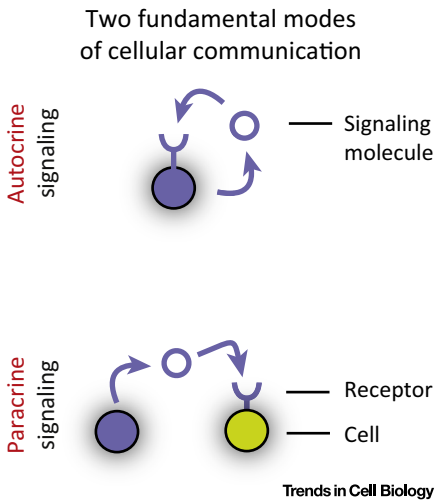

Figure 1. Autocrine and Paracrine Signaling as Two Fundamental Means of Cellular Communication. Cells often communicate by secreting a signaling molecule. Autocrine signaling and paracrine signaling are two fundamental and ubiquitous modes of communication through a secreted signaling molecule. In autocrine signaling, a cell secretes a signaling molecule and simultaneously makes a receptor that captures that molecule. In paracrine signaling, one type of cell secretes a signaling molecule without making its cognate receptor, while another cell type makes a cognate receptor without secreting the molecule.

forms of signaling, likely because they have seemingly different functions and purposes. Autocrine signaling has been historically understood, albeit only recently demonstrated in live cells [24], to enable a single cell to 'talk' to itself [25] whereas quorum sensing is designed for multiple cells to talk to each other, but not for each cell to talk to itself [26]. In this sense, quorum sensing is similar to paracrine signaling in terms of its function because paracrine signaling is designed for a cell to talk to other cells but not to itself. By contrast, quorum sensing is more similar to autocrine signaling than paracrine signaling in terms of its molecular parts (i.e., the same cell produces the receptor and the signaling molecule). Given these observations, it is natural to ask how autocrine signaling and quorum sensing might be related to each other both functionally and through evolution. Recently, researchers have begun to concretely connect the two in terms of their common functions and features of the genetic circuits that control them [24]. Indeed, quorum sensing in mammalian organs [27] and autocrine signaling in microbes have been discovered [24], while additional work has shown that autocrine signaling and quorum sensing are two ends of a continuous spectrum of signaling modes that is spanned by a generic 'secrete-and-sense cell': a cell that secretes a signaling molecule and simultaneously makes its cognate receptor, but can talk to itself (similar to autocrine signaling), and talk to its neighbors (similar to quorum sensing and paracrine signaling) [24,28]. These recent findings are causing a dismantling of the historically established barrier between researchers who have mainly studied quorum sensing in microbes (e.g., bacteria or yeasts) and researchers who have investigated autocrine signaling in metazoan cells (e.g., tumors, T cells, or embryos) [24]. Here, we review how researchers have traditionally thought about autocrine signaling and quorum sensing, and describe recent studies that connect the two.

Autocrine Signaling: A Cell That Talks to Itself

One of the first descriptions of autocrine signaling arose during the 1980s, when researchers proposed how tumor cells could originate in epithelial tissues [25]. It was known that many types of cell in healthy tissues secreted signaling molecules called epidermal growth factors (EGFs) to regulate their proliferation (Figure 2A). It was hypothesized and later confirmed that, when this autocrine signaling, which causes each healthy cell to stimulate its own growth by sensing its own growth factor molecule, is mis-regulated and, thus, overstimulates the cells, cells can grow uncontrollably and initiate tumors. Since then, researchers have found many examples of autocrine signaling in various mammalian cells [2,29–34] (Figure 2B–D). In the human immune system, naive T-helper (Th) cells use the molecules Interleukin (IL)-4 and interferon-γ for autocrine signaling, to differentiate into one of two cell states (Th1 or Th2 cells) [35,36]. $CD4^+$ T cells

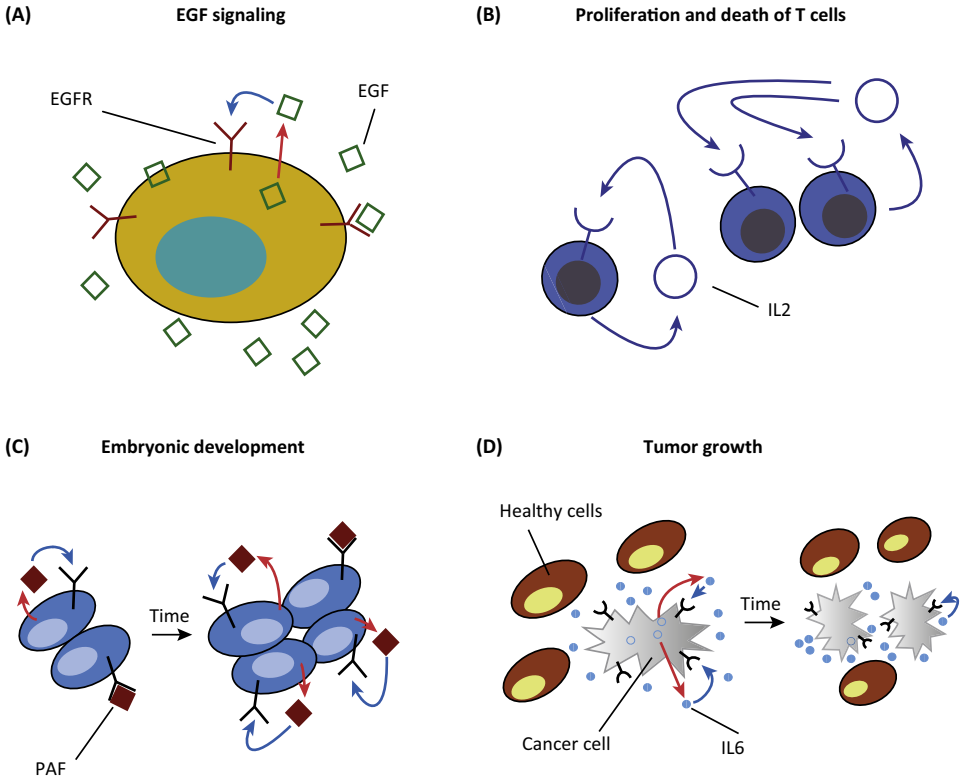

Figure 2. Examples of Autocrine Signaling. (A) Epidermal growth factor (EGF) and its receptor (EGFR) in epithelial cells. (B) $CD4^+$ T cells use autocrine signaling through interleukin (IL)-2 to control their proliferation and apoptosis. (C) Autocrine signaling, for example through the platelet-activating factor (PAF), has an important role in the development of mammalian embryos. A decreased amount of PAF ligand reduces the chances of the embryo surviving through development. (D) Faulty autocrine signaling through IL6 causes uncontrolled growth in healthy cells and initiates tumor formation during the early stages of breast and lung cancers.

use autocrine signaling through IL2 to control their proliferation and apoptosis [2] (Figure 2B). In early mammalian embryos, including human embryos, a decreased level of autocrine signaling through platelet-activating factor (PAF) ligand decreases the chances of survival of the embryo (Figure 2C) [31–33]. Faulty regulations of autocrine signaling turn healthy cells into cancer cells and initiate the growth of tumors [29]. For example, renegade autocrine signaling through IL6 can trigger lung adenocarcinoma in mice and humans. The somatic mutations in the EGF receptor (EGFR) in initially healthy mammary and lung cells cause the cells to secrete IL6 at an abnormally high rate. IL6 then binds to EGFR on these cells, which leads to highly activated signal transducer and activator of transcription 3 (STAT3) signaling in them. This in turn causes the cells to divide at an abnormally high rate, thereby promoting tumor formation [29] (Figure 2D).

Based on these examples, the prevailing belief has been that the primary purpose of autocrine signaling is for a cell to use its receptors to capture the signaling molecule that it had secreted so that it can 'talk' to itself (which we call 'self-communication') instead of sending the molecule to its neighboring cells to communicate with them (which we call 'neighbor communication'). The reasoning behind this is that, for autocrine signaling, cells typically express a high abundance of receptors that have high binding affinity for the signaling molecule [37]. Thus, such a cell would have a high probability of capturing the molecules that it had just secreted. Since the molecule returns to the cell after being secreted, the cell would not be able to communicate with its

neighboring cells. According to this scenario, autocrine signaling would require only a single cell and such a cell would be able to rapidly respond to its own signaling molecule [38–40]. Moreover, this scenario could provide a plausible reason for why autocrine signaling is ubiquitous in controlling the proliferation of cells through growth factors and in embryogenesis. In both embryogenesis and signaling through growth factors, cells have to rapidly undergo changes in their growth, gene expression, and differentiation. A cell that can quickly capture its own signaling molecule would be able to respond more rapidly to the molecule than a cell that relied on a molecule from other cells (i.e., a receiver cell in paracrine signaling) because the molecule would travel a shorter distance than in paracrine signaling. However, this idea of pure self-communication has persistently posed two questions that are only now being resolved: (i) why would a cell go through the many steps of producing and secreting a molecule if it only wanted to communicate with itself; and (ii) why does the cell not rely entirely on intracellular signals? The other challenge had been the difficulty in experimentally showing that autocrine signaling involved self-communication in individual cells. It was not until recently that researchers performed measurements of gene expression with single cell resolution to definitively prove that autocrine signaling enables pure self-communication without any neighbor communication [24]. These measurements and nascent theoretical studies [41–43] are now beginning to resolve the aforementioned two questions. We elaborate these resolutions after first reviewing some basics of quorum sensing.

Quorum Sensing: A Cell That Talks to Other Cells

Quorum sensing is a form of signaling in which a cell secretes a signaling molecule to communicate with other cells (i.e., engaging in a pure 'neighbor communication') in a way that depends on the density of the cell population. It has been the main paradigm for understanding multicellular behaviors and communication among bacteria and microbial eukaryotes [26]. Quorum sensing triggers coordinated and collective actions, such as all cells in the population turning on the same gene once the cell population density is above a certain threshold value. In this way, one can consider quorum sensing to be paracrine signaling that is activated by cells when the density of the cell population is above a certain threshold, whereas the cells do not communicate with self or neighbors when the population density is below the threshold. Quorum sensing is typically used when the benefits of cooperative actions outweigh the benefits of each cell acting autonomously [26].

Microbial cells, rather than being just autonomous individuals, use quorum sensing to accomplish tasks as a collective entity. For example, the marine bacteria *Vibrio fischeri* reside inside the 'light organ' of the Hawaiian bobtail squid *Euprymna scolopes* and use quorum sensing through the secreted molecule acyl homoserine lactone (AHL) to produce light inside the squid (a phenomenon called 'bioluminescence') (Figure 3A) [44–47]. When the population density of *V. fischeri* cells is low, the concentration of secreted AHL also remains low. As the population density increases, so does the concentration of AHL. At a certain population density, the concentration of AHL goes above a genetically encoded threshold, which then turns on downstream genes that lead to bioluminescence [26]. Researchers have also engineered genetic circuits in *Escherichia coli* cells so that the cells can quorum sense through AHL, which has provided investigations into population-level behaviors, such as population density control of the rate of death of *E. coli* [48,49].

Over the past decade, numerous studies have combined mathematical modeling with fluorescence-based methods, such as time-lapse microscopy, for measuring gene expression in single cells to reveal how individual cells encode the threshold for quorum sensing and the kinds of genetic circuit that can achieve quorum sensing [50–53]. In the soil amoeba *Dictyostelium discoideum*, a special form of quorum sensing, called 'dynamic quorum sensing', causes the cells to transition from unicellular individuals to macroscopic aggregates called 'fruiting bodies' (Figure 3B) [54–57]. For example, amoeba cells continuously secrete pre-starvation factor (PSF).

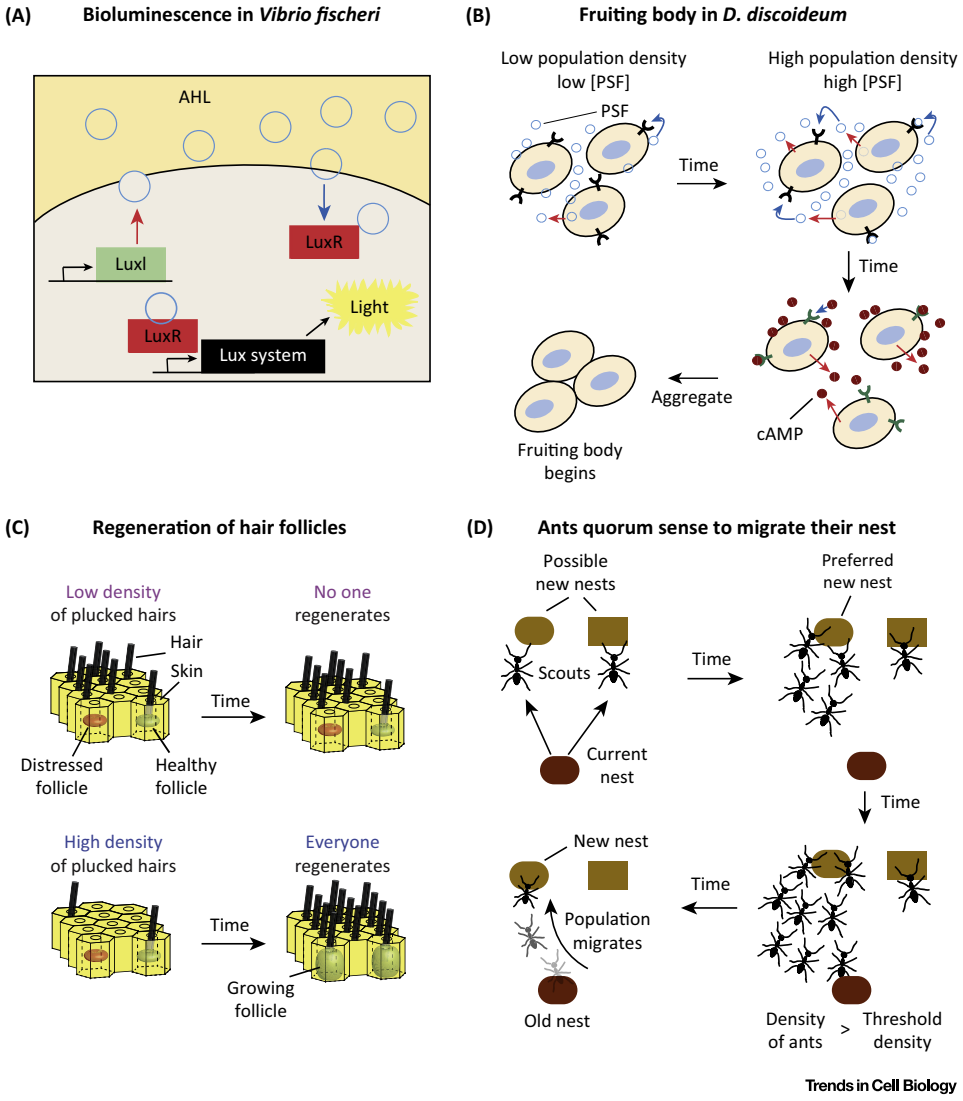

Figure 3. Examples of Quorum Sensing. (A) When the population density of marine bacteria *Vibrio fischeri* is small, the concentration of secreted acyl homoserine lactones (AHL) is low. An increase in the cell population density causes the extracellular concentration of AHL to rise. When the concentration of AHL goes above a certain threshold, the cells generate light through the 'Lux system'. (B) The soil amoeba *Dictyostelium discoideum* continuously secretes pre-starvation factor (PSF). The concentration of PSF increases as the density of starving cells rises. When the PSF concentration reaches a certain threshold, the amoeba responds by secreting cAMP. This eventually leads to the cells aggregating into fruiting bodies. (C) Hair follicles regenerate damaged hairs only if the density of damaged hairs is above a certain threshold. (D) The ant *Temnothorax albipennis* counts the rate at which it encounters other ants as it walks around in search of a new nesting site. Once the rate at which each ant encounters other ants goes above a certain threshold, the ants collectively migrate to the region in which the encounter rate is above the threshold to establish their new nest.

The concentration of PSF increases as the density of starving cells increases [57]. When the PSF concentration reaches a certain threshold, cells respond by turning on the expression of a set of genes that eventually trigger secretion of the chemoattractant, cAMP. cAMP secretion is dynamically regulated by the density of the amoeba, with a positive feedback that regulates secretion of cAMP (i.e., cells increase their average secretion rate of cAMP as they sense more cAMP). This regulation eventually leads to aggregation of cells into fruiting bodies [7,57,58]. This example suggests that quorum sensing was crucial in the evolution of multicellularity.

Quorum sensing is also seen in cooperative and commensal relations among different species [59–63]. Moreover, researchers are currently investigating inhibitors that disrupt quorum sensing in bacteria (i.e., 'quorum quenching') as an alternative to antibiotics, to which many bacteria have developed resistance [60–65], to treat cancer [60,66] and wounds [67].

Based on these examples, quorum sensing can be considered a form of paracrine signaling that depends on the density of the cell population despite the fact that quorum-sensing cells produce both a signaling molecule and its receptor, which is more similar to autocrine cells. Typically, receptors for the signaling molecule used in quorum sensing have a low binding affinity for the molecule [26]. Moreover, these receptors tend to be expressed in low abundance. Thus, microbes that quorum sense would only be able to detect the presence of the signaling molecule when there is a sufficiently high density of it, which would occur only when the cell population density is also sufficiently high [26].

A Secrete-and-Sense Cell Uses One Molecule to Talk to Itself and to Other Cells

One of the main goals of systems biology is to connect seemingly disparate biological systems under common quantitative principles. Recent studies of quorum sensing and autocrine signaling are pointing towards such unification between the two modes. Indeed, researchers are now discovering quorum sensing in metazoan cells and animal populations (Figure 3C, D). For example, researchers have recently found that hair follicles underneath the mouse skin regenerate damaged hairs only if the density of damaged hairs is above a certain threshold (i.e., number of plucked hairs per unit area of skin) (Figure 3C) [27]. This constitutes an example of quorum sensing at the level of a whole organ (hair follicle). Researchers have also found that *Temnthorax albipennis* ants, use quorum sensing to migrate to their nest. Namely, each ant counts the rate at which it encounters other ants as the ants roam about in search of a new nest. Once the rate of encounter of each ant goes above a certain threshold, the ants collectively migrate to the region where each of them (and, thus, everyone) experiences an encounter rate that is above the threshold. This rate informs their new nesting site (Figure 3D) [68]. Similar group decisions have been observed in honeybees migrating to their nests [69].

Adding to the trend of unification has been the recent demonstration of autocrine signaling in microbial cells [24]. A recent study demonstrated autocrine signaling in engineered budding yeasts and, in the process, proposed a fundamental connection between autocrine signaling and quorum sensing [24]. The study engineered a simple genetic circuit in budding yeast cells that caused the cells to secrete a mating pheromone (α-factor) and express a receptor (Ste2) for that pheromone [70]. The different concentrations of the mating pheromone caused cells to express different amounts of a fluorescent protein (but not mate with each other). Four parts of the 'secrete-and-sense' genetic circuit could also be tuned independently of each other over a wide range and demonstrated various 'social behaviors' that engineered yeast cells could achieve (Figure 4, Key Figure). These factors were: (i) receptor expression level; (ii) secretion rate of α-factor; (iii) expression level of a protease that actively degraded α-factor outside the cell; and (iv) strength of a positive feedback that caused the cells to increase the secretion rate of α-factor as the sensed concentration of α-factor increased. Through this tuning, the study showed that autocrine signaling and quorum sensing are merely two extreme ends of a continuous spectrum of a signaling modality, and proposed that a more generic 'secrete-and-sense cell' could span this 'sociability' spectrum (Figure 4). Namely, autocrine signaling is the 'asocial' end of the sociability spectrum, while quorum sensing is the 'social' end (Figure 4). The generic secrete-and-sense cell, which is any cell (mammalian or bacterial) whose genetic circuit contains the four parts mentioned above, would span the rest of this spectrum by tuning these four parts of the secrete-and-sense circuit [24].

Key Figure

Autocrine Signaling and Quorum Sensing Are Two Extreme Ends of a Spectrum of Signaling Modalities that Secrete-and-Sense Cells can Realize

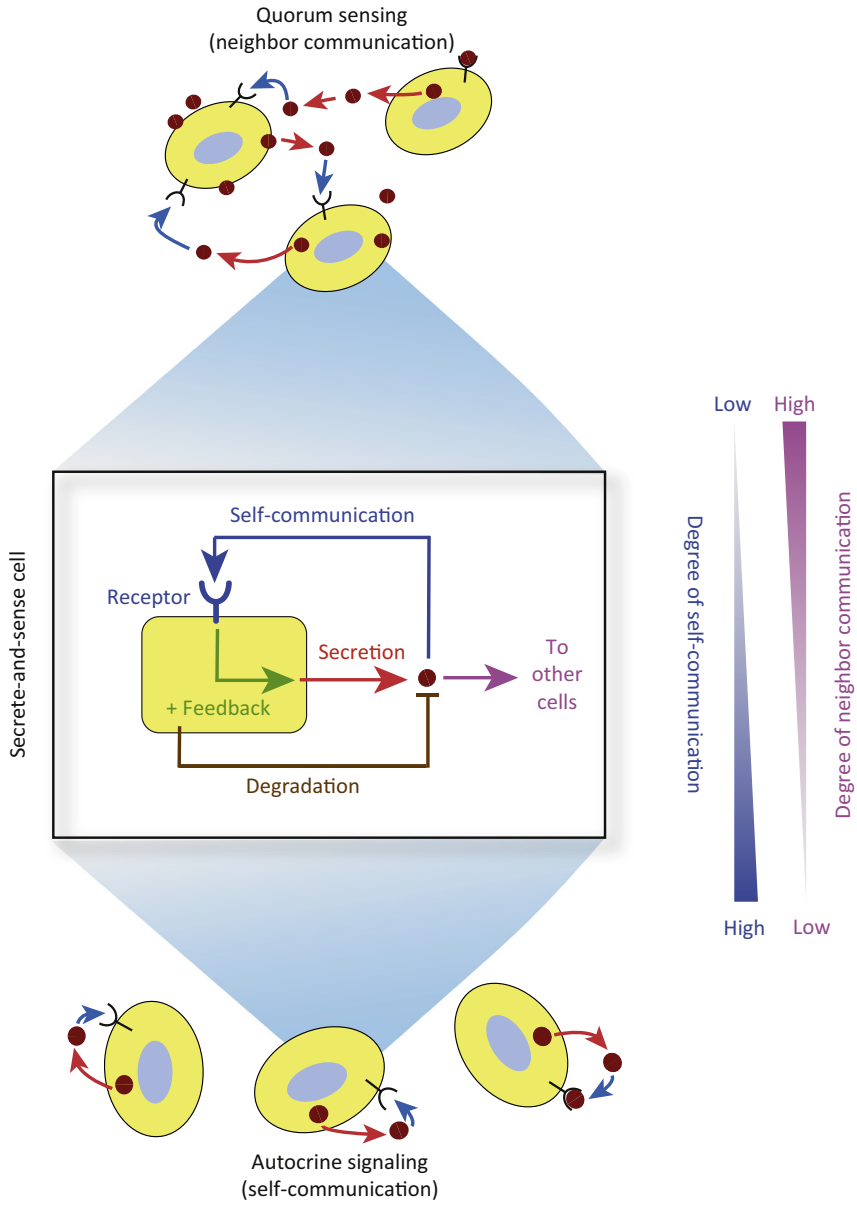

Figure 4. A secrete-and-sense cell can tune each of the four main elements of its genetic circuit to control its degree of self-communication (i.e., extent of autocrine signaling) and its degree of neighbor communication (i.e. extent of quorum sensing). The cell can continuously tune these two degrees of communication to realize a 'spectrum' of signaling modes (i.e., a mixture of autocrine signaling and quorum sensing). A fundamental trade-off is inherent in this spectrum: a high degree of neighbor communication comes at the cost of lowering the degree of self-communication, and vice versa.

In other recent studies [28,42], researchers developed mathematical models to reveal how parameters of secrete-and-sense circuits could be tuned to allow cells to communicate with each other, thus achieving efficient neighbor communication that is the basis of quorum sensing. For example, researchers developed a mathematical model to analyze the secrete-and-sense circuit in T cells of the immune system [42]. Their model showed that a group of secrete-and-sense T cells can compete for the same global pool of secreted IL2. Their model predicted this by tuning the 'activation threshold', which was the concentration of IL2 at which cells can switch on their genes that affect their proliferation rate. Thus, researchers showed that, in a population of polyclonal T cells with distinct activation thresholds, cells could either compete or cooperate with each other. Recent experiments [2,24] confirmed key predictions of this model and affirmed that secrete-and-sense cells could achieve density-dependent paracrine signaling (i.e., quorum sensing).

The use of experiments [2,24] and mathematical models [28,42] has revealed that the secrete-and-sense circuit motif (Figure 4) allows cells to realize autocrine signaling and density-dependent paracrine signaling (i.e., quorum sensing) at different times to achieve distinct goals. They demonstrate that there is no rigid boundary between quorum sensing and autocrine signaling. This division is a historical artifact of researchers in different disciplines having studied quorum sensing and autocrine signaling as separate phenomena. By considering both quorum sensing and autocrine signaling at the same time, recent studies have shown that there is a continuous spectrum between the two [2,24,28,42]. A mammalian or microbial cell can use autocrine signaling and quorum sensing simultaneously. Cells can tune their degree of autocrine signaling and their degree of quorum sensing by tuning each of the four elements of its genetic circuit to regulate the amount of self-communication or neighbor communication, respectively (Figure 4). A cell can continuously tune these two degrees of communication to realize a 'spectrum' of signaling modes (i.e., a self-communication and neighbor communication). However, a fundamental trade-off in this spectrum is that a high degree of neighbor communication comes at the cost of lowering the degree of self-communication, and vice versa [24].

Concluding Remarks

We have outlined nascent studies that demonstrate autocrine signaling to be more closely related to quorum sensing than was previously thought. We can consider quorum sensing to arise from the ability of cells that are conventionally called 'autocrine cells' to engage in pure neighbor communication (Figure 4), as in paracrine signaling. Conversely, cells that quorum sense can engage in self-signaling by tuning their secretion and sensing of the signaling molecule. Importantly, both autocrine-signaling cells and quorum-sensing cells can tune their genetic circuits to realize a mixture of self-communication and neighbor -communication (Figure 4). This unified view of autocrine signaling and quorum sensing shows the deficiency of the term 'autocrine signaling' as it is conventionally used in literature and textbooks [71,72], which refers to cells that secrete a signaling molecule and express its cognate receptor but does not distinguish between whether such a cell communicates with itself and/or with its neighbors. Cells that have been traditionally called 'autocrine cells' can engage in paracrine signaling, including its density-dependent form that we call 'quorum sensing' [24,28]. However, in light of the recent findings outlined in this review, we should focus on which cell communicates with which other cell when referring to metazoan and bacterial autocrine cells.

Despite this recent progress, many important questions remain (see Outstanding Questions), such as the evolutionary origin of autocrine signaling. One possible answer is that quorum sensing first originated in bacteria, and then early forms of multicellular organisms (i.e., animals) inherited the secrete-and-sense circuit of the bacteria that was tuned for quorum sensing. Animals could have tuned each of the four main elements of the secrete-and-sense circuit (e.g., through mutations in the regulatory regions) to achieve pure autocrine signaling or a

Outstanding Questions

Could autocrine signaling in metazoan cells have evolved from microbial quorum sensing?

Are microbial and metazoan autocrine cells able to tune their level of self-communication and neighbor communication at different times to suit different needs?

How does the physical structure of various mammalian tissues affect the degree of self-communication and neighbor communication, including quorum sensing, among the cells in the tissues?

mixture of self- and neighbor communication. Future work that investigates this possibility will likely yield a more comprehensive view of secrete-and-sense cells.

It would also be interesting to investigate the possibility that microbial and metazoan cells might tune their levels of autocrine signaling and quorum sensing at different times to suit different needs. For example, at the beginning of the development of an embryo or a tissue, autocrine signaling may be used to achieve a great biomass and population density within a short time period, and then switch to quorum sensing to enable cells within the embryo or the tissue to coordinate their behaviors. The different timescales involved in the effects of autocrine signaling and quorum sensing may also be worth investigating.

Finally, many mammalian tissues, for example the islets of Langerhans of the pancreas, comprise defined spatial arrangements of distinct cell types that engage in both autocrine and paracrine signaling (e.g., the beta-cells of the pancreas use insulin for autocrine signaling) [73]. Therefore, an interesting question is how the physical structures of various tissues affect the degree of autocrine and potentially of quorum sensing in tissues.

We envision that the above types of studies will reveal deep quantitative principles that govern secrete-and-sense cells, and cellular communication in general.

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