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Review

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

Berkalp A. Doğaner,[1,2] Lawrence K.Q. Yan,[1,2] and Hyun Youk[1,2,*]

'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.

[1]Department of Bionanoscience, Delft University of Technology, Delft 2628CJ, The Netherlands
[2]Kavli Institute of Nanoscience, Delft University of Technology, Delft 2628CJ, The Netherlands

*Correspondence: h.youk@tudelft.nl (H. Youk).

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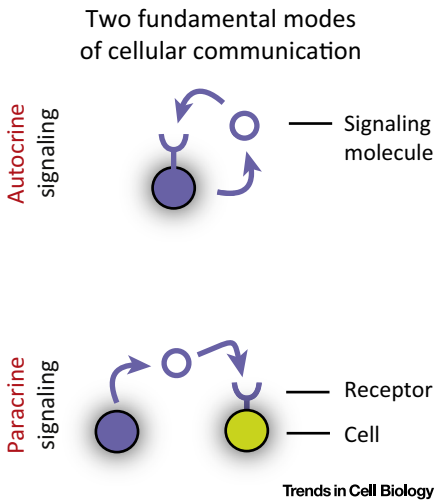

Figure 1. Autocrine and Paracrine Signaling as Two Fundamental Means of Cellular Communication. Cells often communicate by secreting a signaling molecule. Autocrine signaling and paracrine signaling are two fundamental and ubiquitous modes of communication through a secreted signaling molecule. In autocrine 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