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Quorum sensing in the immune system

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Abstract

Quorum sensing is the regulation of gene expression programmes in response to changes in population density. It is probably best recognized as a mechanism through which bacterial communities can synchronize behaviours, such as biofilm formation and bioluminescence. This Comment article highlights the emerging evidence suggesting that quorum sensing also contributes to the regulation of immune cell responses.

Quorum sensing was originally based on the idea that cooperation between bacterial cells of a single species would not be worthwhile unless a sufficient number of cells were present; that is, until a density threshold is reached. In bacterial quorum sensing, bacteria monitor their population density by communicating through the generation and detection of soluble extracellular signals called inducers¹. As the density of quorum sensing bacterial cells increases, so does the concentration of the inducer. Once bacterial density and therefore the concentration of the inducer reaches a certain level, this will result in the collective alterations of bacterial gene expression, which facilitates synchronized behaviours, such as biofilm formation, virulence and bioluminescence¹. Thus, quorum sensing enables cells within a population to function in unison and, in doing so, to carry out behaviours as a collective entity.

It is now well appreciated that quorum sensing does not only occur in bacteria of the same species, but it extends to groups of heterogenous micro organisms that have evolved together, each one with adaptations tethered to the biology of the others, thus establishing evolutionarily stable interactions aimed at shaping and maintaining the equilibrium of the entire bacterial population inhabiting a niche¹. Several features of cellular behaviour that resemble those underlying bacterial quorum sensing can be found in the immune system.

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Competing interests

The authors declare no competing interests.

For example, quorum sensing contributes to regulating the absolute size of some immune cell subsets and helps to optimize their effector functions, such as cytokine secretion. Below we highlight some key examples of quorum sensing in the immune system.

Quorum sensing by lymphocytes

Based on computer simulations and in vitro experiments, Feinerman et al.² proposed that the density of effector CD4⁺ T cells is an important factor for sustaining levels of phosphorylated signal transducer and activator of transcription 5 (STAT5) and effector T cell activation during antigenic stimulation. The authors noted that in the presence of antigenic stimulation there is a quorum sensing threshold, as a minimal number of effector T cells is necessary to secrete sufficient amounts of IL-2 to maintain STAT5 phosphorylation and, presumably, effector T cell population expansion. More recently, Polonsky et al.³ have shown that local cell density could modulate the differentiation of naive CD4⁺ T cells into memory precursor cells, where collective interactions involving more than 30 cells were most efficient in driving memory T cell differentiation.

Quorum sensing mechanisms also operate in CD8⁺ T cells. It was observed that a threshold population density of CD8⁺ T cells was necessary to induce the transcription factor B lymphocyte-induced maturation protein 1 (BLIMP1; also known as PRDM1) and the terminal differentiation of naive CD8⁺ T cells following activation⁴. The size of the natural IgM-secreting B cell pool and plasma IgM levels have also been suggested to be maintained through a quorum sensing mechanism⁵. The B cell population as a whole seems to control the number of activated natural IgM-secreting B cells by secreting IgG⁵; IgG signals through FcγRIIB on natural IgM-secreting B cells to negatively regulate their number and/or activation state⁵. As this negative feedback mechanism is not the result of competition for resources or niche⁵, the authors of this study proposed that B cells can ‘count’ their own numbers, with IgG acting as the inducer that reports the density of B cells⁵.

Quorum sensing by myeloid cells

The fact that macrophages in isolation produce less inflammatory cytokines and chemokines on a per cell basis than macrophages within a network suggests that macrophage quorum sensing is important in determining the magnitude of the inflammatory response. Macrophage coordination also regulates the spread of infection, and macrophages need to be present at a crucial density to control mycobacterial proliferation⁶. While these are examples of positive regulation of macrophage function upon increasing cell density, increasing cell density can also decrease some macrophage functions: chondroitin sulfate expression by macrophages is decreased as their population density increases⁷.

Macrophages also actively participate in quorum sensing mechanisms during tissue regeneration. Chen et al.⁸ recently described a quorum sensing circuit, which provides a way for injured hair follicles to collectively assess the magnitude and extent of injury that the skin containing these hair follicles has sustained and make an all-or-none decision whether or not to regenerate. This quorum sensing circuit is dependent on macrophages, where in a two-step process, release of CC-chemokine ligand 2 (CCL2) from injured hair follicles leads

to recruitment of tumour necrosis factor (TNF)-secreting macrophages, which accumulate and spread among the follicles and signal to the hair follicles to regenerate. Finally, as high macrophage density in tumours typically correlates with poor clinical outcomes, it is possible that high density enhances macrophage suppressive activity. In fact, blockade of colony-stimulating factor 1 receptor (CSF1R), which reduces macrophage density in solid tumours, has been successfully employed as a monotherapy or in combination with other cancer treatments⁹.

An IL-10-mediated coordination of cytokine production was also recently described in dendritic cells, where IL-10 was found to be the quorum sensing inducer¹⁰. An increase in IL-10 concentration signalled to other dendritic cells to collectively decrease their pro-inflammatory cytokine gene expression.

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Future questions

There are several outstanding questions in the burgeoning field of immune quorum sensing. What are the relative roles of quorum sensing versus competition for niche and trophic factors in regulating immune cell numbers? Is there a role for the different environmental niches in determining inducer specificity and the quorum sensing network architecture? Do other immune cells not discussed in this article use quorum sensing to coordinate their functions? Future studies will no doubt increase our understanding of the contribution of quorum sensing to immune responses.