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Does a quorum sensing mechanism direct the behavior of immune cells?

*Quels rôles peuvent jouer des mécanismes de détection de quorum (*quorum sensing*) dans les réponses immunitaires ?*

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ABSTRACT

Quorum sensing is a decision-making process used by decentralized groups such as colonies of bacteria to trigger a coordinated behavior. The existence of decentralized coordinated behavior has also been suggested in the immune system. In this paper, we explore the possibility for quorum sensing mechanisms in the immune response. Cytokines are good candidates as inducer of quorum sensing effects on migration, proliferation and differentiation of immune cells. The existence of a quorum sensing mechanism should be explored experimentally. It may provide new perspectives into immune responses and could lead to new therapeutic strategies.

RÉSUMÉ

Les mécanismes de détection du quorum (*quorum sensing* en anglais) sont utilisés par des groupes tels que des colonies bactériennes pour induire un comportement collectif. Le système immunitaire est sujet à des comportements collectifs du fait de la participation de nombreuses cellules aux réponses immunitaires. Dans cet article, nous explorerons les possibles implications de mécanismes de détection du quorum dans les réponses immunitaires. Notamment, les cytokines pourraient être de bons candidats pour induire des mécanismes de détection du quorum lors de la migration, de la prolifération ou de la différenciation des cellules immunitaires. Une exploration expérimentale de l'existence de tels mécanismes est nécessaire. Les résultats obtenus pourraient ouvrir de nouvelles perspectives quant au fonctionnement des réponses immunitaires et permettre d'envisager de nouvelles stratégies thérapeutiques.

1. Introduction

Quorum sensing is a mechanism used by decentralized groups of cells or individuals. It can trigger a similar behavior by many individuals of a group at the same time, also regarded as synchronization. Evolutionary biologists describe this synchronization as an emergent coordinated behavior [1,2]. Many species of bacteria use quorum

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sensing to trigger their gene expression and perform synchronized specific functions according to the local density of their population [3]. In many bacterial species, quorum sensing processes trigger gene expression according to cell density.

Kourilsky and Truffa-Bacchi have argued that coordinated behavior of immune cells is required for a successful immune response [4]. The immune system, as a dynamical system, may achieve this coordinated behavior through synchronization. Dynamical systems have been demonstrated to be more robust to individual noise and variability when they are synchronized [5], a trait that may have been selected during evolution [6]. Therefore, considering the existence of quorum sensing as a mechanism that increases the robustness of the immune response through synchronization is attractive.

Recently, studies have shown that bacterial quorum sensing signal molecules can disrupt immune response [7,8]. This process invites to question the existence of mechanisms such as quorum sensing within the immune response itself. In this paper, we explore the possibility for quorum sensing mechanisms in the immune response. We also investigate properties of quorum sensing and discuss its possible impact on the robustness of immune responses.

2. Quorum sensing in immune responses

Quorum sensing has been extensively studied in bacteria. It supposes the production and secretion of an extracellular molecule called inducer by a population of bacteria (Fig. 1). Each individual bacterium expresses also the adequate receptor for this inducer, but the likelihood of detecting its own inducer is low. When only a low number of bacteria produce the inducer, the concentration is reduced through diffusion in surrounding medium. However, as the population grows, the concentration of detected inducer passes a threshold, inducing changes in gene expression (activation or inhibition). This change induces behavioral change at the population level, described as an emergent coordinated behavior. It allows biofilm formation, virulence, and bioluminescence [3].

Several similar features can actually also be found in the immune system. Cytokines are perfect candidates for the role of inducer of quorum sensing as they are secreted extracellularly and induce various behaviors observed at the level of the population of immune cells. For example, T-helper lymphocytes produce a large panel of cytokines and express their associated receptor [9–12]. These cytokines induce proliferation and changes in gene expression that lead to the differentiation of T-helper lymphocytes into various T-helper subtypes [9–12]. One of the most obvious examples of such a cytokine is IL-2, which regulates cell activation and division and has been shown to follow a quorum sensing mechanism [13,14]. The dependence on the cell density and on other cytokine concentration in the activation and the differentiation of T-helper cells has also been suggested, but remains unexplored experimentally [15–17].

We believe that coordinated behavior by quorum sensing could be a very broad mechanism used by the immune system to regulate the response of group of cells. It could intervene in the migration, proliferation, and differentiation of the cells. Evidence of behavior relying on cell numbers has been reported, such as the control of type I interferon secretion by the number of plamacytoid dendritic cells in vivo [18], and immunoglobulin M production by the number of immunoglobulin G producing B cells [19]. Such result may be reinvestigated in the light of quorum sensing. Other studies have shown that B lymphocyte cell differentiation is related to cell division and could be interpreted as a causal effect of quorum sensing [20].

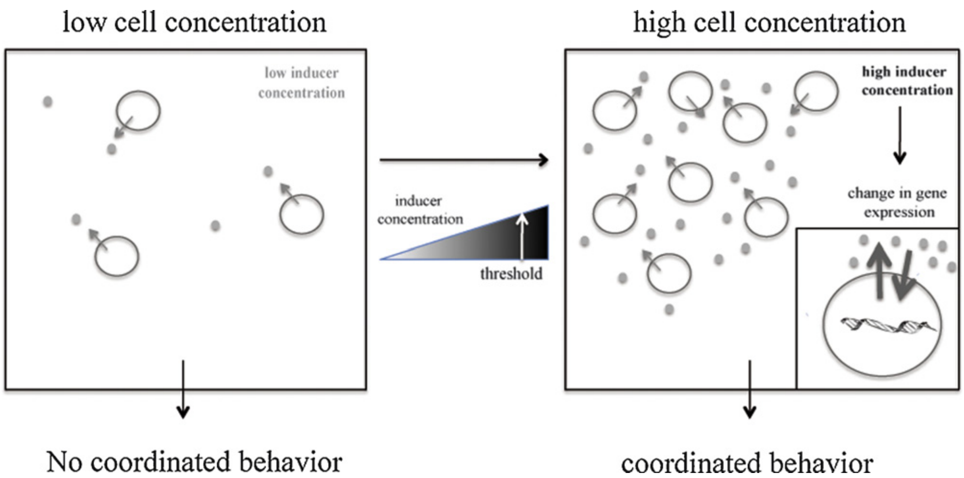

Fig. 1. General principles of quorum sensing. Those principles have been shown for bacteria population, but could happen with immune cells. At low cell concentration, bacteria secrete an inducer but the concentration is too low to induce a coordinated behavior. As the population grows, the concentration of detected inducer passes a threshold, inducing changes in gene expression (activation or inhibition). This change induces a coordinated behavior at the population level, such as biofilm formation or virulence. In the immune system, cytokines are good candidate for inducer. Migration, differentiation, and antibody production are possible coordinated behaviors.

3. Existence of a threshold for triggering collective behavior

The first experimental step to prove the existence of quorum sensing would be to measure the existence of a threshold. For the moment, most studies are performed in vitro at saturating concentration of cytokine. New in vivo technologies should be developed to evaluate concentrations of cytokine in defined microenvironment to explore and quantify possible thresholds.

Another way to appreciate quorum sensing is through new single cell technologies [21,22]. The study of individual cell may help to fill the gap of knowledge between individual and cell population dynamics, allowing us to observe synchronization of cells.

4. Independence from individual cell variations

Another property derived from quorum sensing is the independence of the induced behavior from individual cells variations. For example, a cell might die of infection or migrate. In the case of a coordinated behavior triggered by quorum sensing at sufficiently high population numbers, the other cells will not be affected by such a loss. Not being sensitive to direct individual cell fate could confer an advantage in term of robustness of the immune response, and as such could have been selected by evolution.

5. Benefits of the density dependence

Quorum sensing in bacteria has been proposed as a mechanism for stimulating coordinated behavior when the cell density is the most beneficial, which can be either at a high or low cell density [23–25].

The benefit of quorum sensing during an immune response could be considered either at high or low density. For the clearance of a virus one could argue that the more cells involved, the more viruses are cleared. A study proposes that high density induces terminal differentiation of cytotoxic T cells, which are the cells able to lyse infected cells [26]. However, having too many cells involved in an immune response can generate immunopathology detrimental for the organism [27]. In that regard quorum sensing mechanisms may trigger coordinated behavior at low cell density or a coordinated stop of a behavior at high cell density. The shutdown of an immune response is as critical as it's induction. The detection of large number of cells by quorum sensing may stop the immune response. For example increasing the number of transferred cytotoxic T cells was shown to anticipate the peak of the immune response [28]. It can result both from an induced proliferation at low cell density or a negative effect on the cell growth at high cell density. In conclusion, quorum sensing may act during an immune response both at a high or low cell density, or more likely within a range of cell density, neither too high nor too low.

The requirement for cell density, or a quorum of cells, has been questioned in evolutionary microbiology in favor of a mechanism termed diffusion sensing [29]. The concentration of inducer may not reflect directly the cell density, but is altered by others factors such as spatial distribution [30,31]. Considering diffusion sensing may also be an appropriate approach for immune cells' coordinated behavior where local organization of environments, such as the lymph node, plays a crucial role.

6. Conclusion

Experimental evidences of quorum sensing mechanisms in the immune response are still lacking. The existence of a threshold for synchronization could be already assessed in vitro by varying the cytokine concentration. In vivo assessment would require the development of new technologies.

If such mechanism can be shown experimentally, it may open new perspectives in immunology. For example, quorum sensing mechanism highlights the importance of the microenvironement, modulated by cytokine, in the regulation of the immune response, in particular when a multiplicity of cells are involved. We propose that quorum sensing theories provide a good basis to rethink the dynamics of immune cells.

More properties of the immune system could then be reconsidered in light of quorum sensing and lead to new therapeutic strategies.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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