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Review

Pathogen-derived extracellular vesicles coordinate social behaviour and host manipulation

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ABSTRACT

Infectious diseases are the leading cause of death of children worldwide, causing a tenacious and major public-health burden. The dynamic interplay between pathogens and their host is one of the most complicated themes of the disease progression. Pathogens excel in developing different means to facilitate cell-cell communication via secreted vesicles, among others. The released vesicles are involved in the transfer of biologically active molecules that induce phenotypic changes in the recipient cells. The messages within the vesicles are delivered to coordinate diverse processes, including virulence factor expression, differentiation state and control of their population density. Importantly, production of such vesicles promotes pathogen survival, as it provides a secure means of pathogen–pathogen communication and an ability to manipulate host responses for their own benefits.

This review highlights intriguing findings, which show the important role of EVs in the social activity of pathogens, within and in between their communities. We further present examples of how pathogens use EVs to alter host immune and non-immune responses. Advancing our understanding of cell–cell communication in infectious diseases will be particularly useful to decipher the complexity of the cross-talk between pathogens themselves and their hosts, leading to the development of therapeutic strategies for fighting infectious agents.

Contents

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1. Introduction

The ability to sense extracellular signals and communicate with other cells is essential for all living organisms, especially for pathogens. Social and cooperative behaviour plays an important role in numerous processes, including differentiation, transmission, growth control, host manipulation and virulence coordination. During their lifecycle, pathogens face very hostile environments and need to overcome the immune response of their host. Parasites, for instance, which are transmitted between multiple hosts, e.g. malaria parasites, encounter vastly different environments in these organisms and must fight on distinct "battlefronts".

By communicating and acting as a group, unicellular organisms have advantages over individually acting cells. The communication (i) promotes development and survival by having distinct cell types perform specialized functions, (ii) promotes access to nutrients, and (iii) advances pathogens' defence mechanisms against their common host [1,2].

In recent years, new insights into the cooperative behaviour of parasites, not only bacteria, have changed our view of the behaviour of these unicellular organisms: during infection they do not act as "selfish" individuals, but behave as integrated communities (reviewed in [2,3]). We believe that the parasitology field is in the process of identifying communication strategies between parasites, similarly to the well-established concepts of communication between bacteria.

Understanding the role of secreted extracellular vesicles (EVs) in infectious diseases has added enormously to our understanding of how microbes advance their development during infection. These vesicles impact the course of the infection, alter host responses and help to control pathogen self-communities. The production of EVs is a common phenomenon in microorganisms and is not due to random cell death or lysis [4,5] but to an active mechanism of cell-cell communication. The secreted vesicles are generated by several distinct pathways. In bacteria, vesicles form when a portion of the outer membrane with periplasmic content is selectively "blebbed" off to form round vesicles [6]. Like bacterial EVs, fungal EVs must traverse a cell wall in order to be released [7]. The mechanisms of EV release across the complex network of the fungal cell wall are still unknown. Fungal and parasitic pathogens produce at least one additional vesicle population, whose biogenesis is initiated by inward budding of multivesicular endosomes, similarly to the mammalian vesicle forming mechanism. Consequently, vesicles express markers of their parent cells, but are also specifically enriched in cargo associated with their biogenesis [8,9]. In some cases, the basic features of vesicle production by different microbial cells appear to be conserved, including homologous proteins involved in regulating the mechanisms of release [9].

A comprehensive review of the entire field of EVs in infectious diseases is beyond the scope of this article. Instead, we will highlight key concepts, and describe how pathogens secrete vesicles for their own benefits. Herein, we term the secreted vesicles as EVs and will focus primarily on two aspects of EV function: (i) within the pathogen community (*pathogen to pathogen communication*) and (ii) in the interplay between the pathogen and its host (*pathogen to host communication*).

2. Pathogen to pathogen communication

We describe several examples of cooperative behaviours between pathogens that are, or have been implied to be, mediated by secreted vesicles (Fig. 1).

2.1. Management of the virulence via EVs

The ability to vary immunodominant molecules (known as antigenic variation) is a well-studied mechanism that pathogens use to avoid the immune response. Acquired immunity relies on memory of previous exposure to antigens, and antigenic variation is especially effective in circumventing humoral and cellular responses [10]. Vesicles, often been termed "virulence bags" [7] have been found to deliver active toxins and virulence factors [11,12] in a variety of bacteria [13], parasites [8,14], viruses [15,16] and fungi [17] indicating that they play an important role in disease pathogenesis. Virulence factors can be secreted by microbes that are lacking known secretion systems and are therefore thought to be released from the cells by the mechanism of vesicle production [9].

Pathogens use vesicles to shuttle their own virulence factors between them, promoting specific virulence expression and avoiding the innate immune response [18,19]. Studies on *Pseudomonas aeruginosa*, an opportunistic human bacterial pathogen, which is commonly associated with nosocomial infections, suggest that these pathogens deliver multiple virulence factors via vesicles into the surrounding milieu, not by individual action but in a coordinated manner, simultaneously and directly into the host cell cytoplasm [20].

"**The enemy of my host is my friend**" – EVs facilitate not just communication within a pathogen population, but also between species communities to aid one another in the fight for survival against the common "enemy", the host (Fig. 1). *Moraxella catarrhalis* is frequently found in mixed infections with pathogens such as *Haemophilus influenza*. Secreted vesicles derived from *M. catarrhalis* carry UspA1/A2 that protect species such as *H. influenza* from complement-mediated killing, suggesting that *M. catarrhalis* promote the survival of this species of bacteria during co-infection [21]. EVs are also critical in antimicrobial resistance transfer between microorganism species within the community. Vesicles containing β-lactamase, an enzyme capable of hydrolysing multiple antibiotics, confer resistance not only to the *M. catarrhalis* producer, but also to neighbouring bacteria such as *Streptococcus pyogenes* [22,23].

During co-cultivation, EVs derived from *Trypanosoma brucei rhodesiense* parasites, pathogens responsible for human sleeping sickness, facilitated the transfer of the virulence factor, SRA, to neighbouring non-human infectious trypanosomes. The virulence transfer allowed for the evasion of the human innate immunity, making a non-pathogenic strain virulent for humans [24].

Vesicles have also been found to stimulate negative interactions within inter-microbial communication and be toxic to competing strains of the producer. The non-pathogenic thermophilic archaeon *Sulfolobus solfataricus* uses EVs release to discourage nearby growth of other Sulfolobus species by secreting sulfolobicin toxins [25].

Since microbes use EVs to exchange signals between them, inter- and intra-species communication of the microbe communities, occupies an essential view when dealing with the complexity of human infectious diseases (Fig. 1). Investigating the roles of EVs