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Novel insights into red blood cell physiology using parasites as tools

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ABSTRACT

The mammalian red blood cell is a terminally differentiated cell that lacks a genetic programme and that has only a very limited metabolic capacity. Nonetheless, it serves as habitat for two parasites belonging to the monophyletic group of Apicomplexa, namely *Plasmodium* and *Babesia*. Studies of the parasitized red blood cell have revealed several properties that are unknown in the non-infected cell and that are difficult to conceptualize based on our view of red blood cell function. Here we review the current knowledge on host cell invasion and nutrient acquisition by these parasites. We attempt to dissect the factors that are directly contributed by the parasites from those that exist but have remained undetected in the non-infected cell.

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General principles of intracellular parasitism

Over several decades parasitic protists have been used as models to unravel cell biological phenomena, typically not found in non-parasitic organisms. These include adaptations of the pathogens to a host environment but also responses of the infected cell to the pathogen. Current research interests focus mainly on

(i) the process of host cell invasion,
(ii) the effects of additional genetic programmes introduced by the pathogen,
(iii) defence mechanisms of the infected cell,
(iv) nutritional requirements of the respective pathogens.

Among the mammalian host cells, the completely differentiated red blood cell (RBC) is a most exceptional habitat for pathogens whereas nucleated cells serve as hosts for a broader range of pathogens. Therefore we briefly exemplify the general principles of intracellular parasitism, including nucleated host cells, before we focus on the peculiarities of the parasitized RBC (Fig. 1).

Host cell invasion and compartmentation

Unlike viruses, prokaryotic and eukaryotic pathogens maintain their cellular entities during the phases of invasion, differentiation and multiplication. As a consequence, these organisms are taken up as entire cells and are, at least initially, secluded in a phagosome or phagosome-like compartment. Some parasitic protozoa (e.g. *Trypansomoa cruzi*) and bacteria (e.g. *Shigella*, *Rickettsia*) are found in the host cell cytosol. Most likely, this is a secondary location after disintegration of or escape from early endocytic compartments (Cossart and Sansonetti, 2004; Ley et al., 1990; Schroeder and Hilbi, 2008). Most intracellular pathogens utilize phagocytic properties of their respective host cells and are confronted with the more or less lytic environment of the endosomal network. A group of protists, namely the Apicomplexa, avoid a phagocytic uptake by inducing a unique compartment which, in distinction to the host cell's endogenous phagosomal compartments, is termed 'parasitophorous vacuole' (PV) (Scholtyseck and Piekarski, 1965). The PV differs from phagocytic compartments in its limited ability to fuse with the host cell's endomembrane system and its maintenance of a pH that is close to neutral (Lingelbach and Joiner, 1998). It is generally believed that a group of the apicomplexan-specific compartments, located in the so-called apical complex of these parasites situated at one end of the polarized cell, contribute to the formation of the PV (Soldati et al., 2004). In many cases the receptors and ligands that mediate the initial attachment of the parasite to the target cell surface are known, but the events that lead to the formation of the PV and the parasite macromolecules that contribute to its formation are largely unknown.

Host cell modification

As a general principle the infected host cell shows properties that are different from the non-infected cell. These changes include

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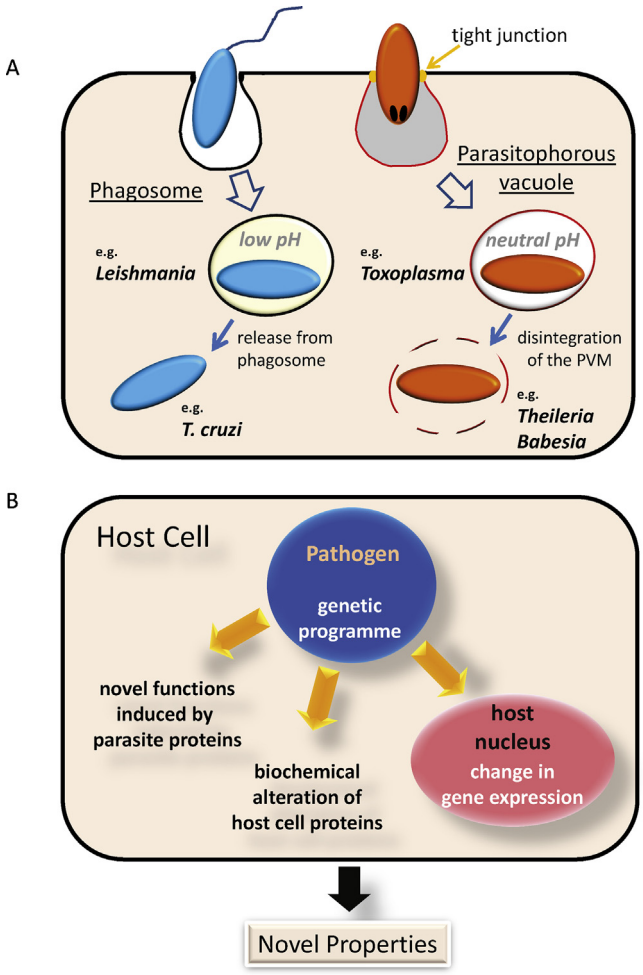

Fig. 1. General principles of intracellular parasitism. (A) Parasites (e.g. *Leishmania*) enter either the endocytic/phagocytic network in which case they are located in a more or less acidic compartment. Alternatively, as is the case for apicomplexan parasites (e.g. *Toxoplasma*), they actively form a unique compartment, called the parasitophorous vacuole (PV), the membrane of which (PVM) has a low tendency to fuse with the host cell's endomembrane system, thus maintaining a pH that is close to neutral. Some parasites (e.g. *Theileria spec.*; *Trypansoma cruzi*) are released from their respective compartments and multiply within the host cell cytosol. (B) Independent of their localization, parasites introduce into the target cell an additional genetic programme the products of which can affect the physiology of the host cell. As a phenotypic result, the infected cell displays novel properties that are most likely the consequence of a complex interplay between protein and host cell derived components.

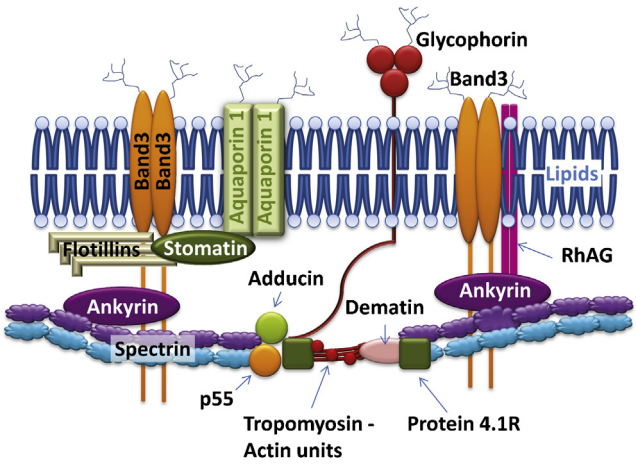

Fig. 2. The erythrocyte cytoskeleton. The structure and physical properties of the erythrocyte are largely determined by a cytoskeleton that underlies its plasma membrane. It consists of actin and spectrin filaments that are anchored to the plasma membrane via several structural proteins that can have additional functions such as the major anion transporter, also known as band 3 protein. It has been reported that other proteins of minor abundance, such as the flotillins and stomatin, are organized in microdomain structures the exact functions of which are still elusive.

the upregulation of innate defence mechanisms by the host cell. In some cases the proteins required for the presentation of foreign antigens on the cell surface and the synthesis of microbicidal oxygen radicals by, for example, the endogenous inducible nitrogen oxydase synthase are stimulated. Conversely, changes in the cytokine profiles and the down regulation of antigen presenting cell surface proteins, appear to be more pathogen-specific and under control of the pathogen's genetic programme. Also, the composition of the phagosomal contents and the phagosomal membrane are altered by several pathogens and is probably investigated in most detail in phagocytic cells infected with *Leishmania* or *Mycobacteria* (Bogdan, 2015). *Theileria* interferes with the apoptotic programme of its host cell, resulting in immortalization of the infected cell.

Nutrient acquisition

Parasites that survive in the host's phagosomal/lyosomal network have no shortage breakdown products from which they build macromolecules. However, nutrient acquisition by apicomplexan parasites appears more complicated because the PVM more or less secludes the parasite from access to the host cell's degradation products. Electrophysiological studies and results obtained with tracer molecules have shown that the PVM acts as a 'molecular sieve' that contains non-selective pores that allow free passage of molecules of approximately 600 Da (Desai and Rosenberg, 1997; Nyalwidhe et al., 2002; Schwab et al., 1994). To what extent the intracellular parasite is dependent on nutrients from the extracellular medium is still unclear. Increasing evidence in *Toxoplasma* parasites suggests that transport of host proteins from the extracellular serum to the vacuolar lumen occurs. Also, proteins have been identified that are inserted by the parasite into the PVM where they tether host cell mitochondria to the PVM. To what extent these pathways are essential in terms of nutrient acquisition and whether they are representative for other apicomplexan parasites remains to be shown.

The mammalian red blood cell—A perfect habitat for parasites?

Owing to its limited metabolic activities the mammalian RBC is a host cell that harbours only very few pathogens. It lacks a genetic programme and has lost its ability to synthesize proteins, lipids and complex carbohydrates. Its life span is predetermined to 120 days and most of the energy required for RBC function is obtained by glycolysis. The differentiated RBC neither phagocytoses nor endocytoses and its structure is maintained by a cytoskeleton which is unusual in that underlies the RBC plasma membrane (Mohandas and Gallagher, 2009). The cytoskeleton is anchored to the RBC membrane via several structural proteins, including as a main component the band 3 anion transporter that also interacts with cytoskeletal proteins (Fig. 2). At a first glance from a cell biological standpoint the RBC lacks most of the prerequisites to allow pathogen invasion and growth. Despite these obvious limitations the RBC is regarded as a 'safe haven' for parasites that have acquired the abilities to infect and to persist in this highly specialized cell. Most notably, the RBC lacks lysosomes and it is unable to present foreign antigens that would signal an infection to the host's immune system. Thus, parasites of the RBC survive largely unrecognized except for the usually short-lived extracellular stages between host cell rupture and re-invasion. Although RBC can

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