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REVIEW

Biologia Futura: stories about the functions of β_2-integrins in human phagocytes

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Abstract
Integrins are essential membrane proteins that provide a tightly regulated link between the extracellular matrix and the intracellular cytoskeletal network. These cell surface proteins are composed of a non-covalently bound α chain and β chain. The leukocyte-specific complement receptor 3 (CR3, $\alpha_M\beta_2$, CD11b/CD18) and complement receptor 4 (CR4, $\alpha_X\beta_2$, CD11c/CD18) belong to the family of β_2-integrins. These receptors bind multiple ligands like iC3b, ICAMs, fibrinogen or LPS, thus allowing them to partake in phagocytosis, cellular adhesion, extracellular matrix rearrangement and migration. CR3 and CR4 were generally expected to mediate identical functions due to their structural homology, overlapping ligand specificity and parallel expression on human phagocytes. Despite their similarities, the expression level and function of these receptors differ in a cell-type-specific manner, both under physiological and inflammatory conditions.
We investigated comprehensively the individual role of CR3 and CR4 in various functions of human phagocytes, and we proved that there is a "division of labour" between these two receptors. In this review, I will summarize our current knowledge about this area.

Keywords β2-integrins · Human phagocytes · Complement receptor · Phagocytosis · Adherence

Background

Personal aspects

I started working with Anna Erdei in the early 1980s as a university student. At the time, I was involved in research investigating the effect of the covalent attachment of the C3b molecule on the cell surface. These studies were continued for about two decades. I truly enjoy being a part of Anna's team. In the early 2000s, our interest turned to the study of β_2-integrins on myeloid immune cells. Our collaboration continues to this day. I am grateful for her dedication to the team and the encouraging atmosphere she has created every day in our department.

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The complement system

The complement system is composed of more than thirty components, including soluble and membrane-bound proteins and their respective receptors. Activation of the complement cascade generates proteolytic fragments which mediate various biological functions. The complement system is a major humoral component of the innate immune system and plays a key role in the elimination of invading pathogens including bacteria, viruses, fungi and parasites. In addition to its indispensable role in innate immunity, it is also involved in pathogen clearance during the effector phase of adaptive immunity. The most effective way of killing the invader is the lysis by the membrane attack complex, which is formed by the terminal complement components upon the activation of the cascade. Not all pathogens are lysed in this way, most of them can be phagocytosed after being opsonized by various complement activation products. The most important complement-derived opsonins are; C1q, the first component of the classical pathway; MBL, initiator of the lectin pathway; and the C3-derived activation fragments, including C3b, iC3b and C3d. These proteins and protein

fragments all serve as ligands to their corresponding complement receptors (Erdei et al. 1991).

Complement receptors present on various immune cells can mediate different effector functions (Fig. 1). Pathogen microbes entering the body become opsonized by complement proteins, mainly by the larger fragments of C3, which helps in the elimination of antigens by engaging complement receptors (Erdei et al. 2016).

The integrins

The integral membrane proteins, *integrins*, can be viewed as molecules connecting the extracellular matrix to the cytoskeleton. Integrins are heterodimeric receptors consisting of one α and one β subunit. These receptors are known to be involved in various cellular processes associated with cytoskeletal remodelling, which are necessary for adherence, phagocytosis and migration (Hynes 2002). The complement receptors *CR3* (CD11b/CD18, $\alpha_M\beta_2$, Mac-1) and *CR4* (CD11c/CD18, $\alpha_X\beta_2$, p150,95) belong to the leucocyte-restricted *β_2-integrin family*. The β_2-integrins contain a common CD18 β-chain associated with respective α-chains: CD11b in CR3 and CD11c in CR4.

A defect in the function of CR3 and CR4 can lead to inadequate apoptotic cell clearance and thereby increase the susceptibility to autoimmune diseases, like systemic lupus erythematosus (SLE) in humans (Rosetti & Mayadas 2016). The deficiency of CD18 is also known to be associated with leukocyte adhesion deficiency (LAD), which is characterized by severe and recurrent bacterial infections (Hynes 2002).

The natural ligand of CR3 and CR4 is the inactivated fragment of C3: iC3b (Fig. 1). Fibrinogen is another major ligand of β_2-integrins, which is an important regulator of inflammation (Davalos & Akassoglou 2012). The ligand binding affinity of *β_2*-integrin depends on their activation-dependent *conformational changes*. Upon stimuli, the extracellular domains undergo structural rearrangements from a bent, inactive state into an extended, ligand binding conformation (inside-out signalling). The ligand binding of integrins stabilizes the high affinity conformation and initiates the outside-in signalling, which modulates various cellular functions such as apoptosis, cytotoxicity, proliferation, cytokine production, antigen presentation and gene activation (Dupuy & Caron 2008).

In humans, CD11b and CD11c are simultaneously present on a wide variety of leukocytes, but they are expressed on phagocytes in the greatest number (Erdei et al. 2017; Nagy-Baló et al. 2020). Moreover, CD11c is a generally accepted myeloid marker in humans. CR3 and CR4 are expected to mediate similar functions due to their structural homology and overlapping ligand specificity. They have an 87% sequence homology in their extracellular domains, but their intracellular tails, important for signal transduction and connection with the cytoskeleton, represent only 56% similarity (Ross et al. 1992). Based on these differences and their parallel expression on human phagocytes, we hypothesize that there is a "division of labour" between these two receptors, resulting in different activity. Moreover, the results obtained in a mouse system are generally accepted as an equivalent to human functionalities in many cases. However, these data cannot simply be translated to the human system due to differences in tissue distribution, receptor number and the resulting differences in functions. Until recently, human studies have been severely hampered for many reasons. First, the experiments were difficult to perform in the absence of sufficiently specific antibodies. Second, CR3 and CR4 were targeted in parallel; hence, the results of experiments cannot be clearly linked to only one of them. Third, the rapid recycling of integrins from the intracellular pool to the cell surface caused an additional methodological problem (Bretscher 1992). Due to deficiencies in the experimental methods used, the *individual role of CR3 and CR4 has*

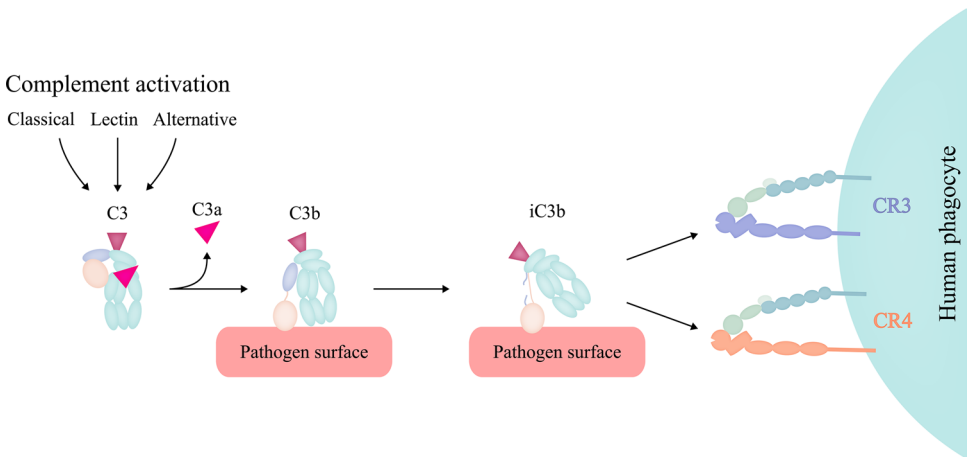

Fig. 1 *Generation of complement-derived ligand iC3b for CR3 and CR4 β_2-integrins*. The complement cascade—activated by either the classical, lectin-dependent or alternative pathway—leads to the activation of the central component C3. The larger cleavage product C3b can be further processed to generate iC3b, which is the main ligand of complement receptors CR3 (CD11b/CD18) and CR4 (CD11c/CD18). CR3 and CR4 are simultaneously expressed on macrophages and dendritic cells

not been tested so far. Our aim was to reveal the different functions of CR3 and CR4 on normal human phagocytes.

Myeloid cells

The main cellular elements of the innate immune system are *neutrophil granulocytes* (Neu), *monocytes* (Mo), *dendritic cells* (DC) and *macrophages* (M). The major role of these myeloid cells is the recognition of pathogens and the initiation of an immune response. Although macrophages and dendritic cells are both phagocytes and professional antigen-presenting cells, their functions are fundamentally different. Macrophages and immature dendritic cells (imDCs) take up pathogens at the site of infection, and while macrophages efficiently eliminate pathogens locally, imDCs transport antigens to the lymph nodes. The antigen-induced maturation rapidly stimulates the expression of costimulatory molecules, such as CD80 and CD86 that is indispensable for a mature DC phenotype capable of stimulating naive T cells (Banchereau et al., 2000). Activated macrophages produce reactive intermediates to destroy pathogens and cytokines establishing an inflammatory environment.

Expression of CR3 and CR4 on myeloid cells

The complement receptors CR3 and CR4 are expressed on monocytes, macrophages, dendritic cells, neutrophils and natural killer cells, and recently they have been detected on certain B lymphocyte populations in human (Erdei et al. 2017; Nagy-Baló et al. 2020).

Studying the expression of CD11b and CD11c, we found that both molecules are expressed constitutively by human phagocytes. We assessed the absolute number of CD11b and CD11c on monocyte-derived dendritic cells (MDC), monocyte-derived macrophages (MM), Mo and Neu by a bead-based technique (Table 1) (Erdei et al. 2017; Sándor et al. 2016). Results demonstrated that the number of CR3 and CR4 differs among the studied cell types. The ratio of CD11b:CD11c was 1.2 for MDC, 1.7 for MM, 7.1 for Mo and 13.4 for Neu, showing a strong shift in favour of CR3 in the case of Mo and Neu, whereas on MMs and MDCs the CD11b/CD11c ratio is close to 1:1. The remarkable differences in the number and ratio of CR3 and CR4 probably contribute to the cell-type-specific functional differences discovered in our experiments. In addition, a low ligand concentration might lead to a competition, resulting in the dominance of one receptor over the other. The differences in the CD11b/CD11c ratios also suggest that the functions mediated by CD11c are the most instrumental in the case of MDCs.

Table 1 Number and ratio of CD11b and CD11c expressed by normal human phagocytes ($\times 10^3$) (Erdei et al. 2017)

	Mo	MM	MDC	Neu
CD11b	50 ± 8	310 ± 62	247 ± 21	47 ± 6
CD11c	7 ± 3	185 ± 40	204 ± 25	3,5 ± 2
Ratio of CD11b and CD11c	*7.1*	*1.7*	*1.2*	*13.4*

Although an enhanced expression of β_2-integrins was observed in inflammatory conditions, their exact role in human phagocytes has not been studied in detail. We estimated the expression of CD11b and CD11c on MMs and MDCs upon LPS stimulation (Lukácsi et al. 2020a, b). We observed a time-dependent change in the appearance of these receptors. After 30 min of LPS treatment, the amount of CD11b decreased, while the expression of CD11c did not change on the surface of MMs and MDCs. 24 and 48 h later, the amount of CD11b decreased further on both cell types. At the same time, the amount of CD11c decreased on MMs but increased significantly in MDCs. These data suggest a cell-type-specific regulation of β_2-integrin expression.

The ligand binding capacity of β_2-integrins is under conformational regulation. We investigated the conformational state of the receptors with the mAb24 antibody that recognizes an epitope only present in the active conformation of CD18 (Sándor et al. 2013, 2016). Data showed that CR3 and CR4 are in an open, ligand binding conformation on the cell membrane under our experimental conditions and the number of active receptors was enhanced after 30 min of LPS treatment, due to the increased turnover of the receptors (Lukácsi et al. 2020a, b).

Function of CR3 during HIV-1 infection

Dendritic cells are known for their importance in forming a bridge between the innate and adaptive immune systems, but as being one of the main targets of the sexually transmitted human immunodeficiency virus (HIV) in genital mucosa, they are also responsible for the transmission of the virus to $CD4^+$ T cells. To infect host cells, the HIV-1 envelope protein (Env) first binds to the CD4 molecule and then to chemokine co-receptors CCR5 or CXCR4. DCs are predominantly susceptible to the R5 virus strains, which use the CCR5 chemokine receptor for entry. ImDCs can be productively infected with R5 viruses, and the produced virus is capable of infecting T cells. Although mature DCs do not produce viral particles, they are still able to transmit HIV to T cells.

HIV activates the host complement system by the classical, alternative and lectin pathway, which results in the opsonization of the virus by complement fragments, for example, iC3b (Eberbichler et al. 1991; Yefenof et al. 1994). Since HIV

particles activate the complement system in infected patients and are coated with complement protein fragments at the site of infection, imDCs could be the first target of the opsonized virus. We aimed to clarify whether CR3 is involved in the uptake and transmission of complement-opsonized HIV.

In our experiments, normal human imMDCs were infected with R5 HIV-1 primary isolate 92UG037 (Bajtay et al. 2004). We demonstrated that imMDCs express both CR3 and CR4, and to investigate the *binding* of the opsonized HIV-1, virus particles were opsonized with specific IgG (HIV_{IgG}) or IgG and complement (HIV_{IgG+C}). As a result of classical pathway activation of the complement system, strong C3 deposition was detected in the HIV_{IgG+C} samples. We found that binding of HIV_{IgG+C} was higher to imMDCs than HIV_{IgG}. When testing the *infection* of imMDCs by opsonized HIV-1, we demonstrated that the opsonization of HIV-1 with complement caused a tenfold higher productive infection of imMDCs than the non-opsonized HIV-1. The key role of CR3 in the efficient uptake of complement-opsonized HIV-1 by imMDCs was proved by using CD11b specific mAbs, as the preincubation of imMDCs with anti-CD11b reduced the binding and decreased the productive infection to the control level.

In this study, we proved that CR3 plays a crucial role in the productive infection of imMDCs by C3-opsonized HIV-1. Our hypothesis was that the binding of complement-coated HIV to CR3 may induce specific signalling cascades that direct HIV to compartments which are favourable for productive infection.

In good agreement with our results, it has been found that the complement opsonization of R5 and X4 HIV resulted in a threefold to fivefold increase in the infection of imDCs compared to the non-opsonized virus (Bouhlal et al. 2007). Enhancement of infection was dependent on CR3 as was demonstrated by using blocking Abs.

Recent data provide an explanation for the possible mechanism underlying the infection enhancing effect of CR3 (Ellegård et al. 2014). The difference in replication activity of non- and complement-opsonized HIV comes from a change in the triggered antiviral response, namely that complement opsonization decreased the production of proinflammatory cytokines and altered the signalling profile. Targeting CD11b, with complement-opsonized HIV or CD11b specific mAb, led to a suppressed inflammatory and antiviral response and increased viral production. In accordance with our previous results, others' data also confirmed that complement opsonization leads to the modulation of DC functions via CR3, serving an important immune escape mechanism used by HIV-1 in vivo.

Role of CR3 and CR4 in adherence and migration

Phagocytes are able to adhere to antigen surfaces and extracellular matrix components—e.g. fibrinogen, via β_2-integrins. The adhesion capacity of myeloid cells has a particular importance in infection and pathologic conditions. Leukocyte-specific CR3 and CR4 β_2-integrins are involved in *cellular adherence* and *migration*, and they are often assumed to perform similar functions; thus, the aim of our work was to determine their participation in these functions.

The adherence of normal human Mos, MDCs and MMs to fibrinogen was investigated. Fibrinogen is an important ligand of β_2-integrins, as it is deposited at the sites of injury and induces the adhesion and migration of leukocytes in inflammatory tissues (Flick et al. 2004).

Georgakopoulos et al. also showed that the involvement of CR3 and CR4 in adhesion of Mos to fibrinogen is dependent on the experimental conditions like the type of stimuli or conditions (Georgakopoulos et al. 2008). However, the exact role of CR3 and CR4 of human Ms and DCs has not been clarified earlier.

A widely used method to characterize cellular adherence is the *classical microscopic measurement*, where the number of adherent cells is counted on a fibrinogen-coated surface. Recent technical developments allow the measurement of cell adhesion by *single cell technologies*, or by a variety of *surface sensitive label-free optical biosensors* (Epic BenchTop) (Orgovan et al. 2014; Salánki et al. 2014). Using these techniques, we can obtain a deeper insight into the process of cellular adherence and spreading. In order to apply the state-of-the-art label-free biosensor equipment, we started a fruitful collaboration with Róbert Horváth, Nanobiosensorics Lendület Group of MTA, and with Bálint Szabó, Department of Biological Physics at Eötvös Loránd University. They are well equipped to monitor the surface adhesion kinetics and adhesion force of living cells in a completely label-free system with extremely high resolution. These techniques offer opportunity for real-time analysis of the force of cellular adherence and the rate of cellular spreading, which we successfully adapted to our experimental system (Lukácsi et al. 2020a, b; Sándor et al. 2016). Our aim was to further explore this area of classic and newly developed techniques in combination. The static end-point adhesion assay measures the number of cells adhering to the substrate, while the computer-controlled micropipette assay measures the strength of adhesion of the same cells.

To study the individual role of CR3 and CR4 in the adhesion to fibrinogen, we blocked either CD11b or CD11c by specific mAbs. Blocking CD11c decreased the number of adhering MDCs and Mos significantly and slightly blocked the adherence of MM as measured by classical microscopic

evaluation. Blocking CD11b had no effect on MDMs and MDDCs, but slightly decreased the number of adherent Mos (Sándor et al. 2016). Applying the state-of-the-art biophysical techniques, we confirmed that CD11c had a defining role in cellular adherence to fibrinogen. Furthermore, we found that blocking CD11b significantly enhances the attachment of MDCs and MMs to fibrinogen, demonstrating a competition between CD11b and CD11c for this ligand. These results demonstrated that in cellular adherence to fibrinogen the role of CR4 is dominant.

Next, we investigated the adhesive capacity of CR3 and CR4 in LPS-induced inflammatory conditions (Lukácsi et al. 2020a, b). LPS has been shown to activate myeloid cells, enhance their inflammatory cytokine and antimicrobial product synthesis, elicit their migration and induce the maturation of DCs. We found that in the case of LPS-treated MMs and MDCs, both CR3 and CR4 participated in cell adhesion, as specific antibodies equally decreased the adhesion to fibrinogen using classical microscopic method.

Employing the micropipette method, we observed a significantly reduced adhesion force by LPS-treated MDCs compared to untreated control cells. In the case of LPS-activated MMs, however, we observed only a slight decrease in the strength of attachment. After using ligand binding site-specific antibodies, we found that both anti-CD11b and anti-CD11c treatment weakened the adhesion to fibrinogen-coated surfaces. Whereas in MMs the extent of inhibition was similar for both blocking antibodies, in the case of MDCs the blocking of CR4 resulted in a stronger inhibition, than the blocking of CR3.

Based on the absolute number of cell surface receptors, we assume that there is a competition for fibrinogen ligands between CR3 and CR4. Receptors on MMs and MDCs are present in high amounts, but Mos have markedly fewer receptors; therefore, under physiological conditions both receptors attend in adherence on Mos. In the case of MMs and MDCs, however, LPS treatment altered the cell surface expression of these receptors differently, which influenced their participation in adherence. On MMs, the number of both receptors decreased providing ligands for both CR3 and CR4. In the case of MDCs, the amount of CR4 significantly increased, whereas the expression of CR3 is diminished, resulting in the dominance of CR4 in the adherence to fibrinogen. Our results suggest that the ratio of ligands to cell surface receptors is the main regulator of adherence.

The migration of immune cells to the site of infection is a crucial step to develop a proper immune response leading to pathogen elimination. Mos and Neus can sense the chemoattractant molecules produced by the tissue resident macrophages and gather near the site of the infection. To leave the blood vessel, leukocytes need to establish a series of cell–cell and cell–substrate contacts. The growing chemokine concentration triggers the integrins' inside-out signalling, making the leukocytes stop and adhere in an integrin-dependent manner. The ligand binding of integrins strengthens the adhesion (outside-in signalling) and initiates cell spreading, intravascular crawling and finally transmigration (Ley et al. 2007).

We experienced that depending on the cell type and the activatory stimuli the participation of CR3 and CR4 in adhesion may be different. We set out to investigate that the role of CR3 and CR4 is transmigration using antibodies specific to the ligand binding site of the receptors in a transwell assay set-up (Lukácsi et al. 2020a, b). Our results showed that both CR3 and CR4 participate in the migration of non-treated and LPS-treated MMs and MDCs as well. In the case of both non-treated and LPS-activated cells, blocking with anti-CD11b resulted in a stronger inhibition comparing to the effect of anti-CD11c, particularly in the case of non-stimulated MDMs.

Role of CR3 and CR4 in phagocytosis

CR3 and CR4 are widely accepted to play an important role in the phagocytosis of pathogen microbes; thus, we studied their individual roles in the phagocytosis of iC3b-opsonized pathogen-derived particles. Analysing the expression and ligand binding ability of CD11b and CD11c, we found that iC3b bound strongly to both β_2-integrins on MDCs. Surface-bound iC3b was internalized by imMDCs within 10 min (Sándor et al., 2013). After treating the cells with iC3b, we found co-localization with CD11b and CD11c as well, demonstrating that both CR3 and CR4 are able to bind iC3b as a ligand. We showed that iC3b bound to CR3 and CR4 stimulate neither the differentiation of MDCs, nor the production of inflammatory cytokines.

Next, we aimed to clarify the role of these receptors in the phagocytosis of iC3b-opsonized particles. The uptake of iC3b-opsonized microbes was measured in imMDCs after treatment with anti-CD11b or anti-CD11c antibody, respectively. We used heat-inactivated *Saccharomyces cerevisiae* and *Staphylococcus aureus* (*S. aureus)* microbes, which are known to fix C3-fragments on their surface, mainly iC3b. We found that treatment with anti-CD11b significantly decreased the phagocytic capacity of imMDCs for both iC3b-opsonized yeast and bacteria. Incubation with anti-CD11c did not affect the uptake of the complement-opsonized microbes. We confirmed our findings obtained by the blocking antibodies using CD11b and CD11c RNA-silenced MDCs; the downregulation of CD11b decreased the uptake of particles, while CD11c downregulation had no effect on phagocytosis.

To analyse the fate of CR3 and CR4 during uptake of iC3b-opsonized microbes, we followed the route of opsonized *S. aureus* by confocal microscopy. We found that

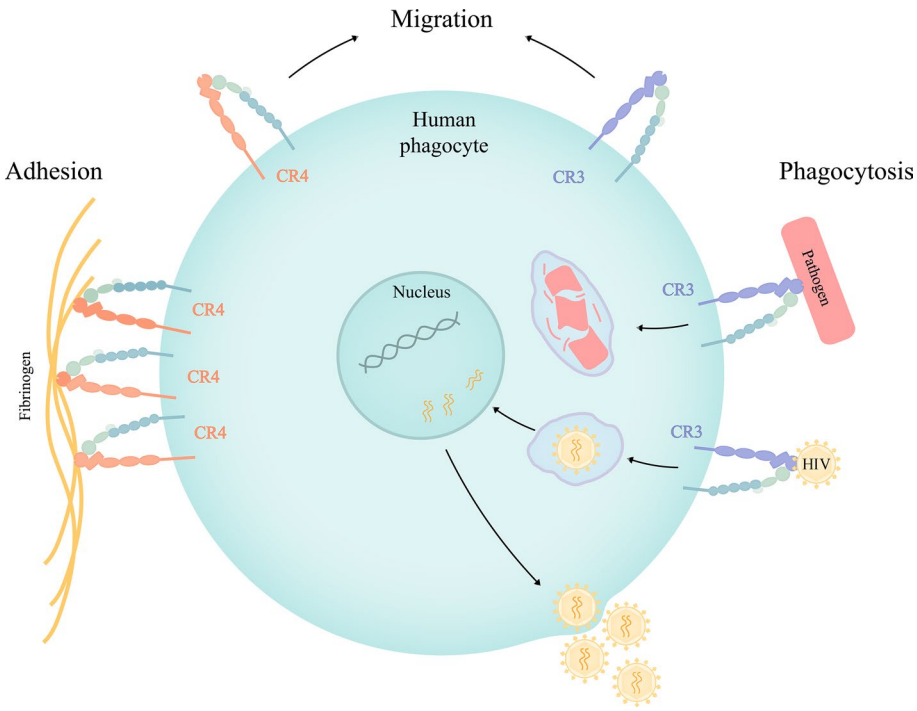

Fig. 2 *CR3- and CR4-mediated functions in human phagocytes.* CR3 and CR4 mediate different functions in human phagocytes. CR3 is the dominant receptor to mediate uptake and digestion of iC3b-opsonized bacteria by human phagocytes. Binding to CR3 strongly enhances the phagocytosis and the productive infection of complement-opsonized HIV. The main role of CR4 on macrophages and dendritic cells has been demonstrated in the process of adherence to fibrinogen. CR3 and CR4 participate equally in the migration of macrophages and dendritic cells

CR3 and CR4 co-localize in the cell membrane of untreated imMDCs, but after the cells were incubated with opsonized *S. aureus*, the CD11b almost completely transferred into the cytoplasm, whereas CD11c remained mainly in the cell membrane. These data proved the dominance of CR3 in the phagocytosis of iC3b-opsonized *S. aureus* and yeast particles.

Earlier studies do not clearly distinguish between the binding, uptake and the digestion of microbes, although the two processes do not necessarily occur in parallel. Most of the pathogens taken up by phagocytes are degraded in the phagolysosomes, but during the investigation of the phagocytosis of HIV, we observed that the productive viral infection by imDCs increased due to the CR3-dependent uptake of the virus. Pathogens can exploit CR3 to evade the host DC, like in the case of HIV, where complement-opsonized particles were shown to enhance infection (Bajtay et al. 2004; Lukácsi et al. 2020a, b).

In our next experiments, we attempted to study the uptake and the digestion separately (Lukácsi et al. 2017). Heat-inactivated *S. aureus* was opsonized with iC3b and labelled with the pH-sensitive pHrodo Green or Alexa 488 dye. The pH-sensitive dye becomes highly fluorescent only in an acidic environment; consequently, bacteria are only visible when entering into acidic phagolysosomes. The phagocytic and digestive capacity of Mos, MMs, MDCs and Neus was measured separately using *S. aureus* conjugated with the two different dyes. To determine the participation of CR3 and CR4 in the uptake of opsonized particles, cells were pre-treated with CD11b- and CD11c-specific antibodies. We demonstrated in all human phagocytes that only CR3 takes part in the ingestion of iC3b-opsonized *S. aureus*, while CR4 is only responsible for the binding of the pathogen.

In these studies, we demonstrated that both CR3 and CR4 are involved in the binding of iC3b-opsonized particles. However, the binding to CD11c alone is not sufficient to initiate phagocytosis, rather CD11b plays a key role in the uptake and digestion of iC3b-opsonized bacteria by human phagocytes.

Discussion

Our group is among the frontrunners who started to dissect the role and function of the β_2-integrin complement receptors CR3 and CR4 on human myeloid cells (Fig. 2). Recently, we have proved that in human phagocytes CR3 is dominantly involved in the uptake of iC3b-opsonized particles, while CR4 has only a supporting role. Regarding adhesion to fibrinogen, however, we demonstrated that CR4 plays the major role in the case of human phagocytes. Applying the state-of-the-art biophysical methods has exploitable opportunities in store for the analysis of cell functions, like adhesion under physiological and pathological conditions. For the analysis of cellular adhesion and spreading, optical biosensors and computer-controlled micropipette can be used. These techniques—in addition to the widely used classical microscopic measurement—helps to better understand the process of cellular adherence and spreading.

We demonstrated that an inflammatory milieu can alter β_2-integrin expression. Moreover, we hypothesize that CR3

and CR4 may have a different, cell-specific trafficking route, which may also affect the function of these receptors. Hopefully, further studies will reveal the complexity of these interactions clarifying the exact molecular mechanisms and specific signalling processes mediated by CD11b and CD11c.

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