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Fc Receptors on CD4+ T cells: A Role in Cytokine Storm and Antibody Dependent Enhancement

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Abstract

Antibody binding to infectious agents results in the formation of Immune Complexes (ICs) and Engaging Fc Receptors (FcRs), which contribute to the enhanced immune memory. FcRs interaction with viral-ICs facilitates viral entry via a process defined as Antibody Dependent Enhancement (ADE) and this interaction also release proinflammatory cytokines. ADE is a known safety Risk for Ribonucleic Acid (RNA) virus vaccines. ADE has been reported in Corona virus infection, where virus utilizes CD32, a FcR. The nucleic acids-based vaccines such as adenovirus vector, Short Interference RNA (siRNA) and Messenger RNA (mRNA) that are being used in Coronavirus disease 2019 (COVID-19) vaccination could possibly trigger nucleic acid sensing in lymphocytes. It will be more so if multiple administration of vaccine is required to acquire protection. How these vaccines will impact the nucleic acid sensing pathways is a matter of critical attention. In this review, I summarize recent advances in Fc signaling and the role of FcRs expressed on the CD4+ T cells that could play a role in the nucleic acid-based vaccines. Additionally, I will address possible co-synergistic responses between FcR and Nucleic-Acid Sensing Toll-Like Receptors (NA-TLRs) signaling that could lead to enhanced viral entry and excessive production of proinflammatory cytokines.

Introduction

Generation of high titer neutralizing antibodies is a desired end-point in the vaccine development. Antibodies binding to target antigens result in the formation of Immune Complexes (ICs), which trigger effector Functions in Fc Receptors (FcRs) bearing cells in particular lymphocytes. These receptors are well studied in innate cells and B lymphocytes, however their role in CD4+ T cells has starting to emerge. Antibodies produced against pathogenic antigens during the vaccination facilitate FcR ligation on immune cells, resulting in the massive production of inflammatory cytokines. Antibody Dependent Enhancement (ADE) is a concomitant phenomenon observed in the Ribonucleic Acid (RNA) viral vaccines i.e. HIV-1, RSV, Ebola, Dengue, SARS and MERS. In HIV-1 infection, both neutralizing and non-neutralizing antibodies cause ADE in macrophages. Cells such as monocytes, macrophages and dendritic cells that express FcRs has been implicated in the ADE, but the participation of CD4+ T cells has not been examined. The majority of vaccine efforts for corona virus disease 19 (COVID-19) have targeted Spike protein. Antibodies against the Spike protein contribute to the ADE. A neutralizing antibody targeted to Receptor Binding Domain (RBD) of Spike protein from Middle East Respiratory Syndrome (MERS), facilitated the conformational changes and utilized FcR (CD32a) for viral entry [1]. A key role for monocytes and macrophages is suggested in the inflammatory responses observed in COVID-19 [2]. Even though, CD4+ T cell lymphopenia is observed both in HIV-1 and COVID-19 infection, thus far, ADE has not been examined in either CD4 or CD8 T cells. A contributing factor to this disengagement is the current accepted paradigm that the CD4+ T cells do not express FcRs [3,4]. This notion is incorrect and is not experimentally validated. Several earlier studies have supported the presence of FcRs on CD4+ T cells and have hypothesized their role in modulating CD4+ T cell responses [5]. In 2011, we reported phosphorylation of T Cell Receptor (TCR) proteins in the human CD4+ T cells and Jurkat cell line, in response to *in vitro* treatment with ICs [6]. Since then we and several other groups have confirmed the presence of FcRs and signaling mediated by these receptors in providing a costimulatory signal that result in the activation and differentiation of human naïve CD4+ T cells [6-

8]. The costimulation from FcR signaling results in the production of proinflammatory cytokines by human $CD4^+$ T cells, that could possibly trigger cytokine storm [9,10]. Now several other groups have shown the presence of various FcR proteins on the human $CD4^+$ T cells i.e. FcγRIIa, FcγR1, and FcμR. Upon ligand binding, the FcR signaling in these cells produce IFN-γ [7-12]. We thus commend that it is important to examine the contribution of FcR signaling in the adaptive immune responses manifested by T cells. In the human airways, epithelial cells are protected by humoral proteins such as collectins, defensins and antibodies. Toll-Like Receptor (TLR) signaling in lung epithelium result in the production of anti-microbial peptides for protection. Thus, it is important to consider the outcome from nucleic acid-based vaccines currently being developed for COVID-19. How these new vaccines will enhance the nucleic-acid sensing in the endosomes and on the cell surface remains unknown. It is thus essential to examine the time of retention of these RNA and DNA vectors in the human system both in tissue and circulation. In this review, I will summarize and evaluate the accumulating evidence for the role of FcRs, Complement Receptors (CRs) and nucleic-acid sensing toll-like receptors (NA-TLR signaling in enhancing antibody mediated viral entry into $CD4^+$ T cells and the consequence that follows.

Fc receptors on $CD4^+$ T cells: Participation in ADE development?

Recognizing and fully understanding the expression pattern of various receptors on cell types and their participation in the ADE during RNA viral infection is critical for vaccine safety. Both FcR and CRs contribute to the process of ADE. These receptor proteins are critical to the viral entry, and they also contribute to the cell death and viral spread in the cell types such as monocytes, macrophages and dendritic cells. A role for CD32a in ADE was recently confirmed in corona virus infection [1]. FcRs are expressed by the activated $CD4^+$ T cells, and hence their role in ADE require validation. It is argued that ADE is an event of innate cells such as macrophages and monocytes. Enhanced viral entry via ADE will likely contribute to the lymphopenia, observed for $CD4^+$ and $CD8^+$ T cells during viral infection. In HIV-1 infected patients, loss of $CD4^+$ T cells correlates with increase in the number of IC bound $CD4^+$ T cells, which suggest that the FcR signaling is an important contributor to the observed cell death [13]. In HIV-1 patients, $CD4^+$ T cell subset is the largest subpopulation that binds to labeled ICs, when compared to $CD19^+$ B cell and $CD8^+$ T cell subset (unpublished observation, data available on request). The viral particles of SARS-CoV-2 RNA are observed in $CD4^+$ T cells. The pro inflammatory responses that are being observed in children infected with COVID-19 could be a result of FcRs engagement by virus-antibody complexes. One possible explanation for inflammation observed in the children is the production of proinflammatory cytokines by activated $CD4^+$ T cells [14]. Thus, it is not that far-fetched to suggest that the Fc mediated signaling in $CD4^+$ T cells contributes to the proinflammatory cytokine production, which then enhance the viral pathology [8-10]. IFN-γ is a well-recognized proinflammatory cytokine that is produced upon CD16a signaling in $CD4^+$ T cells and both moderate and high secretors are observed [9]. Now both, CD32 and CD64 are shown to produce IFN-γ [8,11].

ICs activate classical complement pathway and the byproducts of this pathway are now implicated in COVID-19 infection [15]. Complement receptor proteins are expressed by $CD4^+$ T cells, and upon activation from ligand binding, these cells produce inflammatory cytokines. These cytokines do also contribute to the cellular differentiation [16]. A role for complement receptors, in particular CR2 has been suggested in enhancing the HIV-1 infection [17]. The classical complement pathway is triggered by the binding of ICs to C1q and this ultimately leads to the formation of C5b-9 complex on the cell surface. C5b-9 is a pleotropic signaling molecular protein complex, which triggers the inflammation, apoptosis, and tissue necrosis [18]. Sublytic amounts of C5b-9, the terminal complex of the late complement pathway triggers cellular apoptosis. Apoptosis has been suggested as a contributor to the lymphopenia observed in COVID-19 infection. The deposition of higher amounts of C5b-9 on cells leads to the cellular lysis. We confirmed these events *in vitro* by assembling C5b-9 using purified human late complement proteins on the membranes of purified human $CD4^+$ T cells and in Jurkat cells [6]. Sublytic amount of C5b-9 deposition on the cells includes protein synthesis, DNA synthesis, arachidonic acid metabolism, and activation of polymorphonuclear leukocytes [19]. C5b-9 enhances the production of endothelial intercellular adhesion molecule-1 (ICAM-1), E selectin, interleukin 8 (IL-8), and monocyte chemo-attractant protein-1 (MCP-1). Other notable events that are trigged by C5b-9 are the activation of cell cycle related genes p53, p21, growth arrest DNA damage-45 (GADD45), checkpoint kinase-1 (CHK-1), and CHK-2, mitogen activated protein kinase (MAPK) p38, janus kinase (JAK) 1, signal transducer and activator (STAT) 3, and STAT 4 in endothelial cells [18,20-23]. IC treatment along with sublytic C5b-9 of human $CD4^+$ T cells enhances RNA transcripts from nuclear factor kappa B (NF-kB), Burton's tyrosine kinase (Btk) and activator protein 1 (AP-1) resulting in the production of pro-inflammatory cytokines i.e. IL-1a, IL-1b, IL-10, and IL-12a [10]. These events also occur in cardiac myocytes and muscle cells in response to C5b-9 deposition [24,25]. Both sublytic and lytic amount of C5b-9 deposition does occur on $CD4^+$ T cells, which leads to the inflammatory responses and cell death leading to the viral spread. Both classical complement activation and direct activation of complement by viral particles will enhance the assembly of C5b-9. Thus, it is safe to suggest that complement activation participates in enhancing viral pathology in T cells.

Antibody Dependent Cellular Cytotoxicity (ADCC) is exhibited by Natural Killer (NK) cells. Emerging studies have now shown a role for CD16a in driving ADCC in $CD4^+$ T cell population. A chimeric construct including the high-affinity CD16 (FCGR3A) V158 variant, CD8a hinge, and transmembrane domains, along with signaling domains from CD3z and 4-1BB TNF Receptor Superfamily Member 9 (TNFRSF9), forming a chimeric receptor termed CD16V-BB-z triggered cell death upon the engagement of antibodies [26]. Forced expression of γ-chain of FcR, induced the expression of CD16a in $CD4^+$ T cells and this resulted in enhanced ADCC, establishing a role for this pathway in cell death [26-28]. In our studies that examined the RNA transcript levels, we observed a strong overexpression of granzyme A upon FcRs engagement by ICs, compared to CD28 (Chauhan, unpublished observation, NCBI accession no. GSE127664). Thus, it can be safely stated that both FcR signaling and complement activation contribute to the viral spread and lymphocytic cell death causing lymphopenia. Lesson could be drawn from RV-144 vaccine trial for HIV-1 infection, where a role for FcRs was observed. Decreased risk of infection in this trial was attributed to Fc-mediated functions. Still a role of FcR expressing $CD4^+$ T cells in viral pathologies has yet to be examined. FcR bearing $CD4^+$ T cells population would be critical in understanding COVID-19 pathology.

Toll-like Receptor's on $CD4^+$ T cells: Contribution to ADE

Pattern recognition receptors (PRRs) in particular NA-TLRs are critical players in the viral infections. In humans, TLR3 binds to dsRNA, and ssRNA is recognized by TLR8. The nucleic-acid sensing is extensively studied in innate cell responses. TLR9 signaling in Plasmacytoid Dendritic Cells (pDCs) upon the ligation of CD32 by its ligand ICs composed of dsDNA, drives the Interferon Signature Genes (ISG) expression. Nucleic-Acid Containing Immune Complexes (NA-ICs) engage FcRs on the cell surface, which are then internalized to endosomes or lysosomes, where the nucleic-acid is recognized by NA-TLRs. Such events trigger signaling, leading to the secretion of proinflammatory cytokines. In a landmark study in 2006, it was shown that when TLR9 is forced to relocate to the cell surface, TLR9 recognized altered nucleic acids and CpG Deoxynucleotide (CpG ODN) on the cell surface [29]. Cellular trafficking events are noted during TLR 9 movement. TLR9 is tracked through endoplasmic reticulum and lysosomes, post ligand binding [30]. Acidification of lysosomes and endosomes by drugs such as chloroquine and bafilomycin AI abrogates TLR9 signaling [31]. The natural ligands that forces the NA-TLRs to the cell surface has never been identified. In a 2017 paper, we showed that indeed the CD16a ligation with ICs isolated from human plasma, induces the overexpression of NA-TLRs and forced their relocation to the cell surface in human $CD4^+$ T cells [32]. The three NA-TLRs in $CD4^+$ T cells that are activated by plate-bound ICs localized with CD16a on the cell surface and this triggered secretion of several key proinflammatory cytokines [32,33]. In COVID-19 infection, TLR3 and TLR8 that are present on the cell surface will facilitate direct binding of virus particles, which will lead to the cellular activation, enhanced levels of proinflammatory cytokines production and this will also contribute to the ADE. The nucleic acid-based vaccines could also contribute to enhanced nucleic-acid based signaling events from the endosomes. The mRNA introduced into the cells upon vaccination exists for at least two days, which is sufficient time for NA-TLR signaling. FcR signaling when compared to CD28 showed 20-fold increase in TLR3 and TLR8 RNA transcripts [10,32]. A similar increase was observed at protein level (Figure 1) [10,32]. A statistically significant upregulation of Myeloid Differentiation Factor 88 (MyD88) and Nuclear Factor Kappa B (NF-kB) RNA transcripts upon FcγR signaling were also noted [10,32]. In human $CD4^+$ T cells, drug hydroxychloroquine disrupted the colocalization of all the three NA-TLRs examined with ICs bound to FcRs on the cell surface [32]. In these cells, ICs by triggering FcR signaling induced the overexpression of MyD-88, a signaling protein required for TLR8 signaling and this protein migrated towards the cell surface [32].

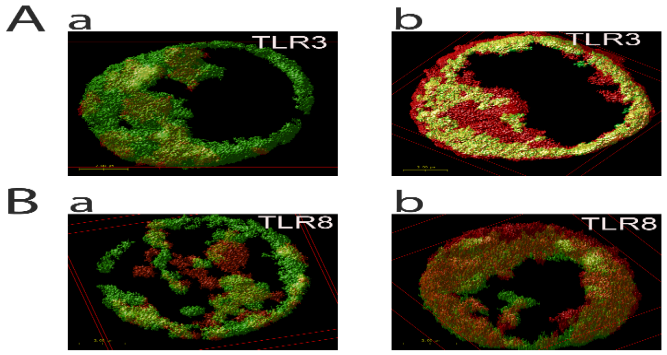

Figure 1: STED confocal microscopy images of human $CD4^+$ T cells stimulated with anti-CD28 or FcR cosignaling in the presence of suboptimal anti-CD3 (0.25 μg/ml). Co-staining for FcRs by binding of Alexa Fluor 488 labeled ICs (green) and TLR3 (red) (A). Cells costimulated via anti-CD28 (1 μg/ml) (Aa) and via FcR cosignaling using plate-bound ICs (Ab). Cells co-stained for FcR by binding of Alexa Fluor 488 labeled ICs (green) and TLR8 (red) (B). Cell costimulated via anti-CD28 (Ba) and FcR cosignaling upon ICs ligation (Bb). FcR signaling relocates both TLR3 and TLR8 to cell surface.

Recycling of TLRs between subcellular compartment and to the cell membrane is governed by various accessory proteins. Trafficking of TLRs3, TLR7, and TLR9 from endoplasmic

reticulum to endosomes is essential for TLR signaling [34]. A glycoprotein unc-93 homologue B1 (UNC93B1) is the only recognized protein that interacts and contributes to the NA-TLRs trafficking from endoplasmic reticulum to endolysosomes. Syk kinase contributes to the microorganism mediated intracellular internalization of TLR4. Thus, it is not far-fetched to suggest that Syk activation contribute to the movement of NA-TLRs in the $CD4^+$ T cells [10,32].

The viral nucleic acid in the cytoplasm is recognized by Retinoic-Acid Inducible Gene I (RIG-I) Melanoma Differentiation-Associated Gene 5 (MDA5) and nucleotidyltransferase cyclic GMP-AMP Synthase (cGAS). Signaling complex formed by these proteins, recruit adaptors including TIR-domain-containing adaptor proteins, Mitochondrial Antiviral-Signalling Protein (MAVS), TIR-Domain-Containing Adapter-Inducing Interferon-B (TRIF) and stimulator of interferon genes Protein (STING) triggers activation of downstream adaptor molecule MyD88, which leads to the activation of the transcription factor NF-κB and Interferon Regulatory Factor 3 (IRF3) (Figure 2). These events lead to the production of type I Interferons (IFN-α /β) and pro-inflammatory cytokines. In $CD4^+$ T cells, these proteins are upregulated upon FcR signaling [10]. We suggest that the formation of joint signaling complex of key receptors such as FcRs, CRs, and TLRs in activated $CD4^+$ T cells, will drive the hyperactivation of cellular responses (Figure 1) [5,6,32,35]. Cytoconjugation among antigen presenting cells, B cells and T cells will trigger formation of receptor clusters, which will facilitate cross-talk. Joint signaling from these receptors will produce robust proinflammatory cytokine responses [10,32]. Formation of these cellular clusters, which will also bind to FcR expressing platelets could lead to clogging of arteries and hypertension. A successful disruption of these receptor clusters should be targeted for therapeutic intervention.

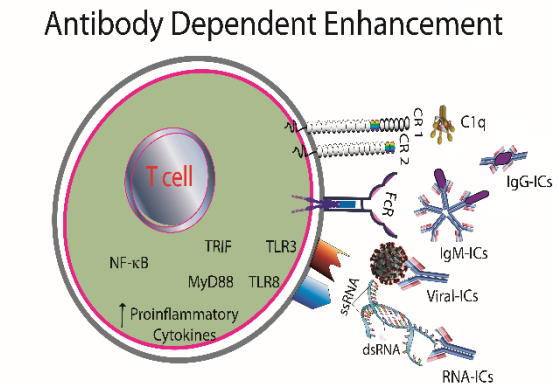

Figure 2: ICs composed with nucleic acids and opsonized with complement engage complement receptors, Fc receptors, and NA-TLRs. These interactions promote and enhance viral entry trigger the release of pro inflammatory cytokines. TRIF and MyD88 both upregulate the NF-kB pathway.

In activated $CD4^+$ T cells, TLR3 and TLR8 are relocated to the cell surface, where they will recognize the viral RNA from HIV-1 and COVID-19 viruses. Studying these signaling events from the cell surface will open the possibilities to target disruption of signaling complexes for developing therapies and enhancing the efficacy of vaccines. FcR signaling will drive epigenetic changes and microRNA expression in CD4 population [36] and unpublished observation (Chauhan, et. al, NCBI accession no. GSE127664). The effector cell responses generated upon the formation of ICs and their subsequent Fc/FcR interactions, provided the limited benefits observed in RV144 HIV-1 trial and broadly neutralizing antibodies 3BNC117, PG16 clinical trial [37,38]. The existing literature thus suggest a coordinated role for NA-TLRs and FcRs in triggering $CD4^+$ T cell responses in RNA-viral infections.

Fc R signaling in $CD4^+$ T cells: regulate pro-inflammatory cytokines

In viral infections including SARS-CoV-2, increase in cytokine levels correlate with disease pathology Innate cells i.e. monocytes, macrophages, and dendritic cells are considered as primary contributors to the cytokine storm. IL-1, IL-6, IL-8, IFN-γ, IL1-a, and IL1-b are observed at enhanced levels in infectious pathology. Interferon responses are critical for the resolution of the viral infection; however, these responses also contribute to the pathology [39]. It has been previously suggested that Th2 subset contributes to the lung pathology in SARS-Cov- 2 infection. IFN-γ producer Th1 cells are critical for viral pathology and these cells have been identified in SARS-CoV-2 infection. The emerging data now implicates both the Th1 as well as Th17 cell types exists in COVID-19 pathology [40,41].

Although, not a prominent response, early results from Moderna's mRNA-1273 vaccine show the development of Th1 and Tfh responses and lack of the Th2 response [42]. We and others have reported production of IFN-α, IFN-β and IFNγ upon FcR signaling in $CD4^+$ T cells [8,10,11]. Engagement of FcγgRIIIa by ICs triggers a strong production of IFN-γ, compared to CD28 cosignal [9]. Engagement of FcγRI, FcγRIIa, FcγRIIIa and FcμR by their ligands on $CD4^+$ T cells, triggers the release of proinflammatory cytokines such as IL-1a, IL-1b, IL-10, IL-12a, IFN-γ, IL-17A, IL-17F, IL-21, IL-22 and IL-23 [7,8,10,11]. IFN gene signature (ISG) upregulation was observed in the human $CD4^+$ T cells upon FcR signaling, and some patients show predominant type 1 response [10, 32] Peripheral blood monocytes obtained from COVID-19 patients produced IFN-γ, TNFα, IL-2, IL-5, IL-13, IL-10, IL-9, IL-17A, IL-17F and IL-22 after stimulation with Spike protein peptide MP_S. [41].

Interestingly, peripheral follicular helper $CD4^+$ T cells (pTfh) cells which are $CXCR5^+ICOS^+PD1^+$ are induced upon vaccination against influenza virus. Such pTfh cells are also observed before symptomatic recovery of COVID-19 patients

and upon vaccination. These cells were observed prominently in convalescing patients on day 20th [43]. These findings are relevant in the context of our findings, where we have shown that the FcR ligation by ICs *in vitro* triggers the development of such pTfh cells, and these cells do exists in SLE subjects [44,45]. In COVID-19, we expect the increase in the levels of both IgG and IgM containing ICs, and such ICs will drive the generation of these pTfh cells. A prominent role for proinflammatory cytokine storm in COVID-19 pathology has been suggested. These cytokines have also been suggested to be critical to the inflammation in children's that are exposed to SARS-CoV-2 virus and present symptoms similar to Kawasaki disease. In summary, we insinuate a prominent and critical role for adaptive immune cells in modulating responses in viral pathology associated with RNA viruses. Increased expression of FcR is observed as early as 48 h post activation of $CD4^+$ T cells, which is severally enhanced by day 14th [32]. We suggest a need for further examination of the FcR expressing $CD4^+$ T cells in viral pathology such as COVID-19. It will be of significant interest to examine the predictive value of these cells as a potential biomarker for identifying the subjects that show enhanced disease severity during viral infection. It will be useful to assess if FcR^+ $CD4^+$ T cells can serve as a biomarker for testing the efficacy of various vaccines, currently in the development.

References

1. Wan Y, Shang J, Sun S, Tai W, Chen J, et al. (2020) Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. J Virol 2020; 94.
2. Merad M, Martin JC (2020) Author Correction: Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nature reviews Immunology 2020.
3. Nimmerjahn F, Ravetch JV (2008) Fcgamma receptors as regulators of immune responses. Nature reviews Immunology 8: 34-47.
4. Bournazos S, Ravetch JV (2017) Fcgamma Receptor Function and the Design of Vaccination Strategies. Immunity 47: 224-233.
5. Sandor M, Lynch RG (1993) Lymphocyte Fc receptors: the special case of T cells. Immunology today 14: 227-231.
6. Chauhan AK, Moore TL (2011) T cell activation by terminal complex of complement and immune complexes. The Journal of biological chemistry 286: 38627-3837.
7. Meryk A, Pangrazzi L, Hagen M, Hatzmann F, Jenewein B, et al. (2019) Fcμ receptor as a Costimulatory Molecule for T Cells. Cell Rep 26: 2681-91e5.
8. Holgado MP, Sananez I, Raiden S, Geffner JR, Arruvito L (2018) CD32 Ligation Promotes the Activation of CD4(+) T Cells. Front Immunol 9: 2814.
9. Chauhan AK, Chen C, Moore TL, DiPaolo RJ (2015) Induced Expression of FcgammaRIIIa (CD16a) on $CD4^+$ T Cells Triggers Generation of IFN-gammahigh Subset. The Journal of biological chemistry 290: 5127-5140.
10. Chauhan AK, Moore TL, Bi Y, Chen C (2016) FcgammaRIIIa-Syk Co-signal Modulates $CD4^+$ T-cell Response and Up-regulates Toll-like Receptor (TLR) Expression. The Journal of biological chemistry 291: 1368-1386.
11. Rasoulouniriana D, Santana-Magal N, Gutwillig A, Farhat-Younis L, Wine Y, et al. (2019) A distinct subset of FcgammaRI-expressing Th1 cells exert antibody-mediated cytotoxic activity. The Journal of clinical investigation 129: 4151-4164.
12. Abdel-Mohsen M, Kuri-Cervantes L, Grau-Exposito J, Spivak AM, Nell RA, et al. (2018) CD32 is expressed on cells with transcriptionally active HIV but does not enrich for HIV DNA in resting T cells. Sci Transl Med 2018: 10.
13. Daniel V, Susal C, Weimer R, Zimmermann R, Huth-Kuhne A, et al. (2001) Association of immune complexes and plasma viral load with $CD4^+$ cell depletion, $CD8^+$ DR^+ and $CD16^+$ cell counts in HIV^+ hemophilia patients. Implications for the immunopathogenesis of HIV-induced $CD4^+$ lymphocyte depletion. Immunol Lett 76: 69-78.
14. Bour-Jordan H, Esensten JH, Martinez-Llordella M, Penaranda C, Stumpf M, et al. (2011) Intrinsic and extrinsic control of peripheral T-cell tolerance by costimulatory molecules of the CD28/ B7 family. Immunol Rev 241: 180-205.
15. Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, et al. (2020) Complement as a target in COVID-19? Nature reviews Immunology 20: 343-344.
16. Kwan WH, van der Touw W, Heeger PS (2012) Complement regulation of T cell immunity. Immunol Res 54: 247-253.
17. Willey S, Aasa-Chapman MM, O'Farrell S, Pellegrino P, Williams I, et al. (2011) Extensive complement-dependent enhancement of HIV-1 by autologous non-neutralising antibodies at early stages of infection. Retrovirology 8: 16.
18. Niculescu F, Niculescu T, Rus H (2004) C5b-9 terminal complement complex assembly on apoptotic cells in human arterial wall with atherosclerosis. Exp Mol Pathol 76: 17-23.
19. Shankland SJ, Pippin JW, Couser WG (1999) Complement (C5b-9) induces glomerular epithelial cell DNA synthesis but not proliferation *in vitro*. Kidney Int 56: 538-548.
20. Hansch GM, Seitz M, Betz M (1987) Effect of the late complement components C5b-9 on human monocytes: release of prostanoids, oxygen radicals and of a factor inducing cell proliferation. Int Arch Allergy Appl Immunol 82: 317-320.
21. Lovett DH, Haensch GM, Goppelt M, Resch K, Gemsa D (1987) Activation of glomerular mesangial cells by the terminal membrane attack complex of complement. J Immunol 138: 2473-2480.
22. Torbohm I, Schonermark M, Wingen AM, Berger B, Rother K, et al. (1990) C5b-8 and C5b-9 modulate the collagen release of human glomerular epithelial cells. Kidney Int 37: 1098-1104.
23. Badea TD, Park JH, Soane L, Niculescu T, Niculescu F, et al. (2003) Sublytic terminal complement attack induces c-fos transcriptional activation in myotubes. J Neuroimmunol 142: 58-66.
24. Viedt C, Hansch GM, Brandes RP, Kubler W, Kreuzer J (2000) The terminal complement complex C5b-9 stimulates interleukin-6 production in human smooth muscle cells through activation of transcription factors NF-kappa B and AP-1. FASEB J 14: 2370-2372.
25. Zwaka TP, Manolov D, Ozdemir C, Marx N, Kaya Z, et al. (2002) Complement and dilated cardiomyopathy: a role of sublytic terminal complement complex-induced tumor necrosis factor-alpha synthesis in cardiac myocytes. Am J Pathol 161: 449-457.
26. Kudo K, Imai C, Lorenzini P, Kamiya T, Kono K, et al. (2014) T lymphocytes expressing a CD16 signaling receptor exert antibody-dependent cancer cell killing. Cancer Res 74: 93-103.

27. Clemenceau B, Vivien R, Berthome M, Robillard N, Garand R, et al. (2008) Effector memory alphabeta T lymphocytes can express FcgammaRIIIa and mediate antibody-dependent cellular cytotoxicity. J Immunol 180: 5327-5334.

28. O'llier J, Vivien R, Vie H, Clémenceau B (2017) Transfection of FcgRIIIa (CD16) alone can ee sufficient to enable human abTCR T lymphocytes to mediate antibody-dependent cellular cytotoxicity. ImmunoHorizon 1: 63-70.

29. Barton GM, Kagan JC, Medzhitov R (2006) Intracellular localization of Toll-like receptor 9 prevents recognition of self DNA but facilitates access to viral DNA. Nature immunology 7: 49-56.

30. Leifer CA, Kennedy MN, Mazzoni A, Lee C, Kruhlak MJ, et al. (2004) TLR9 is localized in the endoplasmic reticulum prior to stimulation. J Immunol 173: 1179-1183.

31. Hacker H, Mischak H, Miethke T, Liptay S, Schmid R, et al. (1998) CpG-DNA-specific activation of antigen-presenting cells requires stress kinase activity and is preceded by non-specific endocytosis and endosomal maturation. EMBO J 17: 6230-6240.

32. Chauhan AK (2017) FcgammaRIIIa Signaling Modulates Endosomal TLR Responses in Human CD4$^+$ T Cells. J Immunol 198: 4596-4606.

33. Chauhan AK, Moore TL (2006) Presence of plasma complement regulatory proteins clusterin (Apo J) and vitronectin (S40) on circulating immune complexes (CIC). Clinical and experimental immunology 145: 398-406.

34. Brinkmann MM, Spooner E, Hoebe K, Beutler B, Ploegh HL, et al. (2007) The interaction between the ER membrane protein UNC93B and TLR3, 7, and 9 is crucial for TLR signaling. J Cell Biol 177: 265-275.

35. Chauhan AK, Moore TL (2011) Immune complexes (ICs) from systemic lupus erythematosus and complement activate ERK1/2 and PI3K/Akt pathway in primary human mesangial cells. Arthrits and Rheumatism 63: S298.

36. Chauhan AK (2016) Human CD4$^+$ T-cells-A Role for low affinity Fc-receptors. Front Immunol 2016.

37. Parsons MS, Chung AW, Kent SJ (2018) Importance of Fc-mediated functions of anti-HIV-1 broadly neutralizing antibodies. Retrovirology 15: 58.

38. Caskey M, Klein F, Nussenzweig MC (2019) Broadly neutralizing anti-HIV-1 monoclonal antibodies in the clinic. Nat Med 25: 547-553.

39. Acharya D, Liu G, Gack MU (2020) Dysregulation of type I interferon responses in COVID-19. Nature reviews Immunology 2020.

40. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP (2020) The trinity of COVID-19: immunity, inflammation and intervention. Nature reviews Immunology 20: 363-374.

41. Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Nisreen MA, et al. (2020) Phenotype of SARS-CoV-2-specific T-cells in COVID-19 patients with acute respiratory distress syndrome. BioRxiv 2020.

42. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, et al. (2020) Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. N Engl J Med 2020.

43. Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, et al. (2020) Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med 26: 453-455.

44. Chauhan AK (2019) Immune Complex (ICs) generate PD1int CD4$^+$ T cells which are Bcl6$^+$IFN-γ$^+$ unlike exhausted PD1high cells. J Immunology 202: 13.

45. Chauhan AK (2018) A contribution of FcγRIIIa cosignaling in Tfh subset development in Systemic Lupus Erythematosus. BioRxiv 2018.