The Martyrdom of St. Julia: on Microbial Strategies to Evade the Immune System

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1 **ABSTRACT**
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Bacteria and viruses use an array of evasion mechanisms to escape from the host immune system. Due to antigenic variation, pathogenic micro-organisms can escape the immune system. Micro-organisms can occur in different types, such as the 97 serotypes of *Streptococcus pneumoniae*. Influenza viruses change their antigenic make-up, in particular the hemagglutinin molecule by antigenic drift and antigenic shift. Trypanosomes and malaria parasites use DNA programmed expression of highly variable surface antigens. Micro-organisms can also produce proteins that degrade (IgA protease) or inactivate antibody molecules (protein A and protein G). Some bacteria and viruses produce proteins that inhibit complement activation. Virus can become invisible for recognition by T-lymphocytes by interference with antigen presentation. Antiviral immunity can be suppressed by viral homologues of cytokines and cytokine receptors and other proteins. Despite the extensive immune evasion strategies used by viruses, bacteria and other micro-organisms, the immune system in most cases is ultimately able to control an infection.

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4 *Keywords: evasion mechanisms, IgA proteases, capsular polysaccharides, antigenic drift, antigenic shift, complement*
5 *inhibitors, antigen presentation, cytokine homologues*
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8 **1. INTRODUCTION**
9

10 Micro-organisms and parasites use a number of different ways to escape the immune system. The Christian religious history

11 has the legend of Saint Julia, who tried to escape from her future husband. The story of this legend is that in the 14th century,

12 Julia, the daughter of a heathen King in Portugal, was promised by her father to be the bride of the King of Sicily. Julia

13 refused because she wanted to remain a virgin and in order to prevent she had to marry, she prayed to God for help. Soon

14 thereafter she grew a beard and her husband-to-be then refused her. Unfortunately Julia's father became so mad that this

15 prearranged marriage was cancelled that he had her crucified. Saint Julia has been popular through the ages and her

16 crucifixion is depicted in many works of art, including statues, drawings and paintings [1]. The scene of her crucifixion is

17 also depicted by Jheronimus Bosch in the Martyrdom of Saint Julia (Figure 1). For the occasion of the 600th anniversary of

18 Jheronimus Bosch in 2016, the painting was loaned by the Gallerie dell'Accademia, Venice, Italy to the Noord-Brabants

19 Museum in 's Hertogenbosch, The Netherlands, the home town of Jheronimus Bosch. As a part of the deal the painting was

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fully restored and only then the beard of Saint Julia became clearly visible. Growing a beard as a strategy to escape marriage.

Figure 1.

Detail of the painting The Martyrdom of Saint Julia by Jheronimus Bosch (around 1497). The painting is alternatively named Saint Wilgefortis Triptych, because Saint Julia had such as strong (fortis) will (wilge). Gallerie dell'Accademia, Venice, Italy. (http://boschproject.org/#/artworks/Saint_Wilgefortis_Triptych).

Various microorganisms and parasites have evolved different strategies to escape the immune system of the host. This strategy is called evasion. Evasive mechanisms contribute strongly to the virulence and pathogenicity of these organisms. Different categories of evasive mechanisms can be distinguished, each with different targets on the immune system, which will be discussed in this review.

2. IMMUNE EVASION MECHANISMS

2.1 Due to antigenic variation pathogenic micro-organisms can escape the immune system

One of the ways in which a microorganism can escape elimination by the immune system is by altering its antigenic make up [2]. Such a makeover can occur in three different ways.

First, a micro-organism can occur in different types. For example, the bacterium *Streptococcus pneumoniae* has ninety seven serotypes that differ in the structure of the capsular polysaccharide [Figure 2] [3]. Infection with a given serotype leads to type-specific immunity, which, however, does not protect against infection with any of the other pneumococcal

serotypes [4]. For the acquired immune system, every pneumococcal serotype is therefore a separate micro-organism. This means that *Streptococcus pneumoniae* can cause a primary infection several times in the same individual.
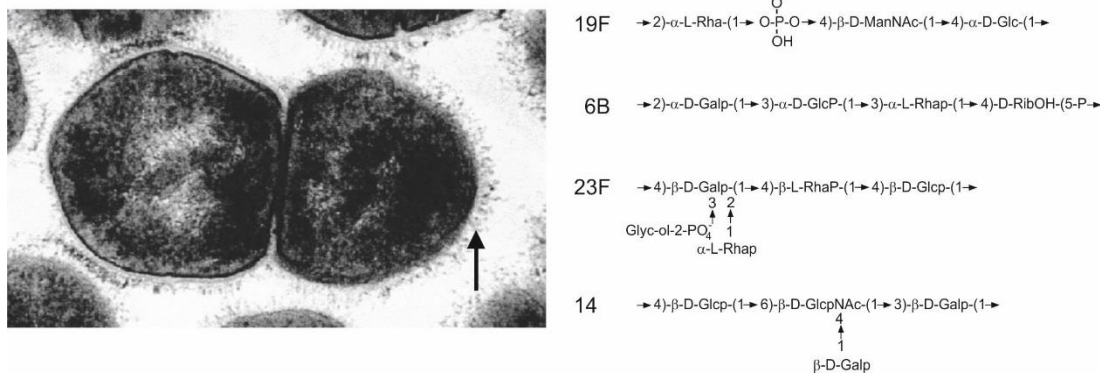

19F →2)-α-L-Rha-(1→ O-P-O→ 4)-β-D-ManNAc-(1→4)-α-D-Glc-(1→

6B →2)-α-D-Galp-(1→3)-α-D-GlcP-(1→3)-α-L-Rhap-(1→ 4)-D-RibOH-(5-P→

23F →4)-β-D-Galp-(1→4)-β-L-RhaP-(1→ 4)-β-D-Glcp-(1→
Glyc-ol-2-PO₄   α-L-Rhap

14 →4)-β-D-Glcp-(1→ 6)-β-D-GlcpNAc-(1→ 3)-β-D-Galp-(1→
β-D-Galp

Figure 2.

Streptococcus pneumoniae, a Gram-positive facultative anaerobic bacterium is encapsulated by a thick layer of polysaccharides (arrow in left panel). The capsule is made up by one of 93 different types of polysaccharides; the structural composition of four common occurring serotypes is shown in the right-hand panel.

A second way of antigenic variation is more dynamic and is found among others in the influenza virus, the cause of influenza. There are three different types of influenza virus, A, B and C, of which influenza A causes the most serious disease symptoms [5]. Most infections that occur worldwide during the influenza season (autumn and winter) are caused by a single type of the influenza A virus. Over time, protective immunity arises in the population, which mainly consists of antibodies and cytotoxic T-lymphocytes directed against the viral hemagglutinin protein [6]. The hemagglutinin is involved in attachment to target cells and antibodies against hemagglutinin can (thereby) prevent the spread of the virus in the body [7, 8]. Due to changes in the hemagglutinin protein (see below), a virus type is created against which the accumulated immunity in the population does not work or does not function properly [9]. Such a changed virus can therefore cause a new infection. The influenza virus can alter the antigenic makeup of the hemagglutinin in two ways: antigenic drift and antigenic shift (Figure 3) [10]. Mutations in the gene coding for the hemagglutinin (and for the second important virus surface protein neuraminidase) produce a new variant of the influenza virus (antigenic drift) every two or three years [11]. This variant is less well recognized by the antibodies and cytotoxic T lymphocytes present. This allows the influenza virus to cause a - generally mild - flu epidemic [12]. Such an epidemic is mild because although some epitopes of the hemagglutinin and / or neuraminidase have changed, not all of them have. So there is still a certain amount of residual immunity in the population. Antigenic shift is a much rarer event, but with far greater consequences [13]. An antigenic shift can occur when a (human) influenza A virus ends up in a secondary host (e.g. a bird). The influenza RNA genome is segmented into eight genes, one of which is coding for hemagglutinin and one for neuraminidase [14]. In a secondary host, in a cell that is infected with two different influenza viruses, exchange of a complete RNA segment can take place [15]. Thus, in a host cell infected with both the human and avian influenza virus, exchanges between both viruses can occur. From this, a (human) virus variant can emerge with an avian hemagglutinin (Figure 3). At least 18 subtypes of the hemagglutinin occur (H1 to H18), of neuraminidase 11 (N1 to N11) [16]. The most common influenza A types in humans are H1N1, H2N2 and H3N2 [17]. H5, H6, H7 and H8 are especially common in birds [18]. Due to antigenic shift, the H5N1 variant originated in which the avian H5 ended up in a human influenza A virus [19, 20]. The differences between the human and avian influenza hemagglutinin

77   are so great that antibodies and cytotoxic T lymphocytes formed during previous infections do not give any cross protection.

78   Influenza strains in which such an antigenic shift has occurred occur once every 15 to 20 years [10]. The so-called Hong

79   Kong influenza pandemic in 1968, with world-wide one million deaths, was caused by a virus variant due to antigenic shift
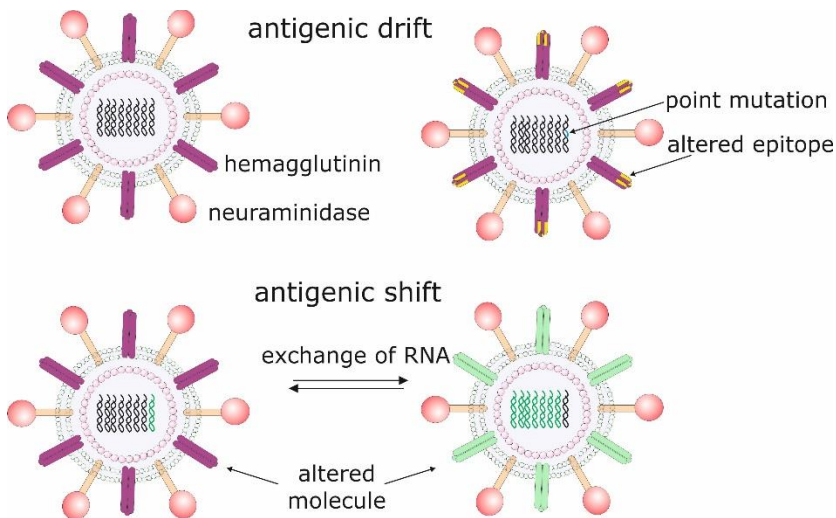
80   [19, 21].

81

82

83   Figure 3.

84   *Antigenic shift and antigenic drift of influenza A virus. The major surface antigens of the influenza A virus are*

85   *hemagglutinin and neuraminidase. By point mutations in the RNA encoding hemagglutinin, the antigenic make-up of the*

86   *molecule can change somewhat. This is called antigenic drift. This allows original antibodies to bind less well or not at all*

87   *and the mutated virus has a better chance of survival. In an antigenic shift, two different influenza A virus particles*

88   *exchange a complete RNA segment, allowing a completely different hemagglutinin molecule to be expressed.*

89   *Accumulated immunological memory from previous influenza contacts is then no longer effective because antibodies (and*

90   *memory T lymphocytes) no longer recognize the altered hemagglutinin molecule. Such an altered influenza virus is*

91   *therefore more easily able to cause an epidemic.*

92

93

94   The most recent influenza pandemic started in Mexico in 2009 and was initially called swine flu. Later, under pressure from

95   Mexico, this name was changed to new influenza A (N1H1) (Figure 4). What was special was that this variant particularly

96   affected young children, while normally older people are particularly susceptible to influenza [22, 23]. In retrospect, many

97   people aged about 50 years and older were already found to have (cross-reactive and protective) antibodies against this

98   virus, due to exposure to a similar influenza in their youth [24]. The N1H1 spread rapidly around the world, and initially there

99   was fear that millions of people would be killed.

100   A vaccine against H1N1 has been accelerated and offered to major risk groups i.e. children between 6 months and 4 years,

101   household members of younger children, and adults with chronic disease [25]. In retrospect, the H1N1 pandemic was mild,

102   probably mainly because the elderly - in which the mortality is concentrated during the annual flu season - were barely

103   susceptible to the new influenza A (N1H1) [24]. An estimated 300,000 people worldwide have died directly or indirectly from

104   the virus [26]. A total of 65,600 deaths was confirmed in Africa, 29,700 in the Americas, 31,000 in Europe, and 78,600 in

105   Asia [26]. At the moment the H1N1 vaccine became available, the peak of the pandemic might already have passed.
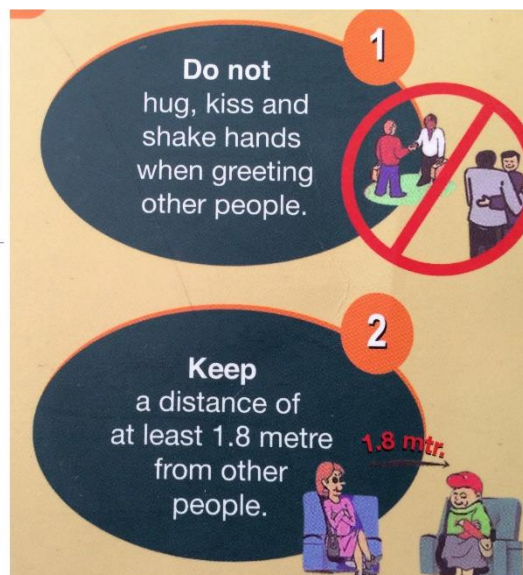
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Figure 4.

Worldwide outbreak of new N1H1 influenza virus in 2009, as reported in the press and communicated to travelers.

The third way in which antigenic variation can occur is due to programmed changes in the DNA of the micro-organism or the parasite [27]. In its most extreme form, this mechanism is used by trypanosomes. Trypanosomes are protozoans that are transmitted by insects and cause sleeping sickness [28, 29]. The trypanosome is surrounded by a single protein, the variant-specific glycoprotein (VSG) [30]. After infection, this VSG generates a powerful antibody response that neutralizes the parasite. However, trypanosomes have a thousand different VSG genes of which only one is expressed each time. The single trypanosome that has been altered from VSG expression thus escapes the immune system and leads to renewed outgrowth and flare-up of the disease [30]. This will result in a chronic cycle of trypanosome degradation with immune complex formation and inflammation, followed by renewed disease activity. Ultimately, this leads to severe neurological damage and coma.

The malaria parasite also uses this mechanism of antigenic variation to protect itself against the immune system [31]. In the erythrocyte stage of malaria there is expression of parasite proteins on the membrane of the red blood cell, especially of the PfEMP1 protein [32, 33]. The PfEMP1 protein suppresses the production of IFN-γ and thus a cellular immune response [34]. Via PfEMP1 an infected erythrocyte adheres to vascular wall tissue and can thus prevent phagocytosis by spleen macrophages. PfEMP1 does elicit an antibody response and these antibodies can bind to infected erythrocytes. Antibody-loaded erythrocytes are captured in the spleen and phagocytosed. The malaria parasite has sixty variants of PfEMP1, of which only one is expressed each time [35]. Switching to another variant of PfEMP1 means that the already produced antibodies can no longer bind and that infected erythrocytes are no longer trapped.

2.2 Micro-organisms produce proteins that can degrade or inactivate antibody molecules

Micro-organisms can protect against antibody-mediated complement lysis or phagocytosis by enzymatic degradation of the antibodies. A number of bacteria, including *Neisseria* species, *Haemophilus influenzae* and *Streptococcus pneumoniae* form proteolytic enzymes that can split secretory IgA (SIgA) antibodies into two monomeric Fab fragments and an Fc fragment [36, 37]. This IgA protease is capable of cleaving both free SIgA and bound SIgA antibodies. The Fab fragments

135 remain on the surface of the microorganism but are unable to activate effector mechanisms (complement, phagocytosis)
136 [38]. Infections with the above bacteria occur on mucous membranes and IgA is the most important isotype of the antibodies
137 present [39]. The bacterial IgA proteases are especially capable of splitting SIgA1 while SIgA2 is relatively resistant to IgA
138 proteases [36, 37]. But because the IgA1 Fab fragments remain bound on the surface of the microorganism, binding of IgA2
139 antibodies can be inhibited thereby [40, 41].
140 IgG antibodies can also be broken down by bacterial enzymes. *Pseudomonas aeruginosa* and other bacteria produce
141 cysteine proteases that can cleave IgG molecules at the hinge region.
142 Besides proteolytic cleavage of the molecule, IgG can also be functionally inactivated by certain bacterial proteins [42-44].
143 *Staphylococcus aureus* expresses a protein on its surface called protein A, which can bind to the Fc portion of IgG. Binding
144 of protein A to IgG blocks Fc receptor-mediated phagocytosis [45, 46]. Moreover, it inhibits the binding of C1q to IgG and
145 thus complement activation [47]. In other bacteria, proteins with similar functions are found: Group-G streptococci produce
146 protein G and *Peptostreptococcus* produces protein-L. These proteins can also bind to IgG [48-50].
147

2.3 Some bacteria and viruses produce proteins that inhibit complement activation

149 Many bacteria produce N-formyl peptides such as fMLP [51]. These peptides are very potent chemoattractants for
150 phagocytes [52]. fMLP is bound to phagocytes via specific receptors: formyl peptide receptor (FPR) and the related FPR-
151 like-1 receptor (FPRL1) [53]. The fMLP is not only a chemoattractant but also stimulates phagocytosis [54, 55].
152 *Staphylococcus aureus* has developed a strategy to prevent the attraction of phagocytes to the site of the infection by
153 producing the protein CHIPS (chemotaxis inhibiting protein of *S. aureus*) [56]. CHIPS binds to FPRL1 and thus blocks the
154 functioning of this receptor [57]. CHIPS also binds to the C5a receptor on phagocytes and thereby blocks the function of
155 another chemotactic peptide, the complement fragment C5a [58]. Another staphylococcal protein that interferes with the
156 complement system is SCIN (staphylococcal complement inhibitor) [59]. SCIN blocks the C3 converter activity of C4b2a
157 and C3bBb [60-62]. In total, *S. aureus* possesses about ten different proteins that can all inhibit complement activation.
158 Together, this will disrupt all functions mediated by the complement system (chemotaxis and lysis and opsonization) [62-
159 64]. These and other proteins that are used to escape the immune system of the host lie encoded on the bacterial genome
160 together in a so-called immune vascular cluster (IEC), of which *S. aureus* possesses two [65, 66].
161 Not only *S. aureus* and other bacteria use proteins to prevent activation of the complement system (Figure 5) but also
162 certain viruses. Vaccinia virus encodes a strong complement inhibitor, vaccinia complement control protein (VCP). VCP
163 strengthens the split of C3b and C4b by factor I and thus inhibits both the classic and alternative complement activation
164 path [67-70].
165

2.4 Interference with antigen presentation makes viruses invisible for recognition by T-lymphocytes

167 Viruses have developed different ways to escape the immune system. It is of course important that virus replication occurs
168 only in host cells, where the virus is not immediately accessible to the immune system. During viral replication, components
169 of viral proteins are presented to the immune system by MHC class I and class II proteins. In that way the virus would betray
170 its presence in an infected cell. However, if the virus does not replicate, but remains latent, it is invisible.
171 Herpes simplex virus type I infects epithelial cells and sensory neurons [71]. After a cellular immune response the infection
172 is under control, but the virus can still remain latent in the nerve cells [72]. Reactivation of the virus can, if the antiviral
173 immunity is reduced or temporarily disturbed, lead to a re-infection of the skin [73]. Another herpes virus, the previously

174 discussed Epstein-Barr virus, can remain latent in B lymphocytes [74]. For this it must express a certain viral protein, EBNA-
175 1, since this is necessary to maintain the viral genome. EBNA-1 cannot be presented in the context of MHC class I, because
176 it cannot be broken down by the proteasome. This keeps the virus invisible to the immune system [75-77].

177 Other viruses also have proteins that interfere with antigen presentation and thus try to prevent a cellular immune response
178 from getting under way. For example, the cytomegalovirus (CMV) has at least twelve different proteins that block the
179 presentation of CMV peptides in the MHC at different sites [78]. These CMV proteins are encoded on the unique long (UL),
180 or unique short (unique short, US) part of the CMV genome [79]. US3 and US10 proteins prevent MHC class I molecules
181 from leaving the endoplasmic reticulum [80, 81]. If nonetheless MHC class I molecules are formed, US2 and US11 proteins
182 bind to this, after which the MHC molecules are degraded by proteasomes [82, 83]. Disabling MHC class I expression
183 prevents recognition by cytotoxic T lymphocytes, but makes the cell susceptible to killing by NK cells [84]. The CMV protein
184 UL16, however, blocks the activating NK cell receptor NKD2D and UL18 stimulates the inhibitory NK cell receptors [85, 86].
185 CMV therefore has an extensive package of viral proteins at its disposal to combat killing by CD8$^+$ T lymphocytes or by NK
186 cells.

187

188 2.5 Viral homologues of cytokines and cytokine receptors and other proteins suppress antiviral
189 immunity

190 If a virus, despite its attempts to prevent recognition by the immune system, would still evoke an immune response, it can
191 try to suppress that response. One of the strategies employed is that the viral genome encodes homologues of suppressive
192 cytokines and/or soluble cytokine receptors. [87-90]. EBV encodes a viral homolog of IL-10, which is very similar to human
193 IL-10 but has only its immunosuppressive properties [91, 92]. EBV also encodes an IL-12p40 related protein [93]. Pox
194 viruses use soluble cytokine receptor homologous proteins and cytokine binding proteins to neutralize proinflammatory
195 cytokines [94]. These viruses also code for a soluble chemokine antagonist that binds with high affinity to CC-chemokines
196 .Fungi also use inhibition of cytokines to escape the immune response of the host. Virulent cryptococcal strains secrete
197 proteins with anti-TNF-α and anti-IL-12 activity, while stimulating the IL-10 production of the host [95].

198 In addition to blockade of the cytokine function, viruses can also neutralize the action of antibodies by synthesis of viral Fc
199 receptors (herpes simplex and cytomegalovirus) [96, 97]. Finally, viruses can also resist apoptosis in order to escape
200 cytotoxic T lymphocytes and NK cells. The most successful is the adenovirus, which possesses a protein that is very similar
201 to the anti-apoptotic Bcl-2. EBV also has two proteins that resemble Bcl-2 [98]. Inhibition of caspase activity and reduction
202 of the expression of apoptosis receptors such as FasL are other ways in which viruses prevent apoptosis [99-101].

203 Despite the extensive immune evasion strategies used by viruses, bacteria and other micro-organisms, the immune system
204 in most cases is ultimately able to control an infection. However, when components of the immune system do not function
205 adequately, such as with congenital or acquired immune deficiencies, even seemingly innocent microorganisms can lead
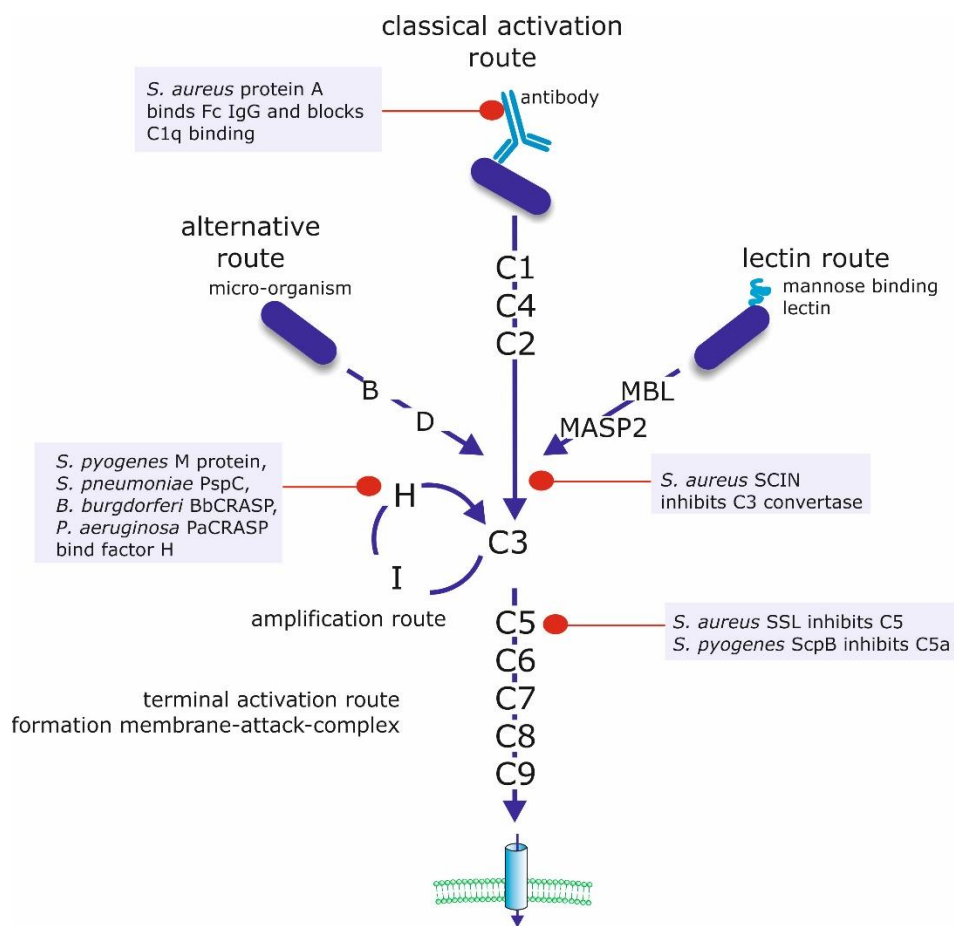206 to serious infections.

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208
209 *Figure 5.*
210 *Complement evasion by bacterial proteins. Figures shows examples of bacterial proteins which can interfere with specific*
211 *pathways of the complement system. Further explanation is given in the text.*
212

213 3. EPILOGUE

214 Saint Julia, by changing her antigenic make up, tried to evade from her husband to be. This relief was only temporary,
215 because another man, notably her own father, had her crucified. The analogy with micro-organisms that try to escape the
216 immune system partly holds true. Escape from complement mediated killing does not prevent phagocytosis and subsequent
217 intracellular killing.

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COMPETING INTERESTS

REFERENCES

1. Friesen IE. The female crucifix: Images of St. Wilgefortis. Waterloo, Ontario, Canada: Wilfried Laurier University Press; 2001.

2. Hornef MW, Wick MJ, Rhen M, Normark S. Bacterial strategies for overcoming host innate and adaptive immune responses. Nat Immunol. 2002;3(11):1033-40. doi: 10.1038/ni1102-1033

3. Geno KA, Gilbert GL, Song JY, Skovsted IC, Klugman KP, Jones C, et al. Pneumococcal capsules and their types: past, present, and future. Clin Microbiol Rev. 2015;28(3):871-99. doi: 10.1128/cmr.00024-15

4. Brown J, Hammerschmidt, S., Orihuela, C. *Streptococcus pneumoniae*: molecular mechanisms of host-pathogen interactions. San Diego, CA: Elsevier; 2015.

5. Ghebrehewet S, MacPherson P, Ho A. Influenza. Bmj. 2016;355:i6258. doi: 10.1136/bmj.i6258

6. Chen X, Liu S, Goraya MU, Maarouf M, Huang S, Chen JL. Host immune response to Influenza A virus infection. Front Immunol. 2018;9:320. doi: 10.3389/fimmu.2018.00320

7. Sriwilaijaroen N, Suzuki Y. Molecular basis of the structure and function of H1 hemagglutinin of influenza virus. Proc Jpn Acad Ser B Phys Biol Sci. 2012;88(6):226-49. doi:

8. Altenburg AF, Rimmelzwaan GF, de Vries RD. Virus-specific T cells as correlate of (cross-)protective immunity against influenza. Vaccine. 2015;33(4):500-6. doi: 10.1016/j.vaccine.2014.11.054

9. Schrauwen EJ, de Graaf M, Herfst S, Rimmelzwaan GF, Osterhaus AD, Fouchier RA. Determinants of virulence of influenza A virus. Eur J Clin Microbiol Infect Dis. 2014;33(4):479-90. doi: 10.1007/s10096-013-1984-8

10. Treanor J. Influenza vaccine--outmaneuvering antigenic shift and drift. N Engl J Med. 2004;350(3):218-20. doi: 10.1056/NEJMp038238

11. Gordon A, Reingold A. The burden of influenza: a complex problem. Curr Epidemiol Rep. 2018;5(1):1-9. doi: 10.1007/s40471-018-0136-1

12. Poovorawan Y, Pyungporn S, Prachayangprecha S, Makkoch J. Global alert to avian influenza virus infection: from H5N1 to H7N9. Pathog Glob Health. 2013;107(5):217-23. doi: 10.1179/2047773213y.0000000103

13. Fauci AS. Pandemic influenza threat and preparedness. Emerg Infect Dis. 2006;12(1):73-7. doi: 10.3201/eid1201.050983

14. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev. 1992;56(1):152-79. doi:

15. Bouvier NM, Palese P. The biology of influenza viruses. Vaccine. 2008;26 Suppl 4:D49-53. doi:

16. Lloren KKS, Lee T, Kwon JJ, Song MS. Molecular markers for interspecies transmission of avian influenza viruses in mammalian hosts. Int J Mol Sci. 2017;18(12). doi: 10.3390/ijms18122706

17. Taubenberger JK, Kash JC. Influenza virus evolution, host adaptation, and pandemic formation. Cell Host Microbe. 2010;7(6):440-51. doi: 10.1016/j.chom.2010.05.009

18. Fouchier RA, Guan, Y. Ecology and evolution of influenza viruses in wild and domestic birds. In: Webster RG, Monto, A.S., Braciale, T.J., Lamb, R.A., editor. Textbook of Influenza. London, UK: Wiley; 2013. p. 175–87.

19. Peiris JS, de Jong MD, Guan Y. Avian influenza virus (H5N1): a threat to human health. Clin Microbiol Rev. 2007;20(2):243-67. doi: 10.1128/cmr.00037-06

20. Subbarao K, Luke C. H5N1 viruses and vaccines. PLoS Pathog. 2007;3(3):e40. doi: 10.1371/journal.ppat.0030040

21. Viboud C, Grais RF, Lafont BA, Miller MA, Simonsen L. Multinational impact of the 1968 Hong Kong influenza pandemic: evidence for a smoldering pandemic. J Infect Dis. 2005;192(2):233-48. doi: 10.1086/431150

22. Cox CM, Blanton L, Dhara R, Brammer L, Finelli L. 2009 Pandemic influenza A (H1N1) deaths among children--United States, 2009-2010. Clin Infect Dis. 2011;52 Suppl 1:S69-74. doi: 10.1093/cid/ciq011

23. Garcia MN, Philpott DC, Murray KO, Ontiveros A, Revell PA, Chandramohan L, et al. Clinical predictors of disease severity during the 2009-2010 A(HIN1) influenza virus pandemic in a paediatric population. Epidemiol Infect. 2015;143(14):2939-49. doi: 10.1017/s0950268815000114

24. Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N Engl J Med. 2009;361(20):1945-52. doi: 10.1056/NEJMoa0906453

25. World Health Organization. Report of the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative http://www.who.int/influenza_vaccines_plan/resources/h1n1_deployment_report.pdf [Accessed: 29 March 2018.

26. Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng PY, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. Lancet Infect Dis. 2012;12(9):687-95. doi: 10.1016/s1473-3099(12)70121-4

27. Vink C, Rudenko G, Seifert HS. Microbial antigenic variation mediated by homologous DNA recombination. FEMS Microbiol Rev. 2012;36(5):917-48. doi: 10.1111/j.1574-6976.2011.00321.x

28. Haines LR, Hancock RE, Pearson TW. Cationic antimicrobial peptide killing of African trypanosomes and *Sodalis glossinidius*, a bacterial symbiont of the insect vector of sleeping sickness. Vector Borne Zoonotic Dis. 2003;3(4):175-86. doi: 10.1089/153036603322662165

302   29.   Kennedy PG. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping
303   sickness). Lancet Neurol. 2013;12(2):186-94.   doi: 10.1016/s1474-4422(12)70296-x

304   30.   Mugnier MR, Stebbins CE, Papavasiliou FN. Masters of disguise: antigenic variation and the VSG coat
305   in *Trypanosoma brucei*. PLoS Pathog. 2016;12(9):e1005784.   doi: 10.1371/journal.ppat.1005784

306   31.   Good MF, Xu H, Wykes M, Engwerda CR. Development and regulation of cell-mediated immune
307   responses to the blood stages of malaria: implications for vaccine research. Annu Rev Immunol.
308   2005;23:69-99.   doi: 10.1146/annurev.immunol.23.021704.115638

309   32.   Wahlgren M, Goel S, Akhouri RR. Variant surface antigens of *Plasmodium falciparum* and their roles in
310   severe malaria. Nat Rev Microbiol. 2017;15(8):479-91.   doi: 10.1038/nrmicro.2017.47

311   33.   Stone WJR, Campo JJ, Ouedraogo AL, Meerstein-Kessel L, Morlais I, Da D, et al. Unravelling the
312   immune signature of *Plasmodium falciparum* transmission-reducing immunity. Nat Commun.
313   2018;9(1):558.   doi: 10.1038/s41467-017-02646-2

314   34.   D'Ombrain MC, Voss TS, Maier AG, Pearce JA, Hansen DS, Cowman AF, et al. *Plasmodium falciparum*
315   erythrocyte membrane protein-1 specifically suppresses early production of host interferon-gamma. Cell
316   Host Microbe. 2007;2(2):130-8.   doi: 10.1016/j.chom.2007.06.012

317   35.   Kim K. Malaria var gene expression: keeping up with the neighbors. Cell Host Microbe. 2012;11(1):1-2.
318   doi: 10.1016/j.chom.2012.01.002

319   36.   Chintalacharuvu KR, Chuang PD, Dragoman A, Fernandez CZ, Qiu J, Plaut AG, et al. Cleavage of the
320   human immunoglobulin A1 (IgA1) hinge region by IgA1 proteases requires structures in the Fc region of
321   IgA. Infect Immun. 2003;71(5):2563-70.   doi:

322   37.   Chi YC, Rahkola JT, Kendrick AA, Holliday MJ, Paukovich N, Roberts TS, et al. *Streptococcus*
323   *pneumoniae* IgA1 protease: A metalloprotease that can catalyze in a split manner in vitro. Prot Sci.
324   2017;26(3):600-10.   doi: 10.1002/pro.3110 [doi]

325   38.   Kilian M, Reinholdt J, Lomholt H, Poulsen K, Frandsen EV. Biological significance of IgA1 proteases in
326   bacterial colonization and pathogenesis: critical evaluation of experimental evidence. APMIS.
327   1996;104(5):321-38.   doi:

328   39.   Woof JM, Kerr MA. The function of immunoglobulin A in immunity. J Pathol. 2006;208(2):270-82.   doi:
329   10.1002/path.1877 [doi]

330   40.   Hedges SR, Mayo MS, Kallman L, Mestecky J, Hook EW, 3rd, Russell MW. Evaluation of immunoglobulin
331   A1 (IgA1) protease and IgA1 protease-inhibitory activity in human female genital infection with *Neisseria*
332   *gonorrhoeae*. Infect Immun. 1998;66(12):5826-32.   doi:

333   41.   Ahl T, Reinholdt J. Detection of immunoglobulin A1 protease-induced Fab alpha fragments on dental
334   plaque bacteria. Infect Immun. 1991;59(2):563-9.   doi:

335   42.   Fick RB, Jr., Baltimore RS, Squier SU, Reynolds HY. IgG proteolytic activity of *Pseudomonas aeruginosa*
336   in cystic fibrosis. J Infect Dis. 1985;151(4):589-98.   doi:

337 43. Brezski RJ, Luongo JL, Petrone D, Ryan MH, Zhong D, Tam SH, et al. Human anti-IgG1 hinge
338   autoantibodies reconstitute the effector functions of proteolytically inactivated IgGs. J Immunol.
339   2008;181(5):3183-92. doi: 181/5/3183 [pii]
340 44. Brezski RJ, Jordan RE. Cleavage of IgGs by proteases associated with invasive diseases: an evasion
341   tactic against host immunity? mAbs. 2010;2(3):212-20. doi: 11780 [pii]
342 45. Sulica A, Medesan C, Laky M, Onica D, Sjoquist J, Ghetie V. Effect of protein A of *Staphylococcus aureus*
343   on the binding of monomeric and polymeric IgG to Fc receptor-bearing cells. Immunology.
344   1979;38(1):173-9. doi:
345 46. Iijima M, Kadoya H, Hatahira S, Hiramatsu S, Jung G, Martin A, et al. Nanocapsules incorporating IgG
346   Fc-binding domain derived from *Staphylococcus aureus* protein A for displaying IgGs on immunosensor
347   chips. Biomaterials. 2011;32(6):1455-64. doi: 10.1016/j.biomaterials.2010.10.057 [doi]
348 47. Foster TJ, Geoghegan JA, Ganesh VK, Hook M. Adhesion, invasion and evasion: the many functions of
349   the surface proteins of *Staphylococcus aureus*. Nature Rev Microbiol. 2014;12(1):49-62. doi:
350   10.1038/nrmicro3161 [doi]
351 48. Wikstrom M, Drakenberg T, Forsen S, Sjobring U, Bjorck L. Three-dimensional solution structure of an
352   immunoglobulin light chain-binding domain of protein L. Comparison with the IgG-binding domains of
353   protein G. Biochemistry. 1994;33(47):14011-7. doi:
354 49. Kihlberg BM, Sjoholm AG, Bjorck L, Sjobring U. Characterization of the binding properties of protein LG,
355   an immunoglobulin-binding hybrid protein. Eur J Biochem. 1996;240(3):556-63. doi:
356 50. Ricci S, Medaglini D, Marcotte H, Olsen A, Pozzi G, Bjorck L. Immunoglobulin-binding domains of
357   Peptostreptococcal protein L enhance vaginal colonization of mice by *Streptococcus gordonii*. Microb
358   Pathogen. 2001;30(4):229-35. doi: 10.1006/mpat.2000.0427 [doi]
359 51. Elbim C, Bailly S, Chollet-Martin S, Hakim J, Gougerot-Pocidalo MA. Differential priming effects of
360   proinflammatory cytokines on human neutrophil oxidative burst in response to bacterial N-formyl
361   peptides. Infect Immun. 1994;62(6):2195-201. doi:
362 52. Videm V, Strand E. Changes in neutrophil surface-receptor expression after stimulation with FMLP,
363   endotoxin, interleukin-8 and activated complement compared to degranulation. Scand J Immunol.
364   2004;59(1):25-33. doi: 1351 [pii]
365 53. Murphy PM, Ozcelik T, Kenney RT, Tiffany HL, McDermott D, Francke U. A structural homologue of the
366   N-formyl peptide receptor. Characterization and chromosome mapping of a peptide chemoattractant
367   receptor family. J Biol Chem. 1992;267(11):7637-43. doi:
368 54. Prossnitz ER, Ye RD. The N-formyl peptide receptor: a model for the study of chemoattractant receptor
369   structure and function. Pharmacol Ther. 1997;74(1):73-102. doi: S0163725896002033 [pii]
370 55. Le Y, Murphy PM, Wang JM. Formyl-peptide receptors revisited. Trends Immunol. 2002;23(11):541-8.
371   doi: S1471490602023165 [pii]
372 56. Veldkamp KE, Heezius HC, Verhoef J, van Strijp JA, van Kessel KP. Modulation of neutrophil chemokine
373   receptors by *Staphylococcus aureus* supernate. Infect Immun. 2000;68(10):5908-13. doi:

57. Prat C, Haas PJ, Bestebroer J, de Haas CJ, van Strijp JA, van Kessel KP. A homolog of formyl peptide receptor-like 1 (FPRL1) inhibitor from *Staphylococcus aureus* (FPRL1 inhibitory protein) that inhibits FPRL1 and FPR. J Immunol. 2009;183(10):6569-78. doi: 10.4049/jimmunol.0801523 [doi]

58. Postma B, Poppelier MJ, van Galen JC, Prossnitz ER, van Strijp JA, de Haas CJ, et al. Chemotaxis inhibitory protein of *Staphylococcus aureus* binds specifically to the C5a and formylated peptide receptor. J Immunol. 2004;172(11):6994-7001. doi:

59. de Jong NWM, Vrieling M, Garcia BL, Koop G, Brettmann M, Aerts PC, et al. Identification of a Staphylococcal Complement Inhibitor with broad host specificity in equid *S. aureus* strains. J Biol Chem. 2018. doi: 10.1074/jbc.RA117.000599

60. Rooijakkers SH, Wu J, Ruyken M, van Domselaar R, Planken KL, Tzekou A, et al. Structural and functional implications of the alternative complement pathway C3 convertase stabilized by a staphylococcal inhibitor. Nat Immunol. 2009;10(7):721-7. doi: 10.1038/ni.1756 [doi]

61. Garcia BL, Summers BJ, Lin Z, Ramyar KX, Ricklin D, Kamath DV, et al. Diversity in the C3b [corrected] contact residues and tertiary structures of the staphylococcal complement inhibitor (SCIN) protein family. J Biol Chem. 2012;287(1):628-40. doi: 10.1074/jbc.M111.298984 [doi]

62. Ricklin D, Tzekou A, Garcia BL, Hammel M, McWhorter WJ, Sfyroera G, et al. A molecular insight into complement evasion by the staphylococcal complement inhibitor protein family. J Immunol. 2009;183(4):2565-74. doi: 10.4049/jimmunol.0901443 [doi]

63. Lee LY, Hook M, Haviland D, Wetsel RA, Yonter EO, Syribeys P, et al. Inhibition of complement activation by a secreted *Staphylococcus aureus* protein. J Infect Dis. 2004;190(3):571-9. doi: 10.1086/422259 [doi]

64. Rooijakkers SH, Ruyken M, Roos A, Daha MR, Presanis JS, Sim RB, et al. Immune evasion by a staphylococcal complement inhibitor that acts on C3 convertases. Nat Immunol. 2005;6(9):920-7. doi: ni1235 [pii]

65. Verkaik NJ, Benard M, Boelens HA, de Vogel CP, Nouwen JL, Verbrugh HA, et al. Immune evasion cluster-positive bacteriophages are highly prevalent among human *Staphylococcus aureus* strains, but they are not essential in the first stages of nasal colonization. Clin Microbiol Infect. 2011;17(3):343-8. doi: 10.1111/j.1469-0691.2010.03227.x [doi]

66. van Wamel WJ, Rooijakkers SH, Ruyken M, van Kessel KP, van Strijp JA. The innate immune modulators staphylococcal complement inhibitor and chemotaxis inhibitory protein of *Staphylococcus aureus* are located on beta-hemolysin-converting bacteriophages. J Bacteriol. 2006;188(4):1310-5. doi: 188/4/1310 [pii]

67. Kotwal GJ, Isaacs SN, McKenzie R, Frank MM, Moss B. Inhibition of the complement cascade by the major secretory protein of vaccinia virus. Science. 1990;250(4982):827-30. doi:

68. Meseda CA, Kuhn J, Atukorale V, Campbell J, Weir JP. Glycosylated and nonglycosylated complement control protein of the lister strain of vaccinia virus. Clin Vaccine Immunol. 2014;21(9):1330-8. doi: 10.1128/cvi.00347-14

69. McKenzie R, Kotwal GJ, Moss B, Hammer CH, Frank MM. Regulation of complement activity by vaccinia virus complement-control protein. J Infect Dis. 1992;166(6):1245-50. doi:

70. Sahu A, Isaacs SN, Soulika AM, Lambris JD. Interaction of vaccinia virus complement control protein with human complement proteins: factor I-mediated degradation of C3b to iC3b1 inactivates the alternative complement pathway. J Immunol. 1998;160(11):5596-604. doi:

71. Spear PG. Herpes simplex virus: receptors and ligands for cell entry. Cell Microbiol. 2004;6(5):401-10. doi: 10.1111/j.1462-5822.2004.00389.x [doi]

72. Miranda-Saksena M, Denes CE, Diefenbach RJ, Cunningham AL. Infection and transport of Herpes Simplex virus Type 1 in neurons: role of the cytoskeleton. Viruses. 2018;10(2):10.3390/v10020092. doi: E92 [pii]

73. Cunningham AL, Diefenbach RJ, Miranda-Saksena M, Bosnjak L, Kim M, Jones C, et al. The cycle of human herpes simplex virus infection: virus transport and immune control. J Infect Dis. 2006;194 Suppl 1:11. doi: JID35844 [pii]

74. Izumi KM, Cahir McFarland ED, Riley EA, Rizzo D, Chen Y, Kieff E. The residues between the two transformation effector sites of Epstein-Barr virus latent membrane protein 1 are not critical for B-lymphocyte growth transformation. J Virol. 1999;73(12):9908-16. doi:

75. Levitskaya J, Sharipo A, Leonchiks A, Ciechanover A, Masucci MG. Inhibition of ubiquitin/proteasome-dependent protein degradation by the Gly-Ala repeat domain of the Epstein-Barr virus nuclear antigen 1. Proc Natl Acad Sci USA. 1997;94(23):12616-21. doi:

76. Daskalogianni C, Pyndiah S, Apcher S, Mazars A, Manoury B, Ammari N, et al. Epstein-Barr virus-encoded EBNA1 and ZEBRA: targets for therapeutic strategies against EBV-carrying cancers. J Pathol. 2015;235(2):334-41. doi: 10.1002/path.4431 [doi]

77. Apcher S, Daskalogianni C, Manoury B, Fahraeus R. Epstein Barr virus-encoded EBNA1 interference with MHC class I antigen presentation reveals a close correlation between mRNA translation initiation and antigen presentation. PLoS Pathog. 2010;6(10):e1001151. doi: 10.1371/journal.ppat.1001151 [doi]

78. Ploegh HL. Viral strategies of immune evasion. Science. 1998;280(5361):248-53. doi:

79. Hengel H, Brune W, Koszinowski UH. Immune evasion by cytomegalovirus--survival strategies of a highly adapted opportunist. Trends Microbiol. 1998;6(5):190-7. doi: S0966-842X(98)01255-4 [pii]

80. Furman MH, Dey N, Tortorella D, Ploegh HL. The human cytomegalovirus US10 gene product delays trafficking of major histocompatibility complex class I molecules. J Virol. 2002;76(22):11753-6. doi:

81. Jones TR, Wiertz EJ, Sun L, Fish KN, Nelson JA, Ploegh HL. Human cytomegalovirus US3 impairs transport and maturation of major histocompatibility complex class I heavy chains. Proc Natl Acad Sci USA. 1996;93(21):11327-33. doi:

82. Wiertz EJ, Jones TR, Sun L, Bogyo M, Geuze HJ, Ploegh HL. The human cytomegalovirus US11 gene product dislocates MHC class I heavy chains from the endoplasmic reticulum to the cytosol. Cell. 1996;84(5):769-79. doi: S0092-8674(00)81054-5 [pii]

446 83. Wiertz EJ, Tortorella D, Bogyo M, Yu J, Mothes W, Jones TR, et al. Sec61-mediated transfer of a
447 membrane protein from the endoplasmic reticulum to the proteasome for destruction. Nature.
448 1996;384(6608):432-8. doi: 10.1038/384432a0 [doi]

449 84. Halenius A, Gerke C, Hengel H. Classical and non-classical MHC I molecule manipulation by human
450 cytomegalovirus: so many targets-but how many arrows in the quiver? Cell Mol Immunol. 2015;12(2):139-
451 53. doi: 10.1038/cmi.2014.105 [doi]

452 85. Lin A, Xu H, Yan W. Modulation of HLA expression in human cytomegalovirus immune evasion. Cell Mol
453 Immunol. 2007;4(2):91-8. doi:

454 86. Yang Z, Bjorkman PJ. Structure of UL18, a peptide-binding viral MHC mimic, bound to a host inhibitory
455 receptor. Proc Natl Acad Sci USA. 2008;105(29):10095-100. doi: 10.1073/pnas.0804551105 [doi]

456 87. Schonrich G, Abdelaziz MO, Raftery MJ. Herpesviral capture of immunomodulatory host genes. Virus
457 Genes. 2017;53(6):762-73. doi: 10.1007/s11262-017-1460-0

458 88. Scarborough JA, Paul JR, Spencer JV. Evolution of the ability to modulate host chemokine networks via
459 gene duplication in human cytomegalovirus (HCMV). Infect Genet Evol. 2017;51:46-53. doi:
460 10.1016/j.meegid.2017.03.013

461 89. Kuo NW, Gao YG, Schill MS, Isern N, Dupureur CM, Liwang PJ. Structural insights into the interaction
462 between a potent anti-inflammatory protein, viral CC chemokine inhibitor (vCCI), and the human CC
463 chemokine, Eotaxin-1. J Biol Chem. 2014;289(10):6592-603. doi: 10.1074/jbc.M113.538991

464 90. McSharry BP, Avdic S, Slobedman B. Human cytomegalovirus encoded homologs of cytokines,
465 chemokines and their receptors: roles in immunomodulation. Viruses. 2012;4(11):2448-70. doi:
466 10.3390/v4112448

467 91. Jochum S, Moosmann A, Lang S, Hammerschmidt W, Zeidler R. The EBV immunoevasins vIL-10 and
468 BNLF2a protect newly infected B cells from immune recognition and elimination. PLoS Pathog.
469 2012;8(5):e1002704. doi: 10.1371/journal.ppat.1002704

470 92. Sin SH, Dittmer, D.P. Cytokine homologs of human gammaherpesviruses. J Interferon Cytokine Res.
471 2012;32(2):53-9. doi:

472 93. Pflanz S, Timans, J.C., Cheung, J., Rosales, R., Kanzler, H., Gilbert, J., Hibbert, L., Churakova, T., Travis,
473 M., Vaisberg, E., Blumenschein, W.M., Mattson, J.D., Wagner, J.L., To, W., Zurawski, S., McClanahan,
474 T.K., Gorman, D.M., Bazan, J.F., de Waal Malefyt, R., Rennick, D., Kastelein, R.A. . IL-27, a
475 heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4+ T cells.
476 Immunity. 2002;16(6):779-90. doi:

477 94. Haig DM. Poxvirus interference with the host cytokine response. Vet Immunol Immunopathol. 1998;63(1-
478 2):149-56. doi:

479 95. Vecchiarelli A, Retini C, Pietrella D, Monari C, Tascini C, Beccari T, et al. Downregulation by cryptococcal
480 polysaccharide of tumor necrosis factor alpha and interleukin-1 beta secretion from human monocytes.
481 Infect Immun. 1995;63(8):2919-23. doi:

482 96. Sprague ER, Reinhard H, Cheung EJ, Farley AH, Trujillo RD, Hengel H, et al. The human
483   cytomegalovirus Fc receptor gp68 binds the Fc CH2-CH3 interface of immunoglobulin G. J Virol.
484   2008;82(7):3490-9. doi: 10.1128/jvi.01476-07

485 97. Lubinski JM, Jiang M, Hook L, Chang Y, Sarver C, Mastellos D, et al. Herpes simplex virus type 1 evades
486   the effects of antibody and complement in vivo. J Virol. 2002;76(18):9232-41. doi:

487 98. Kvansakul M, Caria S, Hinds MG. The Bcl-2 family in host-virus interactions. Viruses. 2017;9(10). doi:
488   10.3390/v9100290

489 99. Lotzerich M, Roulin PS, Boucke K, Witte R, Georgiev O, Greber UF. Rhinovirus 3C protease suppresses
490   apoptosis and triggers caspase-independent cell death. Cell Death Dis. 2018;9(3):272. doi:
491   10.1038/s41419-018-0306-6

492 100. Tabtieng T, Degterev A, Gaglia MM. Caspase-dependent suppression of type I interferon signaling
493   promotes KSHV lytic replication. J Virol. 2018. doi: 10.1128/jvi.00078-18

494 101. Yu E, Zhai D, Jin C, Gerlic M, Reed JC, Liddington R. Structural determinants of caspase-9 inhibition by
495   the vaccinia virus protein, F1L. J Biol Chem. 2011;286(35):30748-58. doi: 10.1074/jbc.M111.280149

496
497