Review Paper

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

ABSTRACT

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.

Keywords: evasion mechanisms, IgA proteases, capsular polysaccharides, antigenic drift, antigenic shift, complement inhibitors, antigen presentation, cytokine homologues

1. INTRODUCTION

Micro-organisms and parasites use a number of different ways to escape the immune system. The Christian religious history 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, Julia, the daughter of a heathen King in Portugal, was promised by her father to be the bride of the King of Sicily. Julia refused because she wanted to remain a virgin and in order to prevent she had to marry, she prayed to God for help. Soon thereafter she grew a beard and her husband-to-be then refused her. Unfortunately Julia's father became so mad that this prearranged marriage was cancelled that he had her crucified. Saint Julia has been popular through the ages and her crucifixion is depicted in many works of art, including statues, drawings and paintings [1]. The scene of her crucifixion is also depicted by Jheronimus Bosch in the Martyrdom of Saint Julia (Figure 1). For the occasion of the 600th anniversary of Jheronimus Bosch in 2016, the painting was loaned by the Gallerie dell'Accademia, Venice, Italy to the Noord-Brabants Museum in 's Hertogenbosch, The Netherlands, the home town of Jheronimus Bosch. As a part of the deal the painting was 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.

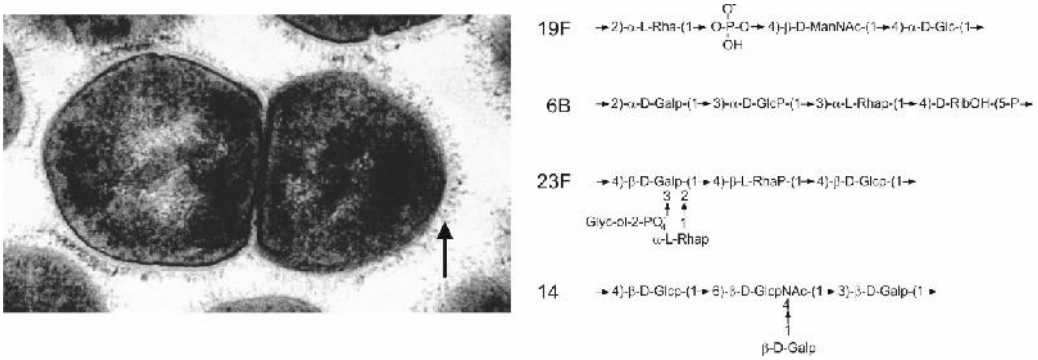

Figure 2.

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 are so great that antibodies and cytotoxic T lymphocytes formed during previous infections do not give any cross protection. Influenza strains in which such an antigenic shift has occurred occur once every 15 to 20 years [10]. The so-called Hong Kong influenza pandemic in 1968, with world-wide one million deaths, was caused by a virus variant due to antigenic shift [19, 21].

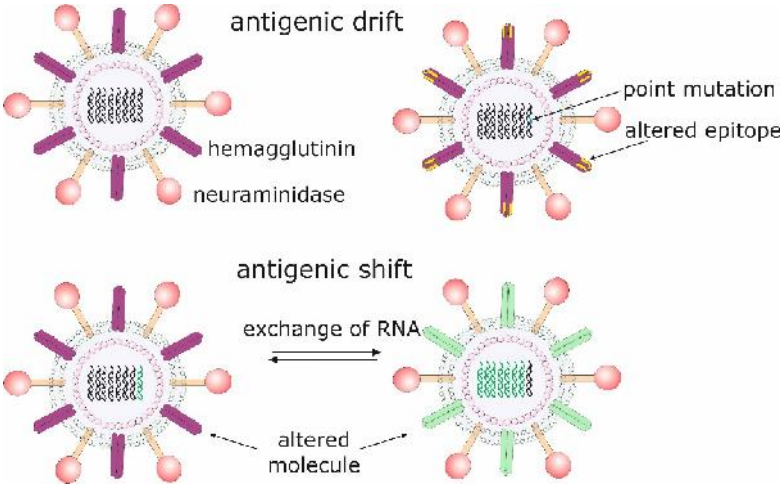

Figure 3.

Antigenic shift and antigenic drift of influenza A virus. The major surface antigens of the influenza A virus are hemagglutinin and neuraminidase. By point mutations in the RNA encoding hemagglutinin, the antigenic make-up of the molecule can change somewhat. This is called antigenic drift. This allows original antibodies to bind less well or not at all and the mutated virus has a better chance of survival. In an antigenic shift, two different influenza A virus particles exchange a complete RNA segment, allowing a completely different hemagglutinin molecule to be expressed. Accumulated immunological memory from previous influenza contacts is then no longer effective because antibodies (and memory T lymphocytes) no longer recognize the altered hemagglutinin molecule. Such an altered influenza virus is therefore more easily able to cause an epidemic.

The most recent influenza pandemic started in Mexico in 2009 and was initially called swine flu. Later, under pressure from Mexico, this name was changed to new influenza A (N1H1) (Figure 4). What was special was that this variant particularly affected young children, while normally older people are particularly susceptible to influenza [22, 23]. In retrospect, many people aged about 50 years and older were already found to have (cross-reactive and protective) antibodies against this virus, due to

exposure to a similar influenza in their youth [24]. The N1H1 spread rapidly around the world, and initially there was fear that millions of people would be killed.

A vaccine against H1N1 has been accelerated and offered to major risk groups i.e. children between 6 months and 4 years, household members of younger children, and adults with chronic disease [25]. In retrospect, the H1N1 pandemic was mild, probably mainly because the elderly - in which the mortality is concentrated during the annual flu season - were barely susceptible to the new influenza A (N1H1) [24]. An estimated 300,000 people worldwide have died directly or indirectly from 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 Asia [26]. At the moment the H1N1 vaccine became available, the peak of the pandemic might already have passed.

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 enzymatically 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 remain on the surface of the microorganism but are unable to activate effector mechanisms (complement, phagocytosis) [38]. Infections with the above bacteria occur on mucous membranes and IgA is the most important isotype of the antibodies present [39]. The bacterial IgA proteases are especially capable of splitting SIgA1, SIgA2 is relatively resistant to IgA proteases [36, 37]. But because the IgA1 Fab fragments remain bound on the surface of the microorganism, binding of IgA2 antibodies can be inhibited thereby [40, 41].

IgG antibodies can also be broken down by bacterial enzymes. *Pseudomonas aeruginosa* and other bacteria produce cysteine proteases that can cleave IgG molecules in the hinge region.

In addition to proteolytic cleavage of the molecule, IgG can also be functionally inactivated by certain bacterial proteins [42-44]. *Staphylococcus aureus* expresses a protein on its surface, protein A, which can bind to the Fc portion of IgG. Binding of protein A to IgG blocks Fc receptor-mediated phagocytosis [45, 46]. Moreover, it inhibits the binding of C1q to IgG and thus the complement activation [47]. In other bacteria, proteins with similar functions are found: Group-G streptococci produce protein G and *Peptostreptococcus* magnus protein-L. These proteins can also bind to IgG [48-50].

2.3 Some bacteria and viruses produce proteins that inhibit complement activation

Many bacteria produce N-formyl peptides such as fMLP [51]. These peptides are very potent chemoattractants for phagocytes [52]. fMLP is bound to phagocytes via specific receptors: formyl peptide receptor (FPR) and the related FPR-like-1 receptor (FPRL1) [53]. The fMLP is not only a chemoattractant but also stimulates phagocytosis [54, 55]. Staphylococcus aureus has developed a strategy to prevent the attraction of phagocytes to the site of the infection by producing the protein CHIPS (chemotaxis inhibiting protein of S. aureus) [56]. CHIPS binds to FPRL1 and thus blocks the functioning of this receptor [57]. CHIPS also binds to the C5a receptor on phagocytes and thereby

blocks the function of another chemotactic peptide, the complement fragment C5a [58]. Another staphylococcal protein that interferes with the complement system is SCIN (staphylococcal complement inhibitor) [59]. SCIN blocks the C3 converter activity of C4b2a and C3bBb [60-62]. In total, *S. aureus* possesses about ten different proteins that can all inhibit complement activation. Together, this will disrupt all functions mediated by the complement system (chemotaxis and lysis and opsonization) [62-64]. These and other proteins that are used to escape the immune system of the host lie encoded on the bacterial genome together in a so-called immune vascular cluster (IEC), of which *S. aureus* possesses two [65, 66].

Not only *S. aureus* and other bacteria use proteins to prevent activation of the complement system (Figure 5) but also certain viruses. Vaccinia virus encodes a strong complement inhibitor, vaccinia complement control protein (VCP). VCP strengthens the split of C3b and C4b by factor I and thus inhibits both the classic and alternative complement activation path [67-70].

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

Viruses have developed different ways to escape the immune system. It is of course important that virus replication occurs only in host cells, where the virus is not immediately accessible to the immune system. During viral replication, components of viral proteins are presented to the immune system by MHC class I and class II proteins. In that way the virus would betray its presence in an infected cell. However, if the virus does not replicate, but remains latent, it is invisible.

Herpes simplex virus type I infects epithelial cells and sensory neurons [71]. After a cellular immune response the infection is under control, but the virus can still remain latent in the nerve cells [72]. Reactivation of the virus can, if the antiviral immunity is reduced or temporarily disturbed, lead to a re-infection of the skin [73]. Another herpes virus, the previously discussed Epstein-Barr virus, can remain latent in B lymphocytes [74]. For this it must express a certain viral protein, EBNA-1, since this is necessary to maintain the viral genome. EBNA-1 cannot be presented in the context of MHC class I, because it cannot be broken down by the proteasome. This keeps the virus invisible to the immune system [75-77].

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

has an extensive package of viral proteins at its disposal to combat killing by $CD8^+$ T lymphocytes or by NK cells.

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

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

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

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. However, when components of the immune system do not function adequately, such as with congenital or acquired immune deficiencies, even seemingly innocent microorganisms can lead to serious infections.

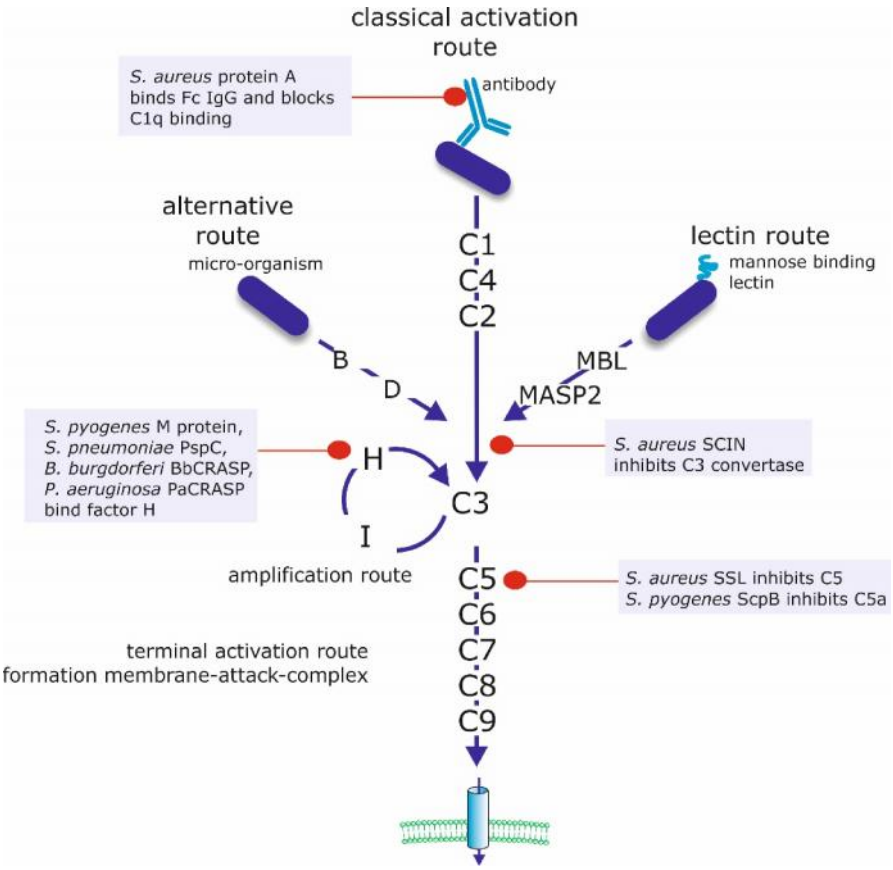

Figure 5.

Complement evasion by bacterial proteins. Figures shows examples of bacterial proteins which can interfere with specific pathways of the complement system. Further explanation is given in the text.

3. EPILOGUE

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

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