Structural and synthetic biology of the human complement system

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Chapter 7

General Discussion & Outlook

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1 The classical complement pathway

The human complement system is part of the innate immune response and is one of the oldest immune systems found in eukaryotes[1-4]. It has an important function as a first-line immune response against pathogens. Additionally, the complement system is involved in cell clearance such as apoptosis and general homeostasis[5]. This makes the complement system an essential part of human immunity. However, complement can also have a disruptive role in the human body. Complement proteins are known to be involved in autoimmune diseases, such as systemic lupus erythematosus (SLE)[6-8], rheumatoid arthritis (RA)[9], Alzheimer[10] and atypical hemolytic uremic syndrome (aHUS)[11] and also cancer, whereas the role of complement in case of cancer is still unclear[12]. These examples underscore the necessity of detailed fundamental studies into the activation mechanism and regulation of the complement system to better understand its dual role in protection but also in pathology.

1.1 Mechanisms of the classical complement pathway

1.1.1 Classical complement initiation and antibody platforms

The classical complement pathway gets activated by antigen bound IgG antibodies on a surface. This leads to lysis of cells, opsonisation and cell clearance[13-16]. To be able to initiate this cascade through antigen-antibody complexes, it is important that antibodies form platforms after binding. This means that multiple IgG antibodies need to bind multiple antigens via their Fab domains and further form platforms through non-covalent bindings of the Fc regions. It is known that at least two IgG antibodies are necessary to activate the complement system[17-20]. However, hexamerization of IgG antibodies via their Fc domains leads to a stronger complement response[21-23]. IgG platforms further act as a “docking station” for C1q, which builds together with four serine proteases $C1r_2$ and $C1s_2$, the C1 complex also known as $C1qr_2s_2$[24]. C1q itself is encoded on three genes resulting in the expression of 3 × 6 polypeptide chains. The three individual chains are called A, B and C. These 18 chains are cross-linked via disulfide bounds between A-B and C-C chains resulting in a hexameric protein, which often gets referred to as a “bouquet of flowers” structure. This hexameric protein has a collagen-like “stalk” region and six globular head domains (gC1q), which are important for ligand binding, such as to the antibody platform[24, 25]. This binding event triggers activation of C1r, which subsequently activates C1s. Both proteins, C1r and C1s, have six domains (CUB1, EGF, CUB2, CCP1, CCP2 and SP), and the N-terminal domains (CUB1, EGF and CUB2) of C1r and also C1s are responsible for binding lysine residues between the C1q collagen helixes through Ca ions[24]. After activation, C1s can further cleave C4 and C2[26]. The cleavage of C4 into C4a and C4b results in C4b deposition on nearby

membranes[24] or proteins[27]. The C1 complex, C4 and C2 are characteristic for the classical complement pathway. However, after C2 cleavage, C4b and C2b build the C3 convertase (C4b2b) cleaving C3. C3b further attaches to the C4b2b complex resulting in the C5 convertase, which cleaves C5. C5b together with C6, C7, C8, and multiple copies of C9 then build the membrane attack complex (MAC) pore, which leads to lysis of the cell. Previous studies used liposomes in combination with antibodies and serum as a source of complement to study the initiation of the activation classical complement system via C1q, C4b deposition and also MAC pore formation[20, 24, 27, 28]. However, although the complement system can be activated via antibodies binding to antigens so that it terminates with the formation of a MAC pore, the trigger between lysis and silent clearance is still not completely understood. Understanding this triggering point is nevertheless required for curing autoimmune diseases related to complement, but also for being able to use complement in a therapeutic setting. Building on the fundamental understanding of complement initiation, is crucial to explore how IgG subclasses, particularly IgG1 and IgG3, uniquely modulate these processes.

1.1.2 IgG1 and IgG3 during complement activation

Among all IgG subclasses, IgG3 has the greatest ability to activate complement. IgG3 was found to lead to more MAC pore formation in comparison to IgG1 on the surface of antigenic liposomes. However, although IgG3 forms more MAC pores and thereby leads to stronger complement activation on the surface of DNP-presenting liposomes, it does not follow that IgG3 is always “better”. The different effector functions of IgG1 and IgG3 regarding complement activation are highly dependent on antigen concentration and most likely also the physical behaviour of the surface. In the systems tested here, there are no physical barriers, such as other proteins, present. Additionally, the activation of the classical complement system can vary between different cell types and also different antigens or even epitopes of antigens[29-31]. Famous examples regarding the difference of binding sites on the same antigens are the clinically relevant anti-CD20 monoclonal antibodies obinutuzumab, ofatumumab and rituximab. All these antibodies are IgG1 antibodies and are used to treat B-cell malignancies, such as non-Hodgkin lymphoma and chronic lymphocytic leukaemia. However, although all these three antibodies bind to the same target and are monoclonal IgG1 antibodies, they behave differently. Whereas both rituximab and ofatumumab are type I CD20 antibodies, obinutuzumab is a glycoengineered type II CD20 antibody. Regarding complement activation, ofatumumab leads to the strongest complement response followed by rituximab, which is still stronger compared to obinutuzumab. On the other hand, obinutuzumab leads to more antibody-dependent cellular cytotoxicity, phagocytosis and direct B-cell killing[32].

1.1.3 Structural insights into IgG3 mediated complement activation

Cryogenic electron tomography (cryoET) allowed the visualization of IgG1 and IgG3 binding to liposomes and thereby build the first full-length model of IgG3 on antigenic surfaces. Despite the low resolution, antigen-binding Fab arrays could be resolved on the surface of liposomes. This array could not be detected for IgG1[22, 27] nor IgM[24], but was uniquely found for IgG3 antibodies. Most likely this is due to the long hinge region of IgG3, which allows Fab arms to divalently bind to surfaces and thereby also achieve higher avidity. However, the resolution of the subtomogram average was not high enough to distinguish between the light and heavy chains of the antibody (**Chapter 2**)[27]. Lately, computational studies focussing on interaction sites between Fab arms could find a great variety of possible interaction sites. Although not all of these interactions sides are accessible if whole antibodies, including Fc domains, are used, they could find possible interactions in line with our research[33]. However, to achieve a higher resolution, one could possibly use pepsin to produce $F(ab')_2$ fragments[34], bind them to size-controlled liposomes and use single particle cryoEM (SPA) instead of cryoET for imaging. Studies have shown that it is possible to use SPA for imaging membrane proteins on liposomes[35]. This approach would have the benefit of being able to use a higher dose and thereby achieve higher resolution for the final 3D average[36]. This would answer the question how these antibodies come together and how they are able to form arrays. An additional control pepsin-cleaved IgG1 and papain-digested IgG1 and IgG3 could be used to study to effect of the hinge region.

Besides the detection of the Fab array, an elevated hexagonal Fc domain built by IgG3 antibodies bound to the surface binding in combination with and without complement proteins could be observed using cryoET (**Chapter 2**)[27]. This showed that IgG3, if allowed to interact, preferably forms hexameric interactions on surfaces, which most likely is beneficial for further immune reaction including complement activation. The elevation of both, the Fc platform and the binding C1 complex can be explained by the elongated, semi-flexible hinge region[30, 37]. CryoET revealed density between the C1q collagen arms, which allocated to the $C1r_2s_2$ protease platform and most likely shows a new intermediate stage of C1s most likely during the cleavage of C1r. This potentially fills the missing gap in how C1s is activated. This additional C1s confirmation is possible due to the high flexibility of C1s at the CUB2-CCP1 region, which results in increased flexibility at the CCP1-CCP2-SP domain. Besides being important for activation by C1r, the increased flexibility of C1s is also important for C4 and C2 cleavage and deposition[24, 38, 39]. Additionally, C1s could also be found bound to C4b. It is known that C1s leads to cleavage of C4b and structural data using IgM as complement activator showed deposition of C4b to the membrane[24]. As IgG3 elevates C1 and

builds a Fab array on the surface, C4b deposition on the membrane is not possible due to the extended IgG3 hinges. Focussed refinement in combination with mass spectrometry further revealed that C4b is deposited on the Fab array instead of the membrane. Mass spectrometry could show that the reactive thioester domain (TED) of C4b is able to covalently interact with IgG3 at multiple positions. Sites of interaction were mainly found at the hinge region. In addition to the hinge region, interactions with IgG3 at the Fab arm close to the hinge region and at the Fc region could be found. The Fc interaction site was also the only interaction which could be found using IgG1. Interestingly the interaction in IgG1 was found on K326, which is known to be important for complement activation[40]. Nevertheless, this might be an explanation of how C4b is cleaved and deposited, as after cleavage of C4 into C4a and C4b, the TED of C4b could "walk" down along the hinge after rotating away from itself and thereby minimize the risk of self-binding, which would result in an inhibition of the next cleaving events. The next step during classical complement activation is the cleavage of C2 into C2a and C2b via C1s, whereas C2b together with C4b builds the C3 convertase (C4b2b). How the elevated and tilted C4b structure is influencing the formation of the C4bC2b complex still needs to be determined.

Previous research suggests increased MAC pore formation in the case of IgG3[31, 37, 41-44], increased pathogen neutralisation[45, 46], antibody-dependent cellular phagocytosis[45, 47, 48] and even immunity against viruses, such as SARS-CoV-2[46, 49]and HIV[50, 51]. Together, this indicates that the Fab-bound C4b might lead to a more efficient building of C3 convertase and thereby also increases complement activation. What is happening regarding complement regulators, such as C4b-binding protein, Factor 1, complement receptor 1, or membrane cofactor protein[52] is still unclear, and more targeted research has to be done to answer this question.

Of interest in the case of IgG3 are also the ~15 different allotypes, more than any other IgG subclass[53, 54]. In **Chapter 2** the allotype G3m5[29, 37, 55, 56] was used. This allotype has four hinge exons resulting in a 62 amino acid long hinge region with eleven disulfide bonds, whereas other allotypes such as G3m3 or G3m17 have a much shorter hinge region of only 47 amino acids [29, 37]. In 2023 Damelang et al. could show that all different IgG3 allotypes still lead to increased C1q, C3b, and C4b deposition as well as increased complement-dependent cytotoxicity in comparison to other IgG subclasses, although the difference between C3b and C4b depositions and also complement-dependent cytotoxicity between IgG3 and IgG1 was not high. By having a closer look at the different IgG3 subclasses in respect to their hinge length, differences in the efficiency to induce complement-dependent cytotoxicity could be detected[29], which is in line previous studies[44, 57]. However, previous studies could also find that IgG complement activity is highly

dependent on the cell type[29, 58], with IgG1 and IgG3 allotypes with a short hinge being better in activating the complement system compared to long hinge IgG3 allotypes on certain cell types, such as Raji cells[29]. Taken together, this indicated that the activation of the complement system using IgG as complement activator relies on many factors and might differ between certain hinge lengths, cell types, and antigens. In the future, an atlas showing the differences between these relations might exist. However, more work and effort has to be put in to answer this question and a general conclusion about which one is "better" cannot be made yet. What we can conclude from our study is that the long hinge region of IgG3 allows the Fab arms to come together on surfaces building a dense Fab array on the surface. This array has not been observed before and is unique to IgG3. This also means that the avidity of IgG3 compared to other IgG subclasses is increased. Besides, Fab array building also forces the Fc platform to elevate from the surface, which makes it more accessible for further effector functions and might explain the increased neutralisation[45, 46], antibody-dependent cellular phagocytosis[45, 47, 48], Fcγ receptor binding[59-61] on certain cell types and virus immunity [46, 49, 50 , 51]. The elevated platform and C4b binding to the Fab array also open up the question of how the C3 convertase building is influenced. Taking the previously discussed increased effector functions into account, it is most likely beneficial. This might be explained by the fact that C4b is closer to C1s, which is responsible for C2 cleavage. However, it still has to be determined how this really looks. In any case, we could for the first time solve the full-length structure of IgG3 on antigenic surfaces. While this study opens up new questions, it shows the potential of IgG3 as a therapeutic candidate.

1.2 Insights in liposomal formulations for complement activation

1.2.1 Stability of liposomes in complement studies

Liposomes are often used as cell mimetics, which here we use to provide near-native surfaces to assess complement activation, as the complement system is not typically activated in solution. Liposomes are also ideal for cryoEM, as they can be synthesised to be small enough for vitrification and imaging. In **Chapter 6** various lipid compositions were evaluated for their stability in human serum. Liposomes composed of DMPC:Cholesterol:DMPG with 50 mol% cholesterol were identified as highly stable in human serum, while those containing DOPC or DSPC lead to leakage of the encapsulated dye and are therefore not suitable to study the termination of the classical complement pathway via MAC pore formation. These findings show how important the selection of the right lipids in designing reliable liposomal models for complement studies, but also for various other studies is. While stable liposomes provide a robust platform for studying

classical complement activation and termination, DNA nanostructures introduce an additional layer of control, allowing precise manipulation of antigen spacing and antibody interaction.

1.3 DNA nanostructures mediating classical complement activation

1.3.1 Antigen patterning and "controlled" activation

DNA nanostructures are powerful tools to investigate the complement system through their ability to act as platforms on which antigens can be precisely positioned. This is possible due to the well-known folding criteria of DNA. Thereby, these DNA nanostructures offer the possibility to study the influence of antibody valency and spatial arrangement during classical complement activation.

In **Chapter 3**[20] DNA nanostructures were used to guide complement to the surface of liposomes and selectively activate the classical complement pathway only if bound to the surface. Double-decker tiles (DDTs) with varying number of antigens and different spatial configurations were used to assess the effects of antibody valency and spacing on the classical complement activation. One position of antigens, the so-called narrow position (DDT-N-DNP) was chosen to meet the distance between gC1q heads bound to antibody Fc platforms using cryoET[22, 24, 27], whereas the other position was specifically chosen to be farther away from each other and thereby do not display the optimal distance for IgG1 antibodies to bind to antigens and build a Fc platform. The different DDT versions were used to study and spatially control antibody valency and thereby get a better understanding of how complement gets activated.

It is known that at least two IgG antibodies are required to enable C1q binding and thereby initiate the classical complement pathway[18, 19, 62]. Mutation-induced hexamerization of IgG antibodies leads to increased classical complement activation and thereby also MAC pore formation compared to wild-type IgG1 antibodies[21, 23, 63, 64]. These hexamerising antibodies are therefore promising therapeutic candidates. However, IgG1 antibodies exist as monomers in the human body, but oligomerisations are needed for classical complement activation. Without oligomerisation, no Fc platforms can be formed, that act as a "landing platform" for C1q. C1q is a disulfide-linked complex, which non-covalently binds the Fc region of antibodies via their six flexible gC1q heads with low binding affinity[65-67]. Structural data have shown that, although a hexameric IgG platform is present, C1q can bind in multiple ways. Binding with six, five or four gC1q heads could be observed[21, 22]. Another interesting example is IgM, which preferably exists in a pentameric form in human bodies, but also hexameric IgM can be found[68, 69]. Both these versions are able to activate the complement

system via C1q binding[24]. All these findings show the importance of antibody oligomerisation and valency in context of complement activation. The prevalence and degree of oligomerization of Fc platforms highly depends on the antigen, in particular the concentration, proximity and epitope location, and it is likely that membrane fluidity also has an impact. However, although it is known that oligomerisation is required for complement activation, it is still not known what happens if two, three, four or five IgG antibodies come together and build Fc platforms.

DNA nanostructures allow antibodies to bind to specially controlled antigens and if combined with human serum activate the complement system on the surface of liposomes (**Chapter 3**)[20]. These DDT DNA nanostructures are designed to be as small as possible to minimise steric hindrances and are rather flexible, meaning that the arms are allowed to move in-plane. Additionally, there is free space between the arms, allowing deposition of C4b on the surface of liposomes without being hindered by DNA. The small size of the DNA nanostructures, ~30 nm in diameter, should also allow C1 cross-activation, which is known to happen under normal conditions[22], as the antigen-bound antibody C1 complexes can move the DNA nanostructures along the fluid surface. Together, this makes the DDTs significantly different in comparison to DNA nanostructures previously used studying antibody spacing and valency[70]. To our knowledge, the DDTs described in **Chapter 3**[20] are the first successful attempt to use DNA nanotechnology to pattern antigens and thereby control the classical complement activation.

Besides the DDTs, we explored different potential DNA nanostructures that might be used as platforms to activate complement (**Chapter 5**). These additional DNA structures were either designed based on the DDTs, but with individual arms – iDDTs – or designed using DAEDALUS and CaDNAno. Using DAEDALUS and CaDNAno, twelve different DNA nanostructures were designed and successfully folded. However, although we were able to successfully design and fold them, not all DNA designs were further used to activate the complement system, or even to nanopattern antigens for antibody binding or to bind the nanostructures to the surface of liposomes. Due to the time and material-intensive experiments, we focussed on the small bpHex (bpHex 31 bp) design. Same as the DDTs (**Chapter 3**)[20], the bpHEX 31 bp DNA structures were also used to bind antibodies to pre-patterned antigens. Binding of antibodies to antigens could be shown using gel electrophoresis and SEC followed by negative-stain TEM. Further cryoET was used to visualise the DNA origami structures on the surface of liposomes during complement activation. Using this technique, binding of the C1 complex as well as MAC pore formation could be observed. However, MAC pore formation could only be observed to a low extent. Interestingly, no MAC pore

formation using the liposomal burst assay could be observed, although MAC pore formation could be visualised to a small extent using cryoET. Possible explanations therefore, might be the rigidity of the bpHex 31 bp DNA nanostructures and the dsDNA strand connecting the arms which might inhibit C4b deposition to the liposomal surface. However, the size of the bpHex 31 bp (~30 nm in diameter) does not inhibit cross-activation of the C1 complex. Thereby, binding of antibodies to two different DNA nanostructures could be possible, which might result in low efficiency complement activation. Anyhow, to be sure what is causing this more biochemical assays should be performed, including C1 deposition, C4b cleavage, C3 as well as quantitative analysis of MAC pore formation. Phagocytosis assays would be as well of great interest.

All these DNA nanostructures might be of interest to activate the classical complement system. Especially the more flexible design such as the DDTs and the iDDTs, which could already be used to successfully activate this extracellular pathway. However, also the scDDT and scHDT designs might be able to activate the complement system resulting in a MAC pore formation. As we could not initiate MAC pore formation using the bpHex 31 bp, DNA designs similar to this one, especially more rigid structures as well as structures, with DNA strands close to where C4b should be placed on the surface should be investigated more. These might especially be interesting in combination with another antibody subclass, namely IgG3, as for this antibody class the C4b gets deposited on the Fab arms (**Chapter 2**)[27]. Depending on the desired outcome, binding of the C1 complex without MAC pore formation might even be preferred[71].

1.3.2 Antibody valency and its effect on complement activation

Nanopatterning one antigen only leads to MAC pore formation at high concentrations and is consistently worse than if more antigens are nanopatterned. Hexameric nanopatterned antigens at the optimal narrow position were most efficient in MAC pore formation, and also C4b deposition on the surface of liposomes, followed by the pentameric, then the tetrameric and the trimeric version. Interestingly, if antigens were differently nanopatterned in the wide position, no clear difference between two to six antigens could be observed. In general, all DNA nanostructures with wide antigen spacing were worse at activating the complement system compared to the narrow position. This indicates that the positive effect of nanopatterning antigens is highly dependent on the distancing (**Chapter 3**)[20]. This difference was noticeable at the C4b deposition step, indicating that either C1 activation, C4 cleavage, or C4b deposition is limited by the inter-antigen distance and antibody geometry.

C1q binding is the first step in complement activation, but how C1q binding results in activation of the C1r protease, and how this inter-antigen distance relates to

activation of C1r, remains unclear. C1r may autoactivate within one C1 complex, or cross-activate between adjacent C1 complexes. Using larger DNA nanostructures may allow inhibition of C1-C1 cross activation, several of which are presented in **Chapter 5.**

1.3.3 Production of single-stranded DNA for DNA origami production

To produce custom-sized DNA origami nanostructures, a single-stranded scaffold with defined length is needed. This scaffold is mixed with an excess of stable strands and through thermal annealing DNA origami nanostructures are folded into the desired structure[72-74]. As a scaffold, the 7,249 nt long viral ssDNA plasmid M13mp18[75] is commonly used[72, 76]. However, not all designed DNA origami structures require such a long scaffold[77] To produce shorter, customised scaffolds, multiple protocols are publicly available, such as the production of ssDNA using asymmetric PCR (aPCR)[78], restriction endonuclease digestion with and without additional ligase treatment for circulation[77], usage of phages and helper phages[79, 80], selective digestion and rolling circle amplification[81], or the usage of RNA[82, 83] and also dsDNA as scaffold[84]. In **Chapter 4**[85] a low-effort one-pot production of ssDNA based on enzymatic digestion based method is described. Compared to the methods mentioned before, no special equipment or expensive material is needed. This method can be used to produce ssDNA fragments from commonly produced PCR products. There only needs to be one adjustment before starting the PCR amplification, which is the addition of five phosphorothioate linkages between the first five 5' nucleotides (nt) of the forward primer. These five phosphorothioates act as inhibitors against the T7 exonuclease. T7 exonuclease digests dsDNA from the 5' end, which results in the digestion of the unwanted antisense DNA strand of the PCR product. The enzymatic activity of the T7 exonuclease can be stopped by the addition of Proteinase K. Without the need for further purification in this way produced ssDNA can be directly used as a scaffold for DNA origami folding using thermal annealing, which is possible as heat inactivates the Proteinase K. As no additional purification, such as gel extraction, which is used in the case of ssDNA production using the aPCR approach[78], is needed, higher yields can be achieved. Comparing the aPCR approach to the one-pot T7 exonuclease approach directly showed that not only the additional purification step during ssDNA production leads to lower yields, but also the amount of dsDNA produced during aPCR. Whereas the T7 exonuclease efficiently works using default desalted primers, lambda requires the highest purity primers to work, resulting in additional expenses and an extra purification step of the ssDNA product. This again results in lower ssDNA yields. It was also shown that long ssDNA strands are highly sensitive to heat. Already an incubation at 95°C for 15 min led to significant

degradation of the ssDNA scaffold. Reacting to this result, the starting temperature for thermal annealing of DNA origamis was lowered to 80°C compared to 95°C as described for the production of wireframe DNA origamis[86]. We also demonstrated that DNA origamis can be folded on more than one ssDNA scaffold, and that scaffolds can be split in two or even three parts. This is especially useful for large DNA origami constructs with long ssDNA scaffolds, as increased thermal degradation of long ssDNA strands can be limiting (**Chapter 4**)[85]. Taken together, this method allows a cheap and reliable production of ssDNA scaffolds at customised lengths in high yields.

1.4 Connecting the insights: From mechanisms to therapeutics

The findings presented in this thesis, from the unique structural features of IgG3 to the precise spatial control enabled by DNA nanostructures and the robustness of liposomal models, collectively provide a framework for improving our understanding of the classical complement pathway and its therapeutic potential. The elevated Fc platform and the Fab arm array of IgG3 which leads to enhanced classical complement activation offers insights into IgG subclass specific immune response. Besides, allows the usage of DNA nanotechnology to precisely control antigen nanopatterning and thereby get a better understanding about antibody valency and geometry. Taken together, these provide a powerful toolbox to investigate and manipulate the classical complement system. In the future, studies containing both, IgG3 and various DNA nanostructures will help the increase our knowledge about this highly important part of the human immune system even more. To be able to study the complement system using cryoEM and other techniques, stable and robust liposomes are crucial as they further provide a reliable system for investigating complement-mediated processes under physiological conditions.

These advances enhance our understanding of the classical complement activation and its impact for health and disease. By unravelling the structural and functional nuances of the complement system, critical questions about its regulation and develop innovative therapies for complement-related diseases ranging from autoimmune disorders to infections and cancer can be addressed.

Complement can lead to an inflammatory response, or it can mediate more mild “silent clearance”. What is triggering these different outcomes of classical complement activation is still unknown. It is hypothesized that structural changes might be responsible. It is known that hexamerization of IgG1 antibodies via mutations leads to a higher complement activation resulting in MAC pore formation and lysis compared to monoclonal antibodies[21]. This makes these antibodies of high interest for therapeutic antibody production[23]. However,

increased complement activation terminating in MAC pore formation is not always preferred, as complement is not only highly important in early defence mechanism against pathogens, but also plays a huge role in clearance of apoptotic cells and cell derbies. Any imbalance in this well-regulated pathway has huge impacts, such as the development of autoimmune diseases such as systematic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis, and many more[87]. Besides, complement can also be involved during tumour growth, but not for all tumours aetiologies complement is beneficial for the diagnosis individuum. This means, that complement can act as a tumour suppressant or a tumour stimulant, depending on the kind of tumour and maybe even the individual suffering from cancer[12]. Because of all these different roles complement has in our bodies, it is important to understand how complement is activated, and what the mechanism is behind the different outcomes of the same cascade. By gaining a greater understanding of the basic mechanisms of complement, modern therapeutics can be designed more efficiently. This also helps to find new treatments for currently incurable diseases.

2 References

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