SVAR COMPLEMENT EXCELLENCE AWARD

New insights into complement pathways and designing artificial complement regulators

An interview with Svar Complement Excellence Award recipient 2022

Dr. Christoph Schmidt has dedicated his career to understanding the complement system. His passion for structural biology and the design of new therapeutic molecules brought him to Edinburgh. There, while learning nuclear magnetic resonance (NMR) techniques to study the structure of proteins, he became interested in the complement system. Today, the complement system remains at the centre of his research, and he uses numerous techniques to investigate it and to design new therapeutic molecules. Dr. Schmidt is a research scientist at the Institute of Pharmacology of Natural Products & Clinical Pharmacology at Ulm University in Germany.

He is one of the recipients of the 2022 Svar Complement Excellence Award awarded for his contribution to the complement field, which includes his extensive work on the regulator Factor H and the complement protein C5. His fundamental contributions to the complement field have started to redefine the understanding of some of the mechanistic foundations upon which the complement cascade is organized.

"This is a very important prize and a great recognition of my work and the people in the lab. It promotes research in the complement field and is a great way to create awareness of the importance of the complement system. An extremely important prize to recognize group work and collaboration."

The complement system is an innate immune cascade and works as an intricately interconnected player. This way, it helps in managing global immune surveillance. It protects from infections by pathogenic microorganisms but also maintains tissue homeostasis by removing damaged cells.

The hallmark of a physiological complement response is to maintain the right measure between activation and regulation according to the needs of any situation. To achieve this, the complement cascade is tightly regulated to avoid the self-damage of healthy tissue. Insufficient regulation of the complement system can result in severe and life-treating complement intrinsic diseases or exacerbate the disease outcome of conditions not primarily caused by complement but aggravated by undue secondary complement responses.

The yin and yang of the complement cascade: the regulation of C3 activation

A key feature of the complement cascade is that it can be rapidly activated and amplified by a positive feedback loop to mount an adequate response to danger. Historically, three activation pathways have been described: The classical, the alternative, and the lectin pathway.

The complement cascade may be viewed as two cycles that rotate in opposite directions – not dissimilar to the concept of yin and yang. The activation cycle causes C3 activation and C3b amplification to drive the complement effector functions. Whereas the regulation cycle of C3 works to counteract the activation cycle. It is the balance between these two cycles that rule whether complement activation results in a mild and not-so-inflammatory response or whether it transitions to the terminal and inflammatory pathway induced by activating the C5 protein.

C3 and C5 activation

C3 and C5 activation is done by a complex of activated proteins called convertases.

These make a cut in C3 and C5 to create smaller effector molecules with different functions. The C3 convertase complex produces C3a and C3b fragments after the cleavage of C3; C3a is an anaphylatoxin with 'mild' inflammatory properties. C3b can form more convertases, but it also helps to prepare C5 for its activation by the convertase.

The C5 convertase generates C5a and C5b from C5; the anaphylatoxin C5a is a potent inflammatory molecule; C5b initiates the assembly of a membrane attack complex that creates pores in the cell membrane, killing bacteria or other cells.

In the case of an imbalance between the C3 activation and regulation cycle, the inflammatory effector function of the complement cascade, mostly C5a and MAC formation, can induce self-damage to healthy tissue.

The correct balance between these two cycles is crucial in ensuring that the right type and appropriate amount of complement effector functions match the biological context.between these two cycles is crucial in ensuring that the right type and appropriate amount of complement effector functions match the biological context.

> **"Targeting complement inhibitors or regulators to specific sites where pathophysiological complement activation is constantly ongoing is another strategy that is gaining momentum."**

Dr. Christoph Schmidt
Research scientist at the Institute of Pharmacology of Natural Products & Clinical Pharmacology at Ulm University in Germany

"If you have a disease that is driven by the complement system, you can expect a benefit if you inhibit the complement cascade; the challenges are to fine-tune the therapeutic strategy to the right target, not too early, not too late, the right tissue, the right molecule. In some diseases, you might have to target C3 or C3b instead of C5 and in other conditions, another complement target may still be more appropriate."

New tricks for an old 'complement' dog

It is traditionally accepted that C5 activation occurs by a protein complex known as C5 convertases. C3b (the bigger, activated split product of C3) was described as one essential molecule of the C5 convertases. Hence it appears logical that inhibiting C3 or C5 activation prevents the transition into the terminal and inflammatory complement pathway. Currently, clinical practice uses therapeutic inhibitors with a high affinity for C3 and C5 proteins. These inhibitors will attach to one or two non-activated molecules of C3 or C5 and thus inhibit their proteolytic activation by the convertases. These inhibitors, which may be referred to as stochiometric inhibitors, have been proven to effectively manage the unwanted effects of inappropriate complement activation. They prove to have a substantial clinical impact saving the lives of patients.

However, in conditions with exacerbated complement activation due to complement amplifying conditions like infections or in the presence of a high amount of complement-activating autoantibodies directed against erythrocytes, inhibiting C3 and C5 by stoichiometric inhibitors is not completely efficient, and the complement cascade is not always wholly suppressed.

Dr. Schmidt's work has provided fundamental new insights into the mechanisms behind these clinically observed phenomena. A C3-bypass mechanism of C5 activation was discovered when the classical or lectin pathway are very strongly activated.

In the absence of functional C3 (either due to its complete absence or due to it being inhibited by a stoichiometric C3 inhibitor), C5 can be activated by the C3-bypass activation mode inducing C5a release and pore formation, which inflicts inflammation and cell damage.

His work has also shown that the inefficient inhibition of C5 during complement amplifying conditions (which is denominated pharmacodynamic breakthrough) cannot be reverted by supplying more of the same C5 inhibitor drug. Instead, it was proposed that a combination of two different C5 inhibitors or a C5 inhibitor together with an inhibitor that acts earlier in the cascade can yield complete inhibition. This may successfully stop terminal pathway activation in conditions when a single C5 inhibitor suffers from a substantial pharmacodynamic breakthrough.

"We are seeing C3 therapeutics in the clinic, and there is the dogma that you fully inhibit the complement cascade if you inhibit C3, but it is not always like that since we have shown that there is a C3 bypass activation route of C5."

Better, stronger, faster, innovative enzyme-like regulators of the complement cascade

The complement convertases, which are the core of the cascade, undergo a slow and intrinsic decay. Once the convertases complexes are decayed, they cannot reassemble and thus have lost their complement activating activity. Natural complement convertase-directed regulators act by dramatically accelerating the slow intrinsic decay of the convertase complexes as well as inactivating the scaffold proteins which assemble these complexes. The essence of the natural convertase-directed regulators is that they act only on the activated complement components and are fully recycled after they have achieved their regulation. Therefore, one of these can act repeatedly on different convertases in a catalytic-like or enzyme-like fashion without getting consumed. Dr. Schmidt and his team would like to harness this inhibition mode for future therapeutic purposes by engineering artificial regulators of enhanced regulatory activity.

"In the coming years, we will see an increase of clinically approved complement therapeutics targeting different complement proteins. The challenges are to design molecules that recognize host surfaces to increase specificity for the host tissues, which is expected to yield a better safety profile."

In one engineering approach, Dr. Schmidt and colleagues looked into optimizing the regulatory function of Factor H. This molecule is a soluble plasma protein and is one of the main endogenous regulators of the alternative complement pathway. It acts as a regulator mainly by enhancing the dissociation of the convertase complexes and enabling the degradation of the C3b scaffold that assembles these convertases. Factor H can also attach to self-surfaces (e.g. cells or basement membranes) by recognizing host-tissue markers. This way, the molecule helps maintaining complement regulation on these, safeguarding healthy host cells and tissues.

Dr. Schmidt's structural and functional work on Factor H has inspired the development of miniFH. MiniFH is an engineered version of the naturally occurring Factor H; however, it is 10-fold more active in important clinically relevant assays. In contrast to miniFH, which almost exclusively regulates the alternative pathway, a novel triple fusion protein comprising selected domains of three different natural complement regulators represents another engineered protein that efficiently regulates all three complement activation pathways: alternative, classical, and lectin pathway. This molecule was engineered to include the capacity to attach to host surfaces allowing it to regulate the cascade more selectively on host cells rather than pathogenic intruders.

"Targeting complement inhibitors or regulators to specific sites where pathophysiological complement activation is constantly ongoing is another strategy that is gaining momentum. There are opportunities for non-stoichiometric inhibitors that have an enzyme-like regulatory mechanism, and in this way, they may be able to perform multiple cycles of regulation and be especially efficient."

Novel and unexpected findings in the complement field to come

The current therapeutic C3 and C5 inhibitors approved for clinical use suffer from incomplete complement control in certain cases of very strong complement activation. The design of other types of inhibitors that act more efficiently is on the horizon.

> **"The novel therapeutics will open new ways to treat diseases with some complement involvement, but they also will bring unexpected findings, and we in the complement field will need to solve the riddles."**

The lessons from the clinical use of complement therapeutics have taught us some expected and unexpected outcomes. Consolidating these findings with what we know about the complement cascade opens avenues to optimize the complement inhibitors of the next generation which hopefully can be translated into more efficient therapeutics that will aid patients.

ABOUT THE PRIZE

The Svar Complement Excellence Award is handed out annually to individuals that have made great contributions to the complement field.

The awards are intended as grants for two recipients, each worth €20.000. In 2022 the prize was handed out during the European Meeting on Complement in Human Diseases (EMCHD), in collaboration with the complement community.

Read more about Dr. Schmidt's work:

Selected References

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