The current issue of Seminars in Immunology is devoted to complement dysregulation and its role in human disease. The various articles in this issue will address key events in the initial complement recognition and regulatory steps and explore the role of complement in glomerulonephritis, pregnancy disorders, rheumatic diseases and during development and disease of the central nervous system. The authors of these special articles have done their best to provide updated, yet compact, summaries of relevant research in these topics.

Complement recognizes its targets with the help of key recognition molecules, like C1q of the classical pathway or ficolins and mannosereceptor-binding lectin in the lectin pathway. Berhane Ghebrehiwet together with his colleagues provides a comprehensive and specific description of the most exciting receptor for C1q, that for the globular domains of C1q, gC1qR. This receptor appears to have a broad range of ligands and functions, to an extent that seems to exceed even that of C1q itself, the notoriously polyspecific complement recognition molecule. Despite the fact that there are other C1q receptors, gC1qR seems to attract interest as a “mystery molecule”. Many research groups from different fields have come across with gC1qR in unbiased analyses. Thus, uncertainty still exists as to the true nature of the receptor. This is despite the fact that its structure and the main ligand, i.e. C1q, is known. The other ligands have been described to include many coagulation and kinin system proteins. Functionally, in addition to the complement system gC1qR may thus play a role in coagulation and in generating bradykinin, a mediator of edema, pain and inflammation. The paper by Ghebrehiwet et al provides also some original data to indicate different interactions of the gC1qR receptor. Intriguingly, the authors suggest effects of gC1qR on metabolism, mitochondria, various types of cells, like endothelial cells and lymphocytes, and finally on infectious microorganisms and cancer cells. How can a single receptor be involved in so many activities? Arguments and explanations can be found in this authoritative and comprehensive review.

The complement system has been considered as complicated by many. However, the complexity of the system does not mean that it would not be important. Quite the contrary – many apparently redundant ways of getting activated or regulated only are the proof of the importance of the system. An elegant, additional way of regulation of the complement system is described by Cserhalmi, Józsi and colleagues. They show how the main regulator of the key activation step in the amplification pathway is itself regulated. It is only relatively recently that a family of complement factor H-related proteins (FHRs) have been found to influence in an opposing way the most important complement regulator factor H. The basic new concept is that FHRs are mostly devoid of their own complement regulatory activity but they can compete with factor H for binding to the C3d part of C3b, the main effector molecule of complement, and in some cases also to the surface poly-anion targets. The paper tells potential reasons why this kind of activity would have developed during evolution. It also describes mechanisms how abnormal FHRs, generated by genetic abnormalities in an unstable region of the human genome, can have excessive activities leading to diseases, like C3 glomerulonephritis. This is despite the fact that, except for FHR1, the concentrations of FHRs are relatively low in circulation. They can be significantly higher at local sites, though, which may mean yet another level of regulation. Also, deletions in the genes, especially the common FHR3-1 deletion, can have a predisposing effect on disease, via generation of autoantibodies against factor H. This seems to be one of the best examples of how tolerance to an endogenous molecule can be dependent on other molecules, and how the tolerance can be lost. Because of their apparent importance, research on FHRs is currently very active. For more discussion on this very exciting topic and the current understanding, please, turn a few pages and have a look.

Kidneys have classically been known to be the target for complement attack. This is because of physiological reasons, abundant blood flow, high filtration rate and direct contact of blood to the basement membranes in the kidney glomeruli. Kaartinen et al describe in their article the role of complement dysregulation in various forms of glomerulonephritis, all characterized by inflammation and damage in kidney glomeruli. A tremendous progress has been made recently in understanding the pathophysiology of some of the diseases in this category. A general lesson has been that the same disease outcome can take place because of multiple different reasons, genetic mutations in different molecules, autoimmunity or microbial infections. Usually, the common denominator for these diseases is dysregulation of complement and its consequent overactivation or misdirected attack against autologous tissues, usually endothelial cells, blood cells or the glomerular basement membrane (GBM). For example, for the rare Dense Deposit Disease (DDD), it is now well understood that overactivation of complement in the fluid phase and consequent deposition of C3b on the GBM is the main problem. This can be due to an autoantibody (called C3 nephritic factor) against the C3 convertase enzyme, C3bBb, or against factor H N-terminus or mutation or deficiency of factor H itself. In some other diseases, like IgA nephropathy and C3 glomerulopathy, a lot is known, but the full picture is not yet clear. As a very useful lesson, the article describes differences in the pathophysiological processes of different diseases, where complement is dysfunctional. The various forms of glomerulonephritis have taught us how different kinds of complement abnormalities can lead to distinctly different types of diseases. In addition, the article takes a clinical point of view to the glomerular diseases, where the nephrologists have various options for treatment. What is vital in choosing the treatment strategy, is to have as good understanding of the disease pathophysiology and of the causative factors as possible.

In early life, already at the embryo stage, a challenging contact between the blastomere with only few cells and the maternal
complement system takes place. Under normal circumstances the embryo is well protected against complement attack by expressing complement regulators or by being able to bind factor H. Infertility is very common but practically we don’t know anything about the role of complement in this condition, which thus remains a challenge for future studies. Once pregnancy gets initiated the challenges continue, not least because the fetoplacental unit represents an “allograft” with partially different tissue antigens and polymorphic variants compared to the maternal tissues or molecules. Therefore, not surprisingly, and despite the maternal immunological adaptation to the situation, there are risks to the pregnancy. The activities and regulation of the complement system during pregnancy and their potential abnormalities are discussed by Laura Teirlilä, Inkeri Lokki and colleagues. One of the most common pregnancy complications is preeclampsia, where the pregnant woman’s blood pressure increases and there is proteinuria suggesting a vascular problem. The nature of the problem and the fact that the condition is usually cured by delivery suggest that there is an overload of material released from the placenta to the maternal circulation. By being “only” a temporary organ, the placenta is somewhat fragile and has a continuum of surface epithelium, the syncytiotrophoblast, surrounding its villi, which are in direct contact with the maternal blood. The article discusses recent observations about the role of complement in pregnancy, its deficiencies and associating genetic variants that can provide clues to the underlying pathogenetic mechanisms. Apparently, multiple mechanisms operate to maintain tolerance to the fetus during pregnancy and to clear any potential microparticles released from placenta. Obviously, pregnancy can be a precipitating factor for diseases like lupus or hemolytic uremic syndrome (HUS), which have a strong underlying genetic predisposition. In addition, mutations in distinct complement factors, regulators or receptors could be involved. These could predispose to impaired clearance, inflammation or manifestations of intolerance. Indirectly the effects would be reflected in the maternal vasculature and especially in the kidneys. One of the best markers of preeclampsia is sFlt-1 (soluble FMS-like tyrosine kinase 1), an inhibitor of the vascular growth factor VEGF (and the receptor – VEGFR1 – for it, when on the cell membrane). It is likely that there is a link between complement, vascular changes and sFlt-1 in preeclampsia. More on this, inflammation, clearance and tolerance during pregnancy can be found in the paper by Teirlilä and her colleagues.

Apart from kidney diseases complement has traditionally been considered to have a clear and significant role also in rheumatic diseases. These are discussed in the article by Dijkstra and colleagues. Early classical pathway deficiencies predispose to lupus (SLE, systemic lupus erythematosus) and lupus-like disorders and excessive complement activation is seen in autoimmune diseases, like rheumatoid arthritis. In a way, these diseases represent the two opposite mechanisms of complement involvement. Thus, paradoxically, both complement deficiency and overactivation can lead to arthritis, and other systemic disease manifestations, like vasculitis. In rheumatoid arthritis complement is believed to become activated by immune complexes, like those between rheumatoid factors and IgG, and by autoantibodies to citrullinated or carbamylated molecules with neoantigenic properties. Complement deficiency-related lupus is thought to be due to an inability to remove debris from injured tissues or apoptotic/damaged cells. Complement is needed for removal of chromatin complexes, phospholipid-containing membrane fragments and immune complexes. If the clearance fails, the material may accumulate in vessel walls and lead to vasculitis and to secondary autoimmunity against e.g. DNA and phospholipids. This model is supported e.g. by a similar disease related to mutations in DNAse or anti-phospholipid antibody syndrome. Recently, however, additional mechanisms related to abnormal activity of T cells, CD8 + T cell metabolism or lack of tolerance in C1q deficiency have also been proposed. The roles of complement dysregulation, abnormal functions of FHRs, insufficient protection by factor H, C4bp or by membrane regulators have received, however, relatively little attention. The team of Leendert Trouw in their article will explore both traditional and novel aspects to provide a balanced update of the role of complement in rheumatoid arthritis, lupus and ANCA vasculitis.

A wide spectrum of functions of complement has been discovered in the central nervous system (CNS). In their article on “Complement dysregulation in the CNS” Lee et al describe not only the protective and damaging complement functions but also the surprising activities in brain development. For example, complement has been suggested to have a role in synaptic pruning to prevent an excess of neuronal connections in the limited space of the brain during its early development. Assumingly, the pruning process of complement together with the brain phagocytes, primarily microglia, is important for a proper function of neuronal networks. Although not yet firmly documented, it is possible that excess synaptic activities could predispose to schizophrenia later in life. Other unexpected, and unbiased, observations suggest that complement is involved in neuronal development, for example in guiding neuronal migration and in promoting progenitor cell proliferation.

Another important role for complement is assumed to take place along with aging, and related events in the brain. Atherosclerosis with all its consequences, like stroke and brain hemorrhage, involves complement at different disease stages, in the long period of disease development as well as in the inflammatory responses to acute attacks. The mechanisms of development of different forms of dementia, like a small vessel disease in the brain or Alzheimer’s disease, are poorly understood. Changes in vascular walls or accumulation of fibrillary material because of an inability to prevent its formation or to clear it are thought to involve also the complement system. Unsuccessful attempts by complement and phagocytes to remove the waste material or protease-resistant fibrils may sustain prolonged inflammation and lead to neuronal damage. Trent Woodruff together with his colleagues provide an in-depth description of the current state of understanding in this very fascinating area that will certainly raise interest also outside the complement field.

Because complement is a central mechanism in causing inflammation and tissue damage, an intense effort is ongoing to develop suitable pharmacological agents to control its excessive activation, to correct misdirected attacks or even to use its enormous biological power for treatment of malignant disease. Initial progress in these attempts has already been made, but surely, more is to come.

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