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Complement: The road less travelled

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Abstract

The complement (C) field has recently experienced a strong resurgence of interest due to, the unexpected discovery of new C functions extending its role beyond immunity and pathogen clearance, a growing list of diseases in which C plays a role, and proliferation of C therapeutics. Importantly, while the majority of C components in circulation are generated by the liver and activated extracellularly, C activation unexpectedly also occurs intracellularly across a broad range of cells. Such cell-autonomous C activation can engage intracellular C receptors, which then drive non-canonical cell-specific effector functions. Thus, much remains to be discovered about C biology. In this short review, we will focus on novel non-canonical activities of C in its 'classic areas of operation': kidney and brain biology, infection and autoimmunity – with an outlook on the next generation of C-targeted therapeutics.

Keywords

complement; brain; kidney; autoimmune disease; infections

Introduction

The complement (C) system is an ancient pathogen recognition receptor system (PRR) discovered by Jules Bordet in the late 19th century(1). It consists of over 50 proteins that

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are mostly generated by the liver and either circulate in the fluid phase or are membrane bound. Most C core proteins exist in a pre-enzymatic form and are activated in a sequential and cascade-like fashion (2–4). There are three activation pathways, the classical (CP), alternative (AP) and lectin pathway (LP) (4). The three pathways are triggered by distinct pathogens or noxious (self) antigens but then cumulate at the activation of the C core proteins C3 (C3a and C3b) and C5 (C5a and C5b) via the formation of C3/C5 convertases. C3 and C5 activation leads to the formation of the membrane attack complex (MAC, C5b-9) that forms pores on the pathogen surface and induces its lytic killing (2, 5). The anaphylatoxins, C3a and C5a signal through G protein-coupled receptors C3aR and C5aR leading to the recruitment and activation of immune cells. C3b (and further break-down products) are strong opsonins and mediate the phagocytic uptake and clearance of pathogens via scavenger cells (6). The C system is regulated by a group of proteins under the umbrella 'Regulators of C Activation' that are placed at strategic locations along the pathways (7).

Overall, C is recognized as the surveillance mechanism and the first line of host defense against pathogenic invasion (Figure 1) and C deficiencies are thus often associated with recurrent infections (8). Importantly, because C is central to the detection and removal of self-derived danger (for example, apoptotic cells and immune complexes (ICs)), C deficiencies can also cause autoimmune diseases such as systemic lupus erythematosus (SLE) (9, 10). Further, unwanted, uncontrolled, or prolonged C activation are all connected with a range of highly prevalent inflammatory disease conditions, including arthritis and cardiovascular disease (11, 12). Thus, C is known for decades to be an important therapeutic target and much time and effort has been invested in 're-setting' hyper-complement activation in acute and chronic inflammation.

Over the last decade, unexpected additional locations of C activation and function have been identified. Liver-derived and serum-circulating C proteins are accepted as key in fighting blood borne pathogens (2, 4, 13). However, studies from as early as the 1980s have indicated that many cell types can synthesize and secrete a range of C components into the close environmental space (14–17) across tissues and organs ranging from brain (18, 19) and eye (20), to kidney (21, 22) and intestine (23). Such local C production is biologically important for protection against infections as, for example, monocyte and macrophage derived C3, C4, and C5 components are required additional drivers in tissue protection against viruses and bacteria (14, 24, 25). An additional layer of complexity with regards to C activity was added by the finding that complement can also be activated within cells and can engage complement activation receptors in subcellular compartments. The activity of intracellular complement ('the complosome')(26) is associated with non-canonical C functions as it controls basic cellular processes such as cell metabolism and autophagy. For example, C3a generated intracellularly by human $CD4^+$ T cells engages the lysosomal C3aR and sustains T cell survival via the activation of tonic mammalian target of rapamycin (mTOR) (27). The cell-autonomous engagement of the C regulator/receptor CD46 during T cell activation by T cell generated C3b, induces metabolic reprogramming needed for Th1 induction and cytotoxic T lymphocyte activation (28) (29). Interestingly, such C driven cell-autonomous immunity can also be triggered by C3 fragments that had been carried into the cells' interior by pathogens that were opsonized with C3 fragments in serum (30).

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Thus, the novel insights into C biology across host tissues, in combination with the development of next-generation C therapeutics holds promise to tackle human inflammatory diseases more effectively. The International Complement Society (ICS) organizes an ICS Guest Symposium at the annual conference of The American Association of Immunologists (AAI) with the aim to inform about the progress and particularly the exciting findings in C research, and to engage immunologists across disciplines. At the 2022 AAI conference in Portland, OR (May 6–10), Jessy Alexander (University of Buffalo), and Jeanne Paz (Gladstone Institutes & UCSF) presented unexpected new findings on C activities in the kidney and in the brain, respectively. Further, Michail Lionakis (NIAID, NIH) gave an update on the role of C in fungal infections and hinted towards a new non-canonical C activity in the protection against candidiasis. The ICS Guest Symposium session was concluded by Michael Holers (University of Colorado) who provided an overview about the complex roles played by C during the natural history of rheumatoid arthritis. In this brief review, we will provide a summary about these presentations with appropriate biological background information and discussion on their future implications for C research and beyond.

Intracellular complement controls kidney disease (Jessy J. Alexander)

The kidney is an immunologically active organ (0.5–1% body weight) with 20-25% (1–1.2 L/min) of cardiac output traversing the kidney, and the glomerulus filtering 90–120 ml/min (31). The kidney becomes a multipronged intersection where the pathogen induces C activation and C evasion strategies, and activated C instructs local innate and adaptive immune system responses. Also, the kidney generates ammonia that interacts with C3 to activate the C alternative pathway (32). The kidney is a major extrahepatic site of C production with different kidney cells synthesizing both C3 and C5 and C regulatory proteins such as CD46, CD55, CD59 and Crry(33) (34). Studies show that along with IC mediated diseases such as lupus nephritis and IgA nephropathy where C levels are a part of the clinical evaluation, C system is also engaged and causes pathology in diseases including anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis(35) and dense deposit disease(36). C inhibitors are effective in diseases such as aHUS, paroxysmal nocturnal hemoglobinuria and ANCA vasculitis but shows only limited benefit in immune complex (IC) mediated diseases such as lupus and rheumatoid arthritis (37–41). ICs are present in 45–65% of patients with glomerular disease(42–44) with varying patterns of glomerular deposition.

As mentioned in the introduction, C activation occurs intracellularly across cells and dictates cellular behavior (26). However, its impact on tissue homeostasis is just beginning to emerge. Dr. Alexander addressed the question whether understanding C compartmentalization, intrinsic complement and its functions better, could be helpful in increasing C therapeutic effectiveness and disease management. To address this, she focused on the central C pathway regulator factor H (FH) (4). Factor H synthesized by the liver restrains the C cascade particularly at the alternative pathway and maintains C3 levels (2, 45). Here, Jessy Alexander presented novel data showing that FH could be serving as the ‘guardian’ (21) from within the kidney endothelial cell (Figure 1). She showed that both human and mouse kidney endothelial cells express FH. Also, reducing

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endothelial FH levels resulted in altered MASP, C1s, C4 expression, which are initiating proteins of the lectin and classical pathways, suggesting cross-communication or -regulation among the three C pathways (46). Absence of FH also altered the actin cytoskeleton with the formation of stress fibers leading to increased endothelial layer permeability(46). The kidney endothelium is a part of the glomerular filtration apparatus (47). Once the endothelial layer loses its integrity, the glomerular basement membrane that has no C regulators(48) becomes exposed to large C proteins and other toxins. In addition, actin cytoskeletal remodeling influences proliferation and angiogenesis and Jessy Alexander showed data that FH deficiency altered these parameters in kidney endothelial cells. Replenishing intracellular FH by transfection reverted cell proliferation close to normal levels. Importantly, earlier work from her laboratory showed that C5a, the breakdown product of C5, causes similar changes of cytoskeletal remodeling and proliferation of brain endothelial cells (49). Thus, controlled local and/or intracellular complement activation may regulate endothelial cells across tissues. Moreover, a recent publication from another group showed that intracellular FH can drive kidney tubular epithelial cell turn over and epithelial-mesenchymal transition and malignant transformation (50). Jessy Alexander's laboratory is now focusing on understanding the roles of downstream effectors in FH induced changes of kidney endothelial cells. Some findings include the observation that FH deficiency causes the translocation of nuclear factor kappa B (NF-κB) into the nucleus, where this transcription factor then modulates different innate and adaptive immune responses and plays a critical role in mediating inflammatory responses. Overall, the results presented suggest that modulating FH in kidney endothelial cells could be an effective target for maintaining the glomerular homeostasis.

Of course, these are early insights and understanding the complexities of and potential cross-communications between intracellular, cell-autonomous and serum-derived C will require substantial future work and research efforts. However, this will likely be rewarding as inflammation of the vasculature is common to the broadest range of diseases – unfortunately as recently demonstrated by the SARS-CoV2-induced Coronavirus Disease 2019 (COVID19) (51, 52) with local and/or widespread vessel inflammation being one of its cardinal features.

New roles for complement during brain injury (Jeanne T. Paz)

In her presentation, Dr. Jeanne T. Paz kept with the scheme of dissecting the roles of locally generated complement in tissue biology. The brain is a uniquely placed and immune-privileged organ, separated from systemic effects by the presence of the blood-brain barrier (BBB) (53), in which endothelial cells with intricate junctional formations prevent the influx of immune cells and large proteins. The brain comprises a complex assembly of functionally different cell types such as neurons that transmit impulses, oligodendrocyte cells that generate myelin, astrocytes that maintain homeostasis and microglia, the critical immune cells in the brain (54). Rather unexpectedly, research on the C system in the brain was and is one of the major drivers in our understanding of extra-hepatic and local C activity (55, 56). Since the brain is considered immune-privileged, one might expect any presence of C to be a sign of disease/neuroinflammation. However, C in the brain is actually a driver of normal development and homeostatic tissue activity (Figure 1). So far, most cells assessed

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in the brain synthesize C proteins. C produced in the brain is involved in neurogenesis (57–59), synaptic pruning (60, 61), scavenging apoptotic debris (62–64) and the response to and removal of inflammatory insults. However, excessive and prolonged C activation does contribute to neurodegenerative disease and to neuropathies during aging (58, 65–67). In addition, C activation in the periphery heavily impacts the brain: the anaphylatoxins C3a and C5a generated during systemic C activation render the BBB leaky (49) and can foster cancer metastasis (68). There is a substantial body of literature on these subjects, and we guide the reader to those for more detailed insights on the exciting and diverse roles of C in the central nervous system (CNS) (61, 65, 69).

Jeanne Paz presented data that further substantiated our understanding that C can indeed play a very sinister role in the brain, specifically during traumatic brain injury (TBI). TBI is a leading cause of disability in children and adults (70). Although TBI acutely disrupts the cortex, the outmost part of the brain, most TBI-related disabilities reflect secondary injuries that accrue over time as consequences of the initial impact. Understanding where, when, and how secondary injuries develop is critical for preventing disability following TBI. The Paz group applied spatial transcriptomics in a mouse model of TBI and found *C1q* and *C4* among the top differentially upregulated genes five weeks after TBI in a subcortical brain region called the thalamus, which is reciprocally connected with the impacted cortex (71). Using immunohistochemistry and *in vivo* electrophysiology, they noted that increased C1q expression colocalized with neuron loss and chronic inflammation, and correlated with disruption in sleep spindles and emergence of epileptic activities. Mice treated with an antibody that blocks the C-activating effect of C1q ameliorated these pathological features, suggesting that C1q is a disease modifier in TBI. Using single-nucleus RNA sequencing, the Paz group pinpointed microglia, as the source for generating the detrimental C1q production, and suggest overall that the activation of the classical C pathway in the thalamus could be a target for treating TBI-related disabilities (71). The latter is a notion that the lab is now following up with further studies.

Revisiting complement in fungal infections (Michail Lionakis)

The role of serum circulating ‘classic’ C in the protection against fungal infections are mostly understood among complementologists. However, the functions of cell-autonomous and intracellular C activities during pathogen sensing and removal have not yet been explored but is an area of growing interest. Dr. Michail Lionakis gave an update on C in fungal infections and shared some initial insights into new and ongoing work on C and candidiasis in his laboratory. In his presentation, Michail Lionakis first summarized the published work on the role of C in host defense against systemic candidiasis (72–75). Fungal infections during hospitalization are a common occurrence especially in critically ill patients in the intensive care unit. In a 2019 Centers for Disease Control and Prevention (CDC) report, fungi were among the major pathogens that were drug resistant in the United States (76). Along with increased infections by nosocomial pathogens, fungi that are emerging due to climatic and other environmental changes enhance the risk further (77, 78). Improving fungal diagnostic modalities and identifying effective therapeutic targets is an urgent need. The recent introduction in the clinic of the C5-targeted monoclonal antibody eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria and hemolytic uremic syndrome

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has uncovered a critical contribution of C5a signaling in antifungal host defense as eculizumab-treated patients were reported to develop meningococcal infections and systemic candidiasis with high mortality (79, 80), as well as invasive pulmonary aspergillosis(81). These observations in humans were unexpected because of the lack of reported invasive fungal disease in patients suffering with inherited *C5* deficiency (Figure 1). C5 deficiency patients are typically at high risk for invasive infections by encapsulated bacteria (82). This susceptibility prompted the United States Food and Drug Administration (FDA) to update the package insert of eculizumab in 2018 to warn for the risk of invasive fungal infections in addition to pyogenic bacterial disease in vulnerable patients receiving the drug.

Prior work had examined inbred DBA/2 and A/J mouse strains, which are *C5*-deficient, and had found them to have significantly greater mortality after systemic challenge with *C. albicans* (72–74), in a model that relies heavily on phagocyte-mediated innate, not lymphocytic, responses for effective host defense (77). These inbred mice had greater fungal burden in several, but not all, examined tissues after infection associated with enhanced pro-inflammatory responses in infected organs (72–74). Yet, the mechanisms of impaired phagocyte-dependent immune responses were not thoroughly examined in those studies and the inbred DBA/2 and A/J mouse strains exhibit additional immunological defects beyond C5 deficiency (83, 84). Another study examined C3-deficient mice after systemic challenge with *C. albicans* and *C. glabrata* and found them to exhibit increased mortality after infection with associated enhanced levels of pro-inflammatory cytokines in infected tissues, yet the precise mechanisms of impaired host defense in the absence of C3 were not defined (75). Recent work from the Lionakis lab dissected the mechanisms by which C critically contributes to host defense against invasive fungal disease. This is particularly timely as the rising infections by systemic candidiasis and the multidrug resistant *Candida auris* (78, 85) infections in response to treatment with eculizumab (79, 86), and other novel complement pathway inhibitors have become a major clinical problem during treatment of various vulnerable patient populations. Michail Lionakis presented unpublished data that shed light on the mechanisms by which C5a-C5aR1 signaling promotes protective phagocyte-dependent host defense against invasive candidiasis in mice and humans – with initial indication that cell-autonomous C5a generation in myeloid cells may be key (Desai et al., under review). The importance of C activation in antifungal immunity was highlighted and underscores the need for careful surveillance of patients treated with various C pathway inhibitors for the development of opportunistic fungal disease.

The three presentations detailed above are examples of changes in our thinking about C biology and C in human disease. Among the key realizations in our field is the understanding that C operates at different and unexpected locations, that is in circulation (liver), locally (cell-derived) and intracellularly (cell-autonomous). In addition, a given role of C in a specific cell manner also changes with the activation state of that cell, and often in a temporal fashion (87, 88). Consequently, we need to understand the distinct roles of C at different locations and over the course of C engagement (onset, progression, resolution) to fully comprehend its role in normal biology and to tackle the system optimally in diseases. This notion was then brought beautifully forward, and applied to the pathogenesis of rheumatoid arthritis by the presentation of Michael Holers.

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Stage- and context-dependent roles for complement in rheumatoid arthritis evolution (V. Michael Holers).

Rheumatoid arthritis (RA) is a chronic autoimmune disease whose exact etiology is not completely understood. The triggers include mucosal inflammation and dysbiosis (89). RA affects most often the peripheral small joints causing the synovium to thicken by accumulating and incorporating immune cells to form the pannus that destroys cartilage and bone (90). The LP, CP and AP are likely all activated in RA by diverse triggers such (11, 91) as autoantibodies, necrotic cells or exposed collagen and thus important contributors to the disease pathology in humans and in mouse models of the disease. The activation of major C components C3 and C5 (92) are increased in the synovium in RA indicating perpetuated local C activation. The presentation by Holers provided a somewhat different angle on C and RA: instead of paying, as most do, attention to the symptomatic site, the inflamed joint, his talk focused on the role of the C system throughout the evolution of RA (Figure 1). Holers stressed the fact that RA exhibits a prolonged preclinical period of time that involves the development of chronic mucosal inflammation, especially prominent in the lung and intestine, which is associated with the local production of RA-related autoantibodies designated ACPA (anti-citrullinated protein antibodies)(93) and RF (rheumatoid factor) (94). His team helped spear-head detailed analyses of intact and cleaved C activation components in the sputum of preclinical RA individuals (95). This work detailed the presence of C activation fragments that are associated with neutrophil extracellular trap (NET) formation and elevated cytokines and chemokines (96). Further, the observed C activation during this earlier pre-clinical phase is causally associated with the development of NETs and autoantibody generation. Transition of the disease to involve the synovium was also associated with informative and specific patterns of C gene expression and localization of activation fragments and receptors. As a major outcome, the team noted positive associations in early RA between a subset of synovial, but not peripheral blood cell, C gene expression levels encoding factors such as Factor B and C5aR1, with clinical disease activity. Conversely, and somewhat unexpectedly, *C5* gene expression itself is inversely associated with disease activity. Immunohistochemical analyses of the inflamed tissue sites demonstrated regional differences in C factor localization, and inverse relationships between activation fragments and regulatory molecules. Therefore, RA is a disease with substantial opportunities for therapeutic impact, and specific attention to early disease and regulation of the C3/C5 convertases may be particularly worthy.

Conclusions

The C system was thought to be fully functionally defined and well understood for many years. Novel C insights and discoveries over the last two decades, however, have proven us wrong. C is not only a pro-inflammatory pathogen fighter but at the heart of normal cell and tissue development and function. The system not only actively operates body-wide in serum, but also participates on a cellular and sub-cellular level in basic cell physiology and regenerative processes. The exact modes of specifically the latter, non-canonical, C activities and their regulation are incompletely understood and therefore need to be explored further. Much progress has been made in several areas of C therapeutics through the

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development of drugs such as Eculizumab (41), Avacopan (97), C1 inhibitor, etc., as well as Ravulizumab (40) (a long lasting C5a inhibitor), and sutimlimab (an inhibitor for C1s) that are approved for diseases such as PNH, ANCA vasculitis and cold agglutinin disease, rendering these diseases more manageable. However, a larger number of C therapeutics have not delivered in the clinical and/or in more common disease settings. Understanding the recently discovered non-canonical C activities on a molecular level and their interplay with the classic, circulating components as well as with other PRR systems may provide new opportunities for drug development. Areas that need more in depth exploration include the role of cell-autonomous C in stromal and parenchymal cells in RA (98), the impact of the mucosal microbiota on local C activities in health and disease and the role of C in pain perception and illness behavior. Finally, one of the hottest subjects in the C field is its clear impact on cancer (for good or for worse) and we expect substantial new insights here soon (50, 99–104).

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Abbreviations

C	complement
FH	factor H
CP	classical
AP	alternative
LP	lectin
MAC, C5b-9	membrane attack complex
ICs	immune complexes
ICS	International Complement Society
AAI	American Association of Immunologists

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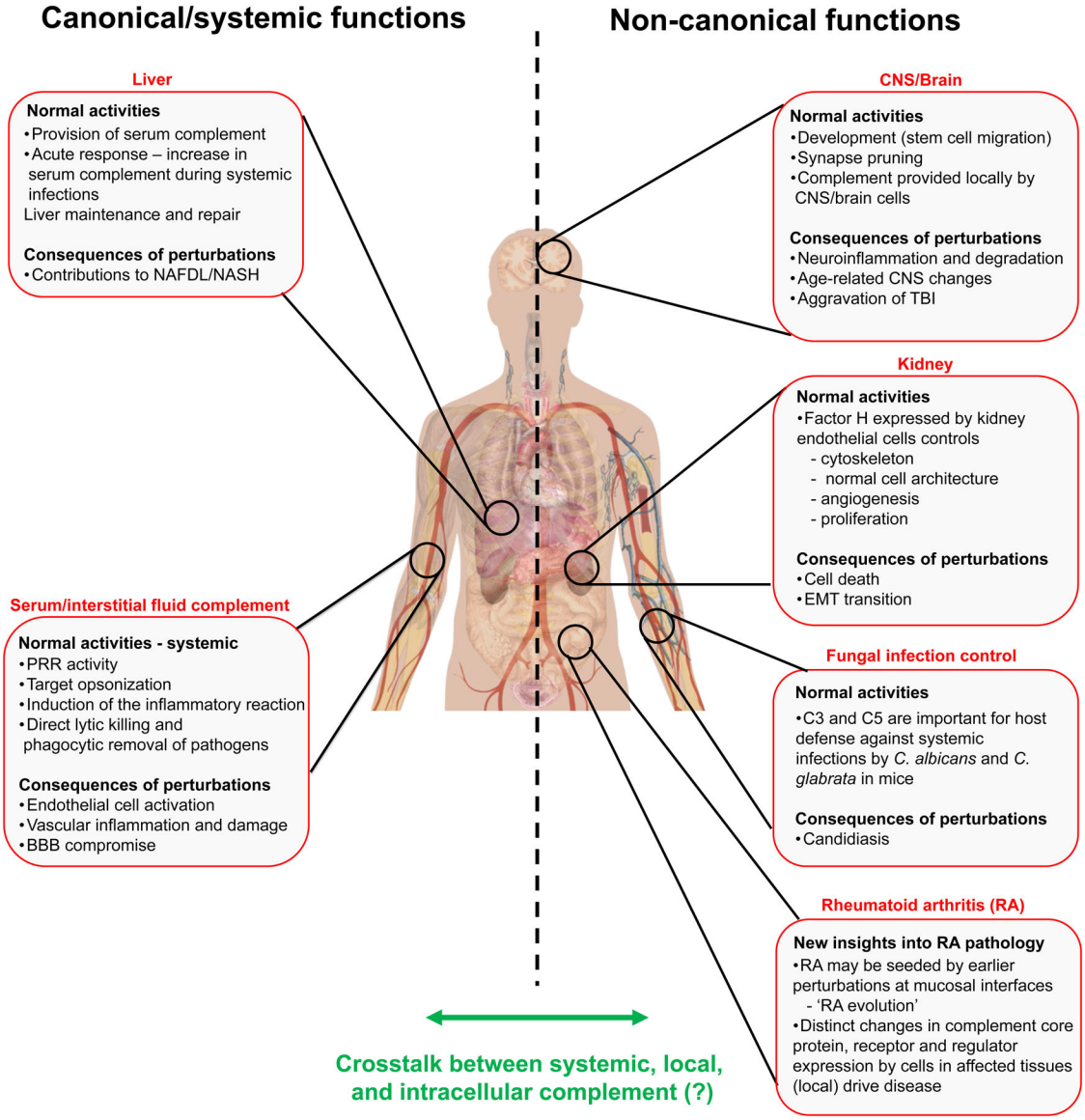

Figure 1. Visual summary of key insights gained at the AAI/ICS Guest Symposium.

The left side of the graphic summarizes the classic role of liver-derived C and consequences of its perturbations. The right side summarizes the discussed new roles of mostly cell-autonomous C activities in the brain, kidney and during candida infection and new insights gained about local C production during the evolution of rheumatoid arthritis. The exact underlying molecular mechanisms of these new activities remain to be defined, as are the potential cross-talks between the different locations of C activation and function (indicated by green arrow). BBB, blood brain barrier; CNS, central nervous system; EMT, epithelial-mesenchymal transition; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RA, rheumatoid arthritis; TBI, traumatic brain injury.