



Review

Local Tissue Complement Synthesis – Fine Tuning a Blunt Instrument

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Abstract. Complement is important to host defense and the regulation of inflammation. The liver is overwhelmingly the major source of circulating complement. However, many other organs are capable of synthesizing some or all of the complement components in a regulated tissue-specific manner. There is increasing evidence that this locally generated complement is biologically active and exerts powerful effects within the local environment. We review the role of local complement synthesis within different organs and speculate on its implication for immune and metabolic functions.

Key words: complement; kidney; brain; bone marrow; adipocyte; glomerulonephritis.

Introduction

The complement system is pivotal in the regulation of inflammation and the host defense against microorganisms. In addition, it also helps target specific adaptive immune responses towards pathogens. It consists of at least 30 structural proteins, inhibitors and enzymes which interact in a cascade manner to generate a number of biologically active products²⁶. Although the liver is the main source of systemic complement, it has become increasingly recognised that many other tissues can synthesize different complement components²⁸. It is likely that most cell types are capable of producing some or all of the complement proteins. Does this ability represent an artefact, or does local complement synthesis serve specific functions in different organs? We review the evidence for the regulated local production of complement in different tissues, and speculate on its biological significance.

The Liver as a Source of Local and Systemic Complement

Elegant studies of C3 allotype conversion in liver transplant recipients in the 1960s illustrated that the liver is the overwhelming source of plasma complement¹. Within the liver, hepatocytes are the primary cell type responsible for the synthesis of these complement proteins²⁹. As C3 behaves as an acute-phase protein²¹, the concept arose that the liver responds to an inflammatory stimulus with increased production of complement, and that this source of complement helps to regulate the systemic inflammatory response. It is now apparent that smaller amounts of complement proteins are also synthesized by a range of other cell types in different organs. This locally produced complement may, additionally allow differential regulation of inflammation and cellular activation within these tissues.

Interestingly, even within the liver, local comple-

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ment production has a paracrine effect. Hepatocytes have receptors for C5a, and locally activated complement stimulates the acute-phase response via stimulation of hepatocytes. Ligation of the C5a receptor results in increased hepatic synthesis of α_1 -antitrypsin, α_1 -antichymotrypsin, and other complement components, and decreased production of albumin and transferrin^{4, 25}. Thus, locally generated complement within the liver can augment systemic inflammatory responses in the early stages of host defense against microorganisms by providing a rapid positive feedback signal to hepatocytes.

Although hepatocytes produce the vast majority of plasma C3, the liver is not the primary source of all the individual complement components. Hepatocytes produce relatively little C7 compared with the bone marrow³¹. It is not clear why the liver should synthesize all of the terminal pathway components yet produce only small amounts of C7. In addition, the liver does not produce any of the classical pathway C1q, nor the alternative pathway components properdin and factor D. Factor D is primarily synthesized by adipocytes and probably plays an important role in the regulation of fat metabolism.

Significant amounts of C3 are also produced in other tissues. It is hard to define exactly how much circulating C3 is derived from extrahepatic sources in health. However, quantitative analysis of C3 allotype conversion following liver transplantation demonstrated that extrahepatic C3 production accounted for up to 5.7% of the total circulating C3³⁰. This extrahepatic complement synthesis was maintained for at least one year. The bone marrow is potentially a major source of extrahepatic circulating C3, as it contributed up to 2.6% of total serum C3 immediately following bone marrow transplantation. However, even at the peak of production, the bone marrow is clearly not responsible for all the circulating C3 derived from extrahepatic sources. Furthermore, as the levels of bone marrow-derived complement become undetectable following successful engraftment, it is likely that other extra-hepatic organs contribute significantly to the circulating pool of complement. Although this spillover into the circulation remains a relatively minor contribution to the systemic pool of complement, it is likely that the concentration of locally produced complement within different tissues is much higher. Furthermore, it is interesting that following transplantation, bone marrow-derived complement is highest in the period of engraftment, a period characterized by graft-versus-host disease and infection. This suggests that local complement synthesis is regulated by inflammatory stimuli.

Many different cell types have subsequently been demonstrated to synthesize some or all of the complement components. The list includes hepatocytes, lymphocytes, monocytes, platelets, neutrophils, macrophages, fibroblasts, endothelial cells, epithelial cells, adipocytes, glial cells, renal and synovial tissue. The potential effects of this local production are only just beginning to be understood. We shall review the evidence that many different tissues are capable of producing complement in a tightly regulated manner, and that this local complement production plays a significant role in health and disease.

Extrahepatic Complement Synthesis

The brain

As many of the complement components are large proteins (typically 150–200 kDa), the blood-brain barrier effectively bars the passage of plasma complement in the absence of inflammation. LEVI-STRAUSS and MALLAT²² first demonstrated that astrocytes are capable of synthesizing complement components. It has subsequently been shown that astrocytes can produce all of the classical, alternative and terminal complement components^{17, 18}, and that these cells are the major source of complement within the brain. In addition, they also express many complement receptors and regulatory proteins^{16, 34}. The expression of regulators of complement activation renders these cells relatively resistant to lysis by the complement they produce. In contrast, oligodendrocytes and neurons can directly activate complement, and are very sensitive to complement-mediated lysis. Microglia also produce classical pathway complement components. The complement produced by these cells and astrocytes may have a role in defense against micro-organisms either by direct killing or via opsonisation. In addition, it will also activate and attract other astrocytes and microglia in the local environment.

The constitutive production of complement *in vitro* by astrocytes is low in comparison with hepatocytes. However, synthesis can be up-regulated 50 fold by IFN- γ ¹⁷. It seems likely that, although the contribution to total plasma complement is very low, significant local concentrations of biologically active complement can be achieved. Furthermore, astrocytes themselves secrete a range of inflammatory cytokines. Thus, a mechanism exists to regulate local complement production within the central nervous system (CNS) to sites of active inflammation. The abundant expression

of complement regulatory proteins by astrocytes ensures that complement activation is restricted to the local environment. This provides an elegant system for augmenting local inflammation without the need for stimulating systemic complement production. Local complement production can be viewed as an initial defence mechanism, allowing rapid, localized inflammation confined to the precise site of invasion by pathogens. It is only when a pathogen escapes this control mechanism that a systemic inflammatory response is necessary. Astrocytes are resistant to the lytic effects of complement and, as they express receptors for C3a and C5a^{18, 27}, it is likely that non-lethal complement attack is itself an important trigger for cellular activation in an autocrine manner.

Complement activation has been demonstrated in many pathological conditions of the brain, including multiple sclerosis⁴³, Alzheimer's disease¹³, stroke and traumatic brain injury⁴². Although some of these conditions are inflammatory, others are degenerative, implying that local complement synthesis occurs within the brain and has a role in the pathogenesis of some CNS diseases. This illustrates the dual nature of complement: protecting against invading pathogens yet being potentially harmful.

Complement undoubtedly has a role in the pathogenesis of many CNS disorders, but it has been difficult to dissect out the relative importance of locally and systemically generated complement. Recently, the biological significance of local complement synthesis in the brain has been illustrated by an elegant study by DAVOUST et al.¹⁰. Transgenic mice with astrocyte-specific expression of the soluble complement inhibitor sCrry were generated. Crry effectively blocks activation of both the classical and alternative pathways. These mice have no detectable sCrry in their serum, but high secretion from astrocytes. This effectively limits local complement activation within the CNS, but not systemically. In a murine model of multiple sclerosis (allergic encephalomyelitis), these mice develop significantly delayed clinical signs of disease and reduced pathological signs of inflammation, demyelination and complement deposition. It will be interesting to see if these observations can be extended to other inflammatory or degenerative central nervous system diseases.

Bone marrow cells

Various bone marrow-derived cells can produce complement, including neutrophils², lymphocytes, macrophages and monocytes⁴⁷. Monocytes and tissue macrophages produce most of this bone marrow-derived

complement. As bone marrow-derived cells infiltrate most tissues during inflammation, these cells can effectively take complement synthesis and activation to the site of injury, amplifying local inflammation without producing systemic effects. It is not clear how much the bone marrow contributes to circulating complement levels. Immediately following bone marrow transplantation, the amount of donor-derived complement in the circulation can be as high as 2.6%, but this rapidly declines³⁰.

FISCHER et al.¹⁵ have demonstrated that this local source of complement synthesis can have important functional consequences. Complement plays an important role in stimulating antibody responses at threshold doses of antigen¹¹. C3^{-/-} mice have impaired antibody responses to T dependent antigens. When reconstituted with bone marrow from C3-sufficient littermates, these mice appear to have a normal antibody response, suggesting that complement produced by bone marrow-derived cells within lymphatic sites is sufficient to compensate for a near absence of circulating complement. Interestingly, following inoculation with antigen, macrophages within the splenic white pulp areas demonstrated dramatic up-regulation of C3 synthesis. This C3 synthesis was dependent on immunization, as C3 mRNA could not be detected in nonimmunized mice. Thus, not only is locally synthesized complement functionally active, but there is also tight regulation of its production. It is likely that local cytokine production within the germinal centres stimulates macrophage complement synthesis. It is conceivable that many other immunomodulatory and cell-activation effects of complement are mediated primarily through local rather than systemic complement production.

Adipocytes

The curious link between mesangiocapillary glomerulonephritis and partial lipodystrophy (PLD) provided the stimulus for observing local complement synthesis by adipocytes. These cells are the primary source of factor D³⁵. In addition, they have the ability to produce all of the complement components of the alternative pathway⁵. In PLD, subcutaneous fat is permanently lost from the face and upper body. These patients often have dysregulated activation of the alternative pathway associated with the presence of nephritic factor (an IgG autoantibody that stabilizes the alternative pathway C3 convertase). Uncontrolled activation of locally produced C3 results in adipocyte killing²⁴.

The alternative pathway is spontaneously activated on and around adipocytes generating C3a. C3a has po-

tent activity as an acylation-stimulating protein, promoting esterification of fatty acids into triglyceride. C3a increases the membrane transport of glucose into adipocytes and increases the activity of diacylglycerol acyltransferase, markedly increasing the rate of triglyceride synthesis⁷. Factor D expression is increased in fasting or catabolic states⁶ and decreased in various models of obesity³³. It seems likely that complement has an unexpected but important role in fat metabolism. The adipocyte may regulate its capacity to activate the alternative pathway according to the need for triglyceride storage or release. Further study of other tissues may reveal unforeseen actions of local complement synthesis other than the well-described systemic functions.

The kidney

Many cells within the kidney are capable of producing complement, including glomerular mesangial³⁶, epithelial³⁷ and endothelial cells⁴¹. However, the predominant source of complement synthesis within the kidney are tubular epithelial cells³. Complement synthesis within the kidney can be up-regulated by inflammatory cytokines such as IL-1 α ¹⁹, TNF- α ^{20, 41}, IL-2³ and IFN- γ ⁴⁹, whilst TGF- β reduces expression of C3 and C4²⁰. A striking observation is that IL-1 and endotoxin administered *in vivo* to mice increased gene expression of complement within the kidney, but not within the liver¹⁴. In addition, various inflammatory conditions stimulate differential complement synthesis within different regions of the kidney⁴⁶. Thus, the kidney, like many other organs, has its own specific sites of complement synthesis, and evidence exists of site-specific regulation, allowing the kidney to adapt its immune response to different stimuli.

Furthermore, this locally derived C3 can make a substantial contribution to circulating complement⁴⁵. It is likely that local tissue concentrations of complement are higher than within other extrahepatic sites. This raises the question of whether local generation of C3 augments any specific function of the kidney. Two particular pathological processes merit consideration. One is the susceptibility to immune-complex injury observed in complement-deficient states. The second is chronic tissue injury consequent to many renal diseases, but especially following transplantation.

The kidney, with its high blood flow and filtration function, is often the major organ affected in systemic complement deficiency. Immune-complex nephritis is common in patients with complement deficiency²³. It is possible, therefore, that local synthesis of complement

has a modifying effect on either the stability of immune complexes reaching the kidney or on their clearance by phagocytic cells, such as mesangial cells. Indeed, the expression of local complement is increased in experimental and clinical forms of immune-mediated nephritis. Although many animal models of glomerulonephritis are complement dependent^{8, 38, 39}, it is likely that complement has a different effect in florid acute tissue injury and either more insidious injury or the more chronic phase of subsequent tubulointerstitial damage. Far from increasing inflammatory injury, local secretion of C3 could produce a damping effect, enhancing the clearance of locally formed or deposited immune complexes. Support for this comes from the finding that C3^{-/-} mice demonstrate an impaired handling of immune complexes across the glomerular basement membrane when exposed to locally formed complexes between planted bovine gamma globulin and autoantibodies⁴⁰. Experiments are currently underway to try to differentiate the local and systemic effects of complement in models of glomerulonephritis.

In renal transplantation, by far the greatest site of complement gene expression is the renal tubule. During rejection episodes, the contribution of the kidney to circulating C3 increases up to 16%, compared with 4.5% in the uninjured kidney⁴⁵. Stimulated tubular epithelial cells secrete complement mainly in a basolateral direction⁴⁴. Fibroblasts¹² (which predominate in the interstitial tissue) as well as proximal tubular epithelial cells⁹ are vulnerable to complement attack. It is possible that hypersecretion of C3 could enhance the inflammatory or destructive effects of complement. Moreover, since complement gene expression seems to be a function of time, in experimental models of renal injury, increasing in parallel with the development of disease^{32, 48}, continued overproduction of complement could contribute to chronic damage. We have recently transplanted mouse kidneys between complement-deficient and -sufficient animals to assess the contribution of local synthesis of C3 to chronic damage. Preliminary results are extremely encouraging and indicate an important effect on graft fibrosis and tubular damage (PRATT personal communication).

Conclusions

Plasma complement is important to host defense and immune-complex handling, but many extrahepatic tissues are capable of producing some or all of the complement components. Although the total contribution of local synthesis to circulating complement levels is rela-

tively minor, there is increasing evidence that local tissue synthesis exerts powerful effects, finely tuned to the demands of the local environment. Some sites of the body are excluded from systemic complement, necessitating local complement production for host defence. At other sites, local production may provide rapid, but geographically limited inflammation and cellular activation at sites of tissue damage. Furthermore, it may regulate cellular metabolism and activation in a tissue-specific manner. Thus, complement activation is not just a blunt first line of defense against pathogens. As yet, although extrahepatic complement synthesis has been demonstrated in many different pathological models, its true significance is poorly understood. It is likely that more subtle effects of complement activation will be recognized in different tissues. Further characterization of the biology of complement within different organs may provide a spur for the development of therapeutic tissue-targeted complement inhibition.

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