Clin Exp Immunol 1997; **107**:1–7

REVIEW

Extrahepatic complement biosynthesis: where, when and why?

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(Accepted for publication 2 September 1996)

INTRODUCTION

The complement (C) system is a key component of innate immunity, playing a central role in defence against microorganisms and in the processing of immune complexes. It is also a powerful drive to inflammation and can, if unregulated, cause pathology. The last few years have seen a gradual realization that these events occur not only in the plasma, with its abundance of C proteins, but also in the tissues, where plasma C may penetrate poorly or not at all. The need for a functioning C system at these tissue sites must be met, either by increased influx of plasma C or by local synthesis. The purpose of this brief review is to summarize the evidence that C synthesis occurs at tissue sites and to advance the concept, suggested by studies in a variety of tissues, that local production of C is important in tissue homeostasis and immune defence.

SOURCES OF PLASMA C

Components of the classical (C1, C4, C2, C3), alternative (factor B, factor D, properdin, C3) and terminal (C5, C6, C7, C8 and C9) pathways of C are all present in plasma at concentrations which range from as low as 2 μg/ml (factor D) to as high as 2 mg/ml (C3). In the late 1960s, elegant studies of C3 allotypes in individuals undergoing liver transplantation provided an unequivocal demonstration that hepatocytes were by far the major source of plasma C3 [1,2]. The demonstration that plasma C activity and the plasma concentrations of several C components behaved as acute-phase reactants, increasing several-fold in response to inflammation, further implicated the liver as the source of plasma C [3,4]. These studies were extended over the following decade to show that hepatocytes were primarily responsible for synthesis of most of the C components in plasma (Table 1). However, there were some important exceptions. No convincing evidence for hepatocyte biosynthesis of the classical pathway component C1q or the alternative pathway components factor D and properdin could be found, and the demonstration that C7 alone among the terminal pathway components was not an acute-phase reactant raised the possibility that it too might be predominantly synthesized elsewhere.

The primary source of plasma C1q remains incompletely resolved. Epithelial cells, fibroblasts and cells of the monocyte/macrophage lineage have all been shown to synthesize C1q *in vitro*, and it is likely that each of these cell types contributes to plasma C1q [5,6]. Monocytes also synthesize C1r and C1s, assemble and secrete the complete C1 macromolecule and are the probable source of the bulk of C1 in plasma. Hepatocytes *in vitro* also synthesize C1r and C1s but produce no C1q, and hence cannot assemble intact C1. The fate of the C1r and C1s molecules generated by hepatocytes is unclear.

The primary source of plasma factor D is the adipocyte [7,8]. The recognition that the serine protease, termed adipsin, secreted by adipose tissue, was identical to factor D established an important bridgehead between the C system and lipid metabolism which will be discussed later. Monocytes and macrophages also synthesize factor D, but their contribution to plasma levels is likely to be minor.

Plasma properdin appears to be derived mainly from monocytes and macrophages [9]. Other circulating cells, including granulocytes and lymphocytes, have been implicated as additional sources of properdin.

A recent study of C7 allotype switching following liver transplantation has confirmed the suspicion that C7 is not primarily derived from hepatocytes [10]. The evidence from this study indicated that the major sources of plasma C7 are monocytes and tissue macrophages (including liver Kuppfer cells). Polymorphonuclear leucocytes (PMN) appear to store large amounts of C7 (and C6), but it is unlikely that these cells contribute much to plasma C levels [11]. However, release of C components from PMN in the tissues might be of considerable importance in inflammation.

Monocytes *in vitro* have been shown to be capable of synthesizing all of the components of C and of generating a haemolytic C system [12,13]. However, under most conditions the contribution of monocytes to plasma C (with the exception of the components noted above) is likely to be minor in comparison with that of the liver. The contribution of tissue macrophages to local C synthesis may, however, be of major importance.

LOCAL SYNTHESIS OF C IN TISSUES

The list of cell types which have been shown *in vitro* to be capable of synthesizing C components is endless (Table 1). For many of these cell types, synthesis only occurs under vigorous cytokine drive, only small amounts of C are produced, and the relevance to the *in vivo* situation is dubious. However, there are other situations where cells generate significant amounts of C, either constitutively or under cytokine drive, and there is supportive evidence from *in vivo* studies for the importance of locally produced C. The role of

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Table 1. Expression of complement components and receptors

Pathway	Classical	Alternative	Terminal	Complement receptors	References
Liver: hepatocyte	C1r/s, C4, C2, C1-INH, C4bp	C3, B, H, I	C5–C9	C1qR, C5aR, C3aR	1, 2, 10, 14, 15, 51, 52, 55–60, 62, 63, 79
Blood cells					
T cells		C3, P	C5	CR1, CR2, CR4, C3aR	64–70
B cells		C3, H, I	C5	C1qR, CR1, CR2, CR4	66, 68–70
Monocytes	C1q, r/s, C4, C2, C1-INH, C4bp	C3, B, D, P, H, I	C5–C9	C1qR, CR1, CR3, CR4, C5aR, C3aR	5, 6, 12–15, 55, 56, 61–63, 70–73, 80, 102
Platelets	C1-INH	H	C5–C9	C1qR, CR2, CR4, C5aR, C3aR	61, 62, 74–77
Neutrophils		C3, P	C6, C7	C1qR, CR1, CR3, CR4, C5aR, C3aR	9, 11, 61, 62, 70, 78
Macrophages	C1q, C1r/s, C4, C2, C1-INH	C3, B, D, P, H, I	C5–C9	C1qR, CR1, CR3, CR4, C5aR, C3aR	6, 12, 14, 15, 55, 56, 61, 62
Fibroblasts	C1q, C1r/s, C4, C2, C1-INH	C3, B, H	C5–C9	C1qR	6, 14, 15, 55, 56, 81–84, 102
Endothelial cells	C1s, C2, C1-INH	C3, B, H, I		C1qR, CR1, C5aR	6, 14, 15, 55, 56, 61, 62, 85–87
Epithelial cells	C1q, C1r/s, C4, C2, C1-INH	C3, B, H	C5	C1qR, C5aR	6, 14, 15, 55, 56, 62, 88, 89, 95, 102
Lung, macrophage + epithelial	C1q, C4, C2	C3, B, D	C5	C5aR	62, 89–91
Kidney, epithelial	C4	C3		C5aR	33–39, 41, 62
Skin, keratinocyte + fibroblast	C1-INH	C3, B, H		CR1, CR2	81, 82, 83, 92–94
Intestine, epithelial	C4	C3, B		C5aR	62, 95, 96
Skin, muscle, myoblast	C1-INH	C3, B, D, P, H, I			97, 98
Fat tissue, adipocyte		C3, B, D			7, 8
Synovial tissue	C1q/r/s, C2, C4	C3, B, D, H, I	C5, C6, C7, C9	CR1	99–102
Brain					
Astrocytes	C1q, C1r/s, C2, C4, C1-INH	C3, B, H, I, D	C5–C9	C1qR, CR1, CR2, C5aR, C3aR	16–21, 23, 28–31
Microglia	C1q, C4	C3		C1qR, CR3, CR4, C5aR	17, 22, 24, 25, 31
Genital tract		C3			103

cytokines in the stimulation of C synthesis has been well reviewed elsewhere [14,15] and is outside the scope of this review. Here we will discuss specific examples to illustrate the role of local production of C.

Synthesis of C in the brain

The brain is a privileged site, tightly shielded from plasma constituents by the blood–brain barrier (BBB). As a consequence, plasma C is unlikely to penetrate the brain parenchyma unless the BBB is disrupted. Given the importance of C in immune defence, the relative deficiency of C within the brain might predispose to infection. We and others have set out to examine whether cells in the brain compensate for this potential deficiency by generating C components locally. *In vitro*, astrocytes, the most abundant glial cell type, can synthesize and secrete all the components of the classical, alternative and terminal pathways and most of the soluble regulators of C [16–21]. Some of the components are synthesized constitutively while others are induced by inflammatory cytokines, notably interferon-gamma (IFN-γ). For all the astrocyte-derived C components, function has been demonstrated. Microglia, cells in the brain which resemble macrophages, have also been shown to synthesize C components *in vitro*, although difficulties in culturing these cells have made it difficult to evaluate this more fully [22]. Evidence for C biosynthesis by astrocytes and microglia *in vivo* is now emerging [23–25]. Reactive astrocytes, present in and around areas of pathology in many inflammatory brain diseases, stain strongly for C components, indicating that these cells may be secreting C [23]. Although the *in vitro* evidence suggests that the amounts of each component produced by astrocytes are modest in comparison with the levels generated by hepatocytes on a cell-for-cell basis, the levels of C attained locally at the inflammatory site may be high and sufficient to contribute to immune defence at this site (Fig. 1). C biosynthesis in the brain may also have negative consequences. Oligodendrocytes and neurons *in vitro* are susceptible to killing by autologous C, and destruction of these cell types by C has been implicated in demyelination and neurodegeneration, respectively [26,27]. Astrocytes and microglia also express receptors for the complement activation products C3d, C3a and C5a [28–31]. Activation of locally synthesized C, whatever the initiating stimulus, will lead to occupancy of these membrane C receptors which may cause activation of these cell types and a further increase in C biosynthesis—a positive feedback which may be an important drive to inflammation in the brain (Fig. 1).

Synthesis of C in the kidney

The kidney performs a vital role in haemofiltration, and as a consequence is the major site for immune complex deposition in health and disease. Proper processing of immune complexes is heavily dependent on the presence of a functioning C system [32]. Evidence that C components are generated locally within the kidney has emerged from studies *in vitro* [33–36] and *in vivo* [32,37–40]. Glomerular epithelial, mesangial and endothelial cells

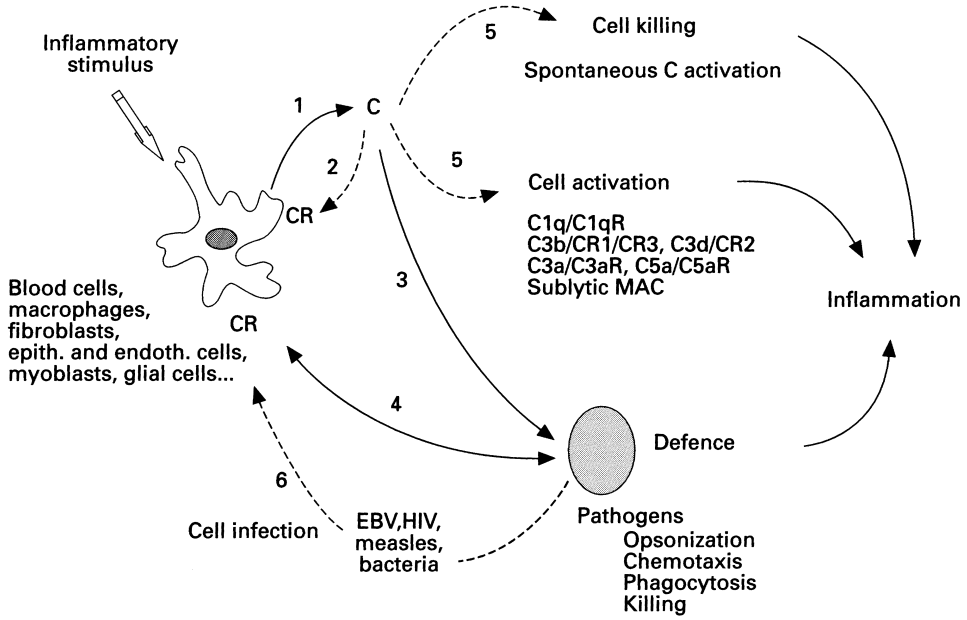

Fig. 1. C biosynthesis in tissues and roles in local inflammation and defence against pathogens. Blood cells (infiltrating myeloid cells), macrophages, fibroblasts, epithelial cells, endothelial cells and resident cells (astrocytes, adipocytes, myoblasts, etc.) are all potential sources of C in the various tissues (brain, fat tissue, muscle, etc.). For most C components in most tissues, constitutive expression is low or absent. However, following stimulation by cytokines such as IFN-γ and IL-1β (inflammatory stimulus, 1) cells are activated either to up-regulate or to express *de novo* a full C system. C components and fragments (C1q, C3a, C5a) will bind C receptors (CR) expressed by both resident and infiltrating cells (see Table 1 for details), causing cell activation and perhaps further enhancing C biosynthesis in an autocrine manner (2). The level of C components produced locally within the interstitial compartment can be sufficient to be a potent weapon against pathogens, either through direct killing (3) or through opsonization followed by interaction with CR expressed by resident or infiltrating cells (4). Many tissue cells can directly activate, in the absence of antibodies, the classical pathway (oligodendrocyte, neurons, etc.) or the alternative pathway (adipocyte) of C. Local synthesis of C may therefore also have other cellular effects such as (i) cell activation mediated by sublytic amounts of the membrane attack complex (MAC); (ii) cell activation by C fragment/CR interactions; or even (iii) cell killing (5). Another negative consequence of C expression in tissues is the utilization by viruses of CR and C regulatory proteins to bind and enter cells (6). Viruses such as Epstein–Barr virus (EBV), HIV and measles virus can thus establish a reservoir of infection in tissues.

and renal tubular epithelial cells have all been shown *in vitro* to synthesize C components either constitutively or under cytokine drive [33–36]. Synthesis and secretion of each of the components of the classical and alternative activation pathways have been demonstrated, but there is no clear evidence for synthesis of terminal C components. Once inflammation begins, infiltrating monocytes and macrophages will also contribute to local production of C in the kidney. Local synthesis of C may play an important role in defence of the kidney against invading microorganisms and might also be involved in renal handling of the physiological or pathological immune complex load *in vivo*. As is the case in the brain, local synthesis of C might also drive inflammation and pathology [31,35–40]. An important role for C as a drive to inflammation has been demonstrated in many animal models of renal disease and in some human renal diseases. The relative contributions of locally produced and plasma C to these physiological and pathological roles of C in the kidney have not been established. Sacks and co-workers have proposed to resolve this by transplantation of normal kidneys to animals deficient in hepatic C biosynthesis (either naturally occurring or engineered) and of kidneys from C-deficient animals to normal recipients [41]. These studies should go some way towards defining the importance of renal C biosynthesis in health and disease. A very recent investigation using a similar strategy has implicated extrahepatic C biosynthesis in transplant rejection [42]. C6-deficient rats reject guinea pig cardiac xenografts slowly in comparison with normal rats, demonstrating that rejection is C-dependent and involves assembly of the membrane attack complex (MAC). Livers were removed from normal rats and replaced with livers from C6-deficient rats, thus eliminating this source of C6. Rejection of guinea pig cardiac xenografts occurred at the same rate in these animals as in normals, indicating that C6 production from extrahepatic sources was sufficient to mediate rejection. Bone marrow-derived cells were implicated as the extrahepatic source of C in these studies.

Synthesis of C in adipose tissue

Adipose tissue is the primary source of plasma factor D [7,8]. A role of local C biosynthesis and activation in the regulation of fat metabolism in adipose tissue was first proposed by Spiegelman and colleagues [7]. They showed that murine adipocytes generated a protein termed adipsin, the mouse analogue of human factor D, and also synthesized the C components C3 and factor B. Further, they showed that these components provided a functioning alternative pathway which was spontaneously activated on and around the adipocytes with the generation locally of C3a. A functional role for adipsin and this local activation of C was suggested by the demonstration that expression of adipsin/factor D was reduced in adipose tissue from obese mice [43]. An independent investigation of human serum factors capable of stimulating triglyceride synthesis in adipocytes by Sniderman and colleagues had identified a basic protein termed acylation stimulating protein (ASP) [44,45]. Sequence analysis of this protein revealed that it was identical to human C3adesArg, the product of the action of serum carboxypeptidase on C3a. These threads were tied with the demonstration that human adipocytes also generated C3, factor B and factor D/adipsin, and locally generated or exogenous C3a triggered increased triglyceride synthesis in these cells [46,47]. A physiological role of this adipsin/ASP system of local synthesis and activation of C is suggested by the observation that plasma levels of ASP (C3adesArg) are high in obese subjects and fall during prolonged fasting, correlating inversely with the rate of triglyceride mobilization [48]. The data indicate that locally generated C3a and/or C3adesArg drives triglyceride synthesis in adipose tissue. Thus, in both human and rodent fat tissue, local synthesis and activation of C appears to play a central role in lipid metabolism. It is likely that adipocytes express specific receptors for C3adesArg and/or C3a, although this remains to be formally demonstrated. An important coda to this exciting work is that individuals deficient in C3 do not have gross deficits in adipose tissue metabolism. It is probable that other signalling systems exist which can compensate for the (presumed) absence of a functioning adipsin/ASP system. A proportion of individuals who have circulating C3 nephritic factors (autoantibodies which stabilize the alternative pathway C3 convertase) do have a deficit in adipose tissue metabolism, partial lipodystrophy, in which there is a loss of subcutaneous fat from the face and upper body. Peters and co-workers have provided evidence that this condition is caused by interaction of the nephritic factor with locally generated C3 convertases in adipose tissue, leading to uncontrolled activation of C and adipocyte killing [49].

OTHER ROLES OF LOCALLY GENERATED C

Local 'priming' by C

The review so far has focused on the 'classical' roles of C in immune defence and inflammation. However, the auto-activation cycle described above for adipocytes represents something rather different. Here the cells are behaving in an autonomous manner, synthesizing all the necessary components, triggering activation (through mechanisms which are unresolved) and responding to the products of that activation through specific receptors—C3a causing stimulation of triglyceride synthesis. We propose that auto-activation cycles of this sort are of physiological importance in many tissues. Local synthesis of C by cells in the tissue is followed by local activation on or around these cells, which in turn triggers responses to activation products through specific receptors on the cell. As well as C3a and C5a, the MAC may also be an important activator, triggering responses in various tissues [50]. Even if the levels of C synthesis are modest, high concentrations of activation products may be generated in the immediate vicinity of the cell, maintaining a basal state of 'priming' and providing a mechanism for rapid auto-activation. A further example to illustrate the potential importance of auto-activation is provided by the hepatocyte itself. It has recently been demonstrated that receptors for C5a are present on hepatocytes, and local activation of C in the vicinity of the cells has been implicated as a major stimulus to the hepatocyte acute-phase response [51,52].

Hijacking of C by microorganisms

A major role of C is to destroy microorganisms through direct killing or through recruitment and activation of phagocytes. However, many microorganisms have evolved strategies to avoid destruction by C, or even to turn C to their advantage (Fig. 1). These strategies are beyond the scope of this review, and are well reviewed elsewhere [53–54]. However, locally synthesized C and expression of C receptors in the tissues may be important factors in enabling microorganisms to successfully colonize tissues. Some microorganisms, including the Epstein–Barr virus (EBV) and the measles virus, directly use membrane C receptors to enter cells, hence any tissue which expresses the appropriate C receptors either

constitutively or during inflammation is a potential target for infection. Other microorganisms, including the HIV virus and several bacteria, interact indirectly with C receptors by first becoming coated with C fragments. Here, local C synthesis and activation in the tissues could provide a source of C fragments for coating, thus permitting infection of the cells.

CONCLUDING REMARKS

Plasma C is primarily derived from hepatocytes and fulfils important roles in immune defence and immune complex handling in the plasma. However, penetration of plasma C into tissues is limited by the large size of the components, particularly at 'protected' sites. In many tissues, locally synthesized C will compensate for this lack of plasma C. Local biosynthesis of C, spontaneous C activation and expression of receptors for C activation products in tissues provide a scenario for auto-activation of cells which has so far been explored in only a few tissues but may be relevant to homeostasis in many more.

ACKNOWLEDGMENTS

We thank The Wellcome Trust for financial support through the award of a Senior Research Fellowship to B.P.M. and a Travelling Fellowship to P.G.

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