

Complement fragments C3a and C5a: The salt and pepper of the immune response

Steven H. Sacks^{1,2}

¹ MRC Centre for Transplantation, King's College London, London, UK

² NIHR Comprehensive Biomedical Research Centre, Guy's and St. Thomas' NHS Foundation Trust and King's College London, London, UK

The influence of complement on B-cell responses has been known for many years, but the notion that T-cell recognition, expansion and differentiation are complement dependent has only recently gained impetus. DC, and to a lesser extent T cells, produce a range of complement components necessary for complement activation, and these cells also express receptors that detect complement-activation products such as C3a and C5a (anaphylatoxins). In the absence of C3a-receptor (C3aR) signalling, DC lose their capacity to induce potent Th1 responses against alloantigen and also favour the emergence of Treg. A study in this issue of the *European Journal of Immunology* not only spotlights the importance of C5aR signalling in DC interaction with T cells, but also shows how cooperation with other signalling pathways determines the outcome of T-cell activation. Remove C5aR from the equation, TLR2-stimulated DC induce naive CD4⁺ Th cells to undergo differentiation not only mainly to Th17 cells but also to Treg, via a TGF- β -dependent pathway. Thus, anaphylatoxins in conjunction with other danger signalling pathways modify the function of DC in antigen presentation and help to shape the primary immune response. Future work will need to address the impact of anaphylatoxins on protective immunity *in vivo* and determine the wider implications of anaphylatoxins for allo- and autoimmunity.

Key words: Complement receptor · DC · Th17 · TLR2 · Treg



See accompanying article by Weaver *et al.*

It was Mark Pepys who, in the 1970s, noted the influence of complement on the adaptive immune response [1]. He found that mice depleted of complement failed to develop potent antibody responses, although the effect was partially overcome by increasing the dose of injected antigen. A possible mechanism was suggested two decades later when complement receptor (CR2), which recognizes the large split fragment of C3, was shown to improve the retention of opsonised antigen in lymphoid tissue and markedly lower the threshold of B-cell activation by antigen [2, 3]. An influence of complement on the T-cell response was not immedi-

ately obvious, probably because complement-deficient mice were noted to have normal T-cell counts and display unexceptional resting T-cell phenotypes; however, studies of induced T-cell-mediated diseases later demonstrated diminished Th1 responses in mice lacking certain complement components [4]. It seemed that complement activation was essential for T-cell priming in these circumstances. A vivid example came from transplant studies, where T-cell-mediated rejection occurred only in the presence of donor kidney synthesis of C3 [5]. Out of this, emerged an understanding that donor APC, most notably DC, are able to synthesise a wide range of complement components [6, 7]. Secreted into the local environment, complement components contribute to local complement activation. DC from mice lacking certain complement components were found to be poor initiators of the T-cell response

Correspondence: Professor Steven H. Sacks
e-mail: steven.sacks@kcl.ac.uk

against donor antigen, and to result in higher proportion of Foxp3⁺ Treg [7]. This defect in antigen presentation can be traced, at least in part, to a lack of MHC class II and costimulatory molecules expressed on DC in the absence of complement activation (Fig. 1A) [7]. It must be noted, however, in addition to DC, T cells can also produce complement components (although at a fraction of the amount expressed by DC), as do various stromal and parenchymal cells, including hepatic cells (the main cellular source of complement in the circulation); thus, complement components from several sources may enhance complement interaction at the DC/T-cell interface [8].

Among the known effectors generated by complement activation, two potential champions have emerged: the anaphylatoxins C3a and C5a. These are the small soluble peptide fragments liberated by cleavage of C3 and C5, and named for their role in the induction of overwhelming inflammation (anaphylaxis). G-protein-coupled receptors that detect C3a or C5a link up with several well-defined intracellular signalling pathways. These convert extracellular signals into biological functions, such as mast cell and neutrophil degranulation, and smooth muscle contraction. Recent work highlighting the immunoregulatory action of anaphylatoxins has focussed on DC and their interaction with naive CD4⁺ Th cells [9–12]. Anaphylatoxin receptors present on DC help to determine the competence of these cells for antigen presentation. For example, in the absence of C3aR signalling on DC, the Th-cell response directed against alloantigen is reduced and dominated by Th2 cells and Treg, instead of Th1 [9]. T cells also have receptors for C3a and C5a, and in the absence of anaphylatoxin signalling, T-cell proliferation and T-cell longevity are both reduced after antigenic stimulation [11]. Being at the point of contact between APC and T cells, bidirectional signalling mediated by anaphylatoxins could thus ramp up the immune response.

In this issue of *European Journal of Immunology*, Köhl and colleagues [13] give careful consideration to the possibility of interaction between C5aR signalling and other danger sensing pathways. This is a sound notion, given that infection initiates multiple danger signals, which are recognised by innate immune receptors on DC [14]. The authors [13] arrange for experiments to

allow or deny C5aR signalling on mouse spleen DC, in the presence of TLR2 stimulation (with PAM), and determine how well these manipulated DC loaded with OVA stimulate OVA-specific CD4⁺ T cells. In full flight, antigen presentation is augmented by TLR2 and C5aR signalling, resulting in a vigorous Th1 response (Fig. 1B) [13]. In contrast, APC lacking C5aR signalling generate mainly Th17 cells and induce some Foxp3⁺ Treg via enhanced TGF- β secretion (Fig. 1C) [13]. This is a significant finding as it suggests that the integration, by DC, of C5aR and TLR2 signals strongly influences the outcome of naive Th-cell activation.

How does C5aR signalling regulate the capability of DC to present antigen? And in what circumstances would C5aR signalling be absent during antigen presentation? The report of Köhl and colleagues [13] provides some answers to these questions. The authors [13] show that DC stimulated in the absence of C5aR express lower cell surface levels of MHC class II and costimulatory (CD40 and CD86) molecules, compared with unmodified DC. As T-cell recognition critically depends on contact with DC through these molecules, variations in their expression mediated by C5aR signalling would be expected to affect antigen presentation. It is notable that both C5aR and C3aR signalling modulate the expression of alloantigen and costimulatory molecules on DC, with the expected influence on T-cell priming [10–12]. This suggests a strong degree of functional overlap in the effects of C3aR and C5aR signalling, which share some of the intracellular signalling pathways (e.g. cAMP, ERK, NF- κ B) that control DC function. Besides surface molecules, DC cytokine production is also affected by anaphylatoxin signalling [10, 12]. Of special interest, the large amounts of TGF- β secreted by DC in the absence of C5aR signalling contributed substantially to the expansion of Th17 and Treg [13].

Some pathogenic organisms express complement regulators that inhibit complement activation and thus allow pathogen evasion of host defence. These regulators usually act by inhibiting the cleavage of C3 and subsequently C5. As Köhl and colleagues [13] suggest, reduced generation of C5a could impair antigen presentation and alter DC cytokine profile, leading to a deviated

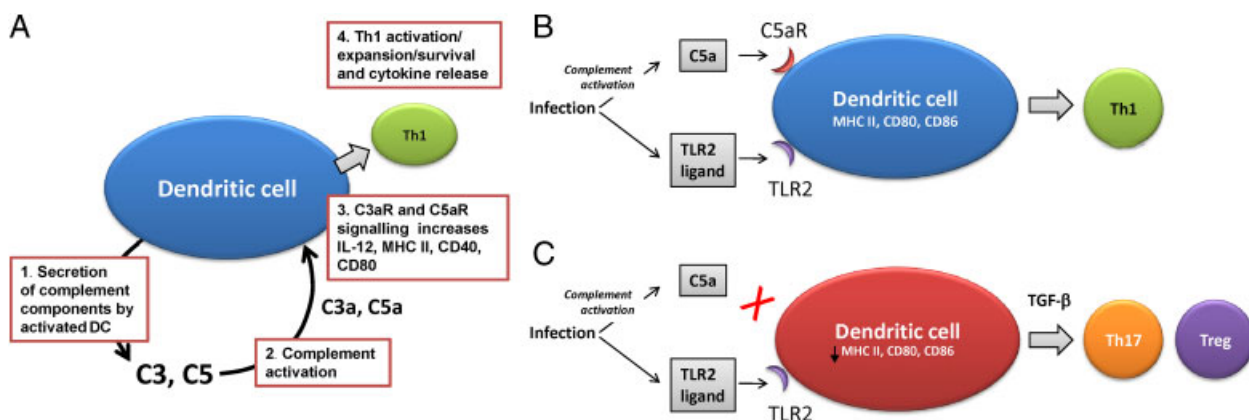


Figure 1. (A) Cell endogenous production of complement enhances antigen presentation and leads to a potent T-cell response in the presence of alloantigen. (B) Cooperation between C5aR and TLR2 signalling in APC induces naive CD4⁺ Th cells to undergo Th1 differentiation. (C) In the absence of C5aR signalling, DC stimulated by TLR2 show reduced expression of MHC class II and costimulatory molecules and increased production of TGF- β . Consequently, Th cells undergo differentiation to Th17 cells and Foxp3⁺ Treg in the presence of antigenic stimulation (OVA peptide).

immune response. Additional studies are needed to assess the influence of C5aR signalling on protective T-cell responses *in vivo*, in particular the potential outcome of replacing a protective Th1 response with a Th17 response in the context of bacterial infection. This could be different from fungal infection, where Th17 cells are known to have a protective role [15, 16].

The recent results with C3aR- and C5aR-mediated immune regulation raise interesting questions for T-cell-mediated diseases. In transplantation, for example, if anaphylatoxin receptors on donor APC are critical for triggering T-cell-mediated rejection [10, 12], then treatment of the donor organ using complement inhibitory strategies should be protective. Work is currently in progress to assess the effect of complement inhibitors or gene silencing in donor organs, largely to block the innate functions of complement on reperfusion injury [17]. The potential for deviating C5aR-mediated immune activation towards an inhibitory mode offers new scope for inducing graft acceptance. Safeguards will need to ensure that Th17-cell differentiation as a result of C5aR blockade is not counterproductive.

Several aspects of complement receptor biology remain unclear. It is implied that either C3aR or C5aR signalling will steer the immune response towards Th1; however, absence of either one of these receptors is sufficient to disrupt the Th1 response, indicating that there is little functional overlap. This is despite the sharing of several signal pathway components activated through C3a and C5a receptors. Whether C3aR and C5aR have overlapping or mutually distinct roles will be valuable to tease out, especially for the purposes of therapeutic application. In addition, there has been some confusion about the role of a third anaphylatoxin receptor, C5L2 – a non-signalling protein with high affinity for the C5a des Arg metabolite. C5L2 has been proposed as a physiological decoy receptor limiting the activity of C5a. The work presented by Köhl and team [13] put this notion to rest, in so far as their results with C5L2-knockout mice show no major effect on TLR2-stimulated antigen-presenting function.

Acknowledgements: The author receives funding from the Medical Research Council, the Wellcome Trust and National Institute for Health Research, UK.

Conflict of interest: The author declares no financial or commercial conflict of interest.

References

- 1 Pepys, M. B., Role of complement in induction of antibody production in vivo: effect of cobra factor and other C3-reactive agents on thymus-dependent and thymus-independent antibody responses. *J. Exp. Med.* 1974. **140**: 126–145.
- 2 Fang, Y., Xu, C., Fu, Y.-X., Holers, V. M. and Molina, H., Expression of complement receptors 1 and 2 on follicular dendritic cells is necessary for the generation of a strong antigen-specific IgG response. *J. Immunol.* 1998. **160**: 5273–5279.
- 3 Dempsey, P. W., Allison, M. E., Akkaraju, S., Goodnow, C. C. and Fearon, D. T., C3d of complement as a molecular adjuvant: bridging innate and acquired immunity. *Science*. 1996. **271**: 348–350.
- 4 Kemper, C. and Atkinson, J. P., T-cell regulation: with complements from innate immunity. *Nat. Rev. Immunol.* 2007. **7**: 9–18.
- 5 Pratt, J. R., Basheer, S. A. and Sacks, S. H., Local synthesis of complement component C3 regulates acute renal transplant rejection. *Nat. Med.* 2002. **8**: 582–587.
- 6 Zhou, W., Patel, H., Li, K., Peng, Q., Villiers, M. B. and Sacks, S. H., Macrophages from C3-deficient mice have impaired potency to stimulate alloreactive T cells. *Blood* 2006. **107**: 2461–2469.
- 7 Peng, Q., Li, K., Patel, H., Sacks, S. H. and Zhou, W., Dendritic cell synthesis of C3 is required for full T cell activation and development of a Th1 phenotype. *J. Immunol.* 2006. **176**: 3330–3341.
- 8 Heeger, P. S., Lalli, P. N., Lin, F., Valujskikh, A., Liu, J., Muqim, N., Xu, Y. and Medof, M. E., Decay-accelerating factor modulates induction of T cell immunity. *J. Exp. Med.* 2005. **201**: 1523–1530.
- 9 Peng, Q., Li, K., Anderson, K., Farrar, C. A., Lu, B., Smith, R. A., Sacks, S. H. and Zhou, W., Local production and activation of complement up-regulates the allostimulatory function of dendritic cells through C3a-C3aR interaction. *Blood* 2008. **111**: 2452–2461.
- 10 Li, K., Anderson, K. J., Peng, Q., Noble, A., Lu, B., Kelly, A. P., Wang, N. et al., Cyclic AMP plays a critical role in C3a-receptor mediated regulation of dendritic cells in antigen uptake and T cell stimulation. *Blood* 2008. **112**: 5084–5094.
- 11 Strainic, M. G., Liu, J., Huang, D., An, F., Lalli, P. N., Muqim, N., Shapiro, V. S. et al., Locally produced complement fragments C5a and C3a provide costimulatory and survival signals to naïve CD4 T cells. *Immunity* 2008. **28**: 425–435.
- 12 Peng, Q., Li, K., Wang, N., Li, Q., Asgari, E., Lu, B., Woodruff, T. M. et al., Dendritic cell function in allostimulation is modulated by C5aR signalling. *J. Immunol.* 2009. **183**: 6058–6068.
- 13 Weaver, D. J., Jr., Reis, E. S., Pandey, M. K., Köhl, G., Harris, N., Gerard, C. and Köhl, J., C5a receptor-deficient dendritic cells promote induction of Treg and Th17. *Eur. J. Immunol.* 2010. **40**: DOI: 10.1002/eji.200939333.
- 14 Iwasaki, A. and Medzhitov, R., Regulation of adaptive immunity by the innate immune system. *Science* 2010. **5963**: 291–295.
- 15 Sallusto, F. and Lanzavecchia, A., Human Th17 cells in infection and autoimmunity. *Microbes Infect.* 2009. **11**: 620–624.
- 16 Zelante, T., De Luca, A., D'Angelo, C., Moretti, S. and Romani, L., IL-17/Th17 in anti-fungal immunity: what's new? *Eur. J. Immunol.* 2009. **39**: 645–648.
- 17 Zheng, X., Zhang, X., Feng, B., Sun, H., Suzuki, M., Ichim, T., Kubo, N. et al., Gene silencing of complement C5a receptor using siRNA for preventing ischemia/reperfusion injury. *Am. J. Pathol.* 2008. **173**: 973–980.

Full correspondence: Professor Steven H. Sacks, MRC Centre for Transplantation, King's College London, 5th Floor Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK
Fax: +44-207-188-5660
e-mail: steven.sacks@kcl.ac.uk

See accompanying article:
<http://dx.doi.org/10.1002/eji.200939333>

Received: 28/1/2010

Accepted: 4/2/2010

Complement fragments C3a and C5a: The salt and pepper of the immune response

Steven H. Sacks^{1,2}

¹ MRC Centre for Transplantation, King's College London, London, UK

² NIHR Comprehensive Biomedical Research Centre, Guy's and St. Thomas' NHS Foundation Trust and King's College London, London, UK

The influence of complement on B-cell responses has been known for many years, but the notion that T-cell recognition, expansion and differentiation are complement dependent has only recently gained impetus. DC, and to a lesser extent T cells, produce a range of complement components necessary for complement activation, and these cells also express receptors that detect complement-activation products such as C3a and C5a (anaphylatoxins). In the absence of C3a-receptor (C3aR) signalling, DC lose their capacity to induce potent Th1 responses against alloantigen and also favour the emergence of Treg. A study in this issue of the *European Journal of Immunology* not only spotlights the importance of C5aR signalling in DC interaction with T cells, but also shows how cooperation with other signalling pathways determines the outcome of T-cell activation. Remove C5aR from the equation, TLR2-stimulated DC induce naive CD4⁺ Th cells to undergo differentiation not only mainly to Th17 cells but also to Treg, via a TGF- β -dependent pathway. Thus, anaphylatoxins in conjunction with other danger signalling pathways modify the function of DC in antigen presentation and help to shape the primary immune response. Future work will need to address the impact of anaphylatoxins on protective immunity *in vivo* and determine the wider implications of anaphylatoxins for allo- and autoimmunity.

Key words: Complement receptor · DC · Th17 · TLR2 · Treg



See accompanying article by Weaver *et al.*

It was Mark Pepys who, in the 1970s, noted the influence of complement on the adaptive immune response [1]. He found that mice depleted of complement failed to develop potent antibody responses, although the effect was partially overcome by increasing the dose of injected antigen. A possible mechanism was suggested two decades later when complement receptor (CR2), which recognizes the large split fragment of C3, was shown to improve the retention of opsonised antigen in lymphoid tissue and markedly lower the threshold of B-cell activation by antigen [2, 3]. An influence of complement on the T-cell response was not immedi-

ately obvious, probably because complement-deficient mice were noted to have normal T-cell counts and display unexceptional resting T-cell phenotypes; however, studies of induced T-cell-mediated diseases later demonstrated diminished Th1 responses in mice lacking certain complement components [4]. It seemed that complement activation was essential for T-cell priming in these circumstances. A vivid example came from transplant studies, where T-cell-mediated rejection occurred only in the presence of donor kidney synthesis of C3 [5]. Out of this, emerged an understanding that donor APC, most notably DC, are able to synthesise a wide range of complement components [6, 7]. Secreted into the local environment, complement components contribute to local complement activation. DC from mice lacking certain complement components were found to be poor initiators of the T-cell response

Correspondence: Professor Steven H. Sacks
e-mail: steven.sacks@kcl.ac.uk

against donor antigen, and to result in higher proportion of Foxp3⁺ Treg [7]. This defect in antigen presentation can be traced, at least in part, to a lack of MHC class II and costimulatory molecules expressed on DC in the absence of complement activation (Fig. 1A) [7]. It must be noted, however, in addition to DC, T cells can also produce complement components (although at a fraction of the amount expressed by DC), as do various stromal and parenchymal cells, including hepatic cells (the main cellular source of complement in the circulation); thus, complement components from several sources may enhance complement interaction at the DC/T-cell interface [8].

Among the known effectors generated by complement activation, two potential champions have emerged: the anaphylatoxins C3a and C5a. These are the small soluble peptide fragments liberated by cleavage of C3 and C5, and named for their role in the induction of overwhelming inflammation (anaphylaxis). G-protein-coupled receptors that detect C3a or C5a link up with several well-defined intracellular signalling pathways. These convert extracellular signals into biological functions, such as mast cell and neutrophil degranulation, and smooth muscle contraction. Recent work highlighting the immunoregulatory action of anaphylatoxins has focussed on DC and their interaction with naive CD4⁺ Th cells [9–12]. Anaphylatoxin receptors present on DC help to determine the competence of these cells for antigen presentation. For example, in the absence of C3aR signalling on DC, the Th-cell response directed against alloantigen is reduced and dominated by Th2 cells and Treg, instead of Th1 [9]. T cells also have receptors for C3a and C5a, and in the absence of anaphylatoxin signalling, T-cell proliferation and T-cell longevity are both reduced after antigenic stimulation [11]. Being at the point of contact between APC and T cells, bidirectional signalling mediated by anaphylatoxins could thus ramp up the immune response.

In this issue of *European Journal of Immunology*, Köhl and colleagues [13] give careful consideration to the possibility of interaction between C5aR signalling and other danger sensing pathways. This is a sound notion, given that infection initiates multiple danger signals, which are recognised by innate immune receptors on DC [14]. The authors [13] arrange for experiments to

allow or deny C5aR signalling on mouse spleen DC, in the presence of TLR2 stimulation (with PAM), and determine how well these manipulated DC loaded with OVA stimulate OVA-specific CD4⁺ T cells. In full flight, antigen presentation is augmented by TLR2 and C5aR signalling, resulting in a vigorous Th1 response (Fig. 1B) [13]. In contrast, APC lacking C5aR signalling generate mainly Th17 cells and induce some Foxp3⁺ Treg via enhanced TGF- β secretion (Fig. 1C) [13]. This is a significant finding as it suggests that the integration, by DC, of C5aR and TLR2 signals strongly influences the outcome of naive Th-cell activation.

How does C5aR signalling regulate the capability of DC to present antigen? And in what circumstances would C5aR signalling be absent during antigen presentation? The report of Köhl and colleagues [13] provides some answers to these questions. The authors [13] show that DC stimulated in the absence of C5aR express lower cell surface levels of MHC class II and costimulatory (CD40 and CD86) molecules, compared with unmodified DC. As T-cell recognition critically depends on contact with DC through these molecules, variations in their expression mediated by C5aR signalling would be expected to affect antigen presentation. It is notable that both C5aR and C3aR signalling modulate the expression of alloantigen and costimulatory molecules on DC, with the expected influence on T-cell priming [10–12]. This suggests a strong degree of functional overlap in the effects of C3aR and C5aR signalling, which share some of the intracellular signalling pathways (e.g. cAMP, ERK, NF- κ B) that control DC function. Besides surface molecules, DC cytokine production is also affected by anaphylatoxin signalling [10, 12]. Of special interest, the large amounts of TGF- β secreted by DC in the absence of C5aR signalling contributed substantially to the expansion of Th17 and Treg [13].

Some pathogenic organisms express complement regulators that inhibit complement activation and thus allow pathogen evasion of host defence. These regulators usually act by inhibiting the cleavage of C3 and subsequently C5. As Köhl and colleagues [13] suggest, reduced generation of C5a could impair antigen presentation and alter DC cytokine profile, leading to a deviated

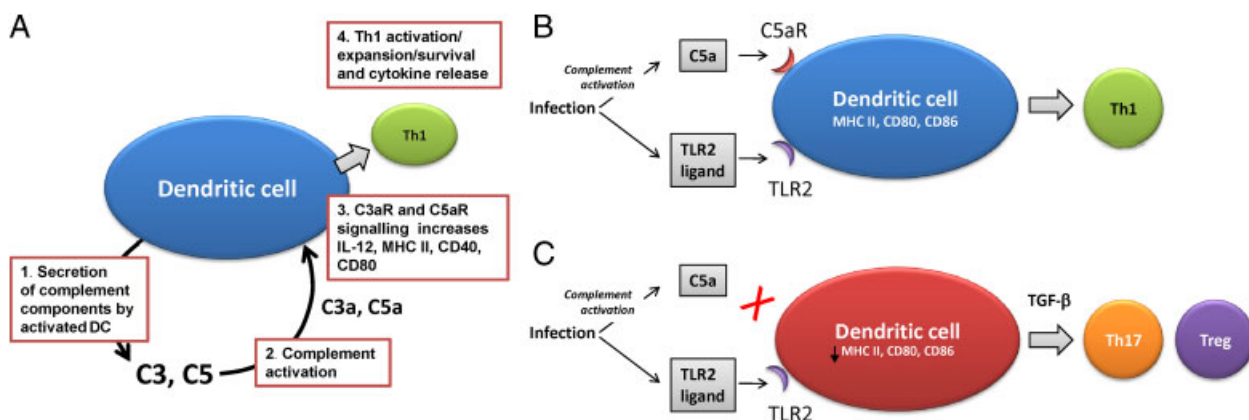


Figure 1. (A) Cell endogenous production of complement enhances antigen presentation and leads to a potent T-cell response in the presence of alloantigen. (B) Cooperation between C5aR and TLR2 signalling in APC induces naive CD4⁺ Th cells to undergo Th1 differentiation. (C) In the absence of C5aR signalling, DC stimulated by TLR2 show reduced expression of MHC class II and costimulatory molecules and increased production of TGF- β . Consequently, Th cells undergo differentiation to Th17 cells and Foxp3⁺ Treg in the presence of antigenic stimulation (OVA peptide).

immune response. Additional studies are needed to assess the influence of C5aR signalling on protective T-cell responses *in vivo*, in particular the potential outcome of replacing a protective Th1 response with a Th17 response in the context of bacterial infection. This could be different from fungal infection, where Th17 cells are known to have a protective role [15, 16].

The recent results with C3aR- and C5aR-mediated immune regulation raise interesting questions for T-cell-mediated diseases. In transplantation, for example, if anaphylatoxin receptors on donor APC are critical for triggering T-cell-mediated rejection [10, 12], then treatment of the donor organ using complement inhibitory strategies should be protective. Work is currently in progress to assess the effect of complement inhibitors or gene silencing in donor organs, largely to block the innate functions of complement on reperfusion injury [17]. The potential for deviating C5aR-mediated immune activation towards an inhibitory mode offers new scope for inducing graft acceptance. Safeguards will need to ensure that Th17-cell differentiation as a result of C5aR blockade is not counterproductive.

Several aspects of complement receptor biology remain unclear. It is implied that either C3aR or C5aR signalling will steer the immune response towards Th1; however, absence of either one of these receptors is sufficient to disrupt the Th1 response, indicating that there is little functional overlap. This is despite the sharing of several signal pathway components activated through C3a and C5a receptors. Whether C3aR and C5aR have overlapping or mutually distinct roles will be valuable to tease out, especially for the purposes of therapeutic application. In addition, there has been some confusion about the role of a third anaphylatoxin receptor, C5L2 – a non-signalling protein with high affinity for the C5a des Arg metabolite. C5L2 has been proposed as a physiological decoy receptor limiting the activity of C5a. The work presented by Köhl and team [13] put this notion to rest, in so far as their results with C5L2-knockout mice show no major effect on TLR2-stimulated antigen-presenting function.

Acknowledgements: The author receives funding from the Medical Research Council, the Wellcome Trust and National Institute for Health Research, UK.

Conflict of interest: The author declares no financial or commercial conflict of interest.

References

- 1 Pepys, M. B., Role of complement in induction of antibody production in vivo: effect of cobra factor and other C3-reactive agents on thymus-dependent and thymus-independent antibody responses. *J. Exp. Med.* 1974. **140**: 126–145.
- 2 Fang, Y., Xu, C., Fu, Y.-X., Holers, V. M. and Molina, H., Expression of complement receptors 1 and 2 on follicular dendritic cells is necessary for the generation of a strong antigen-specific IgG response. *J. Immunol.* 1998. **160**: 5273–5279.
- 3 Dempsey, P. W., Allison, M. E., Akkaraju, S., Goodnow, C. C. and Fearon, D. T., C3d of complement as a molecular adjuvant: bridging innate and acquired immunity. *Science*. 1996. **271**: 348–350.
- 4 Kemper, C. and Atkinson, J. P., T-cell regulation: with complements from innate immunity. *Nat. Rev. Immunol.* 2007. **7**: 9–18.
- 5 Pratt, J. R., Basheer, S. A. and Sacks, S. H., Local synthesis of complement component C3 regulates acute renal transplant rejection. *Nat. Med.* 2002. **8**: 582–587.
- 6 Zhou, W., Patel, H., Li, K., Peng, Q., Villiers, M. B. and Sacks, S. H., Macrophages from C3-deficient mice have impaired potency to stimulate alloreactive T cells. *Blood* 2006. **107**: 2461–2469.
- 7 Peng, Q., Li, K., Patel, H., Sacks, S. H. and Zhou, W., Dendritic cell synthesis of C3 is required for full T cell activation and development of a Th1 phenotype. *J. Immunol.* 2006. **176**: 3330–3341.
- 8 Heeger, P. S., Lalli, P. N., Lin, F., Valujskikh, A., Liu, J., Muqim, N., Xu, Y. and Medof, M. E., Decay-accelerating factor modulates induction of T cell immunity. *J. Exp. Med.* 2005. **201**: 1523–1530.
- 9 Peng, Q., Li, K., Anderson, K., Farrar, C. A., Lu, B., Smith, R. A., Sacks, S. H. and Zhou, W., Local production and activation of complement up-regulates the allostimulatory function of dendritic cells through C3a-C3aR interaction. *Blood* 2008. **111**: 2452–2461.
- 10 Li, K., Anderson, K. J., Peng, Q., Noble, A., Lu, B., Kelly, A. P., Wang, N. et al., Cyclic AMP plays a critical role in C3a-receptor mediated regulation of dendritic cells in antigen uptake and T cell stimulation. *Blood* 2008. **112**: 5084–5094.
- 11 Strainic, M. G., Liu, J., Huang, D., An, F., Lalli, P. N., Muqim, N., Shapiro, V. S. et al., Locally produced complement fragments C5a and C3a provide costimulatory and survival signals to naïve CD4 T cells. *Immunity* 2008. **28**: 425–435.
- 12 Peng, Q., Li, K., Wang, N., Li, Q., Asgari, E., Lu, B., Woodruff, T. M. et al., Dendritic cell function in allostimulation is modulated by C5aR signalling. *J. Immunol.* 2009. **183**: 6058–6068.
- 13 Weaver, D. J., Jr., Reis, E. S., Pandey, M. K., Köhl, G., Harris, N., Gerard, C. and Köhl, J., C5a receptor-deficient dendritic cells promote induction of Treg and Th17. *Eur. J. Immunol.* 2010. **40**: DOI: 10.1002/eji.200939333.
- 14 Iwasaki, A. and Medzhitov, R., Regulation of adaptive immunity by the innate immune system. *Science* 2010. **5963**: 291–295.
- 15 Sallusto, F. and Lanzavecchia, A., Human Th17 cells in infection and autoimmunity. *Microbes Infect.* 2009. **11**: 620–624.
- 16 Zelante, T., De Luca, A., D'Angelo, C., Moretti, S. and Romani, L., IL-17/Th17 in anti-fungal immunity: what's new? *Eur. J. Immunol.* 2009. **39**: 645–648.
- 17 Zheng, X., Zhang, X., Feng, B., Sun, H., Suzuki, M., Ichim, T., Kubo, N. et al., Gene silencing of complement C5a receptor using siRNA for preventing ischemia/reperfusion injury. *Am. J. Pathol.* 2008. **173**: 973–980.

Full correspondence: Professor Steven H. Sacks, MRC Centre for Transplantation, King's College London, 5th Floor Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK
Fax: +44-207-188-5660
e-mail: steven.sacks@kcl.ac.uk

See accompanying article:
<http://dx.doi.org/10.1002/eji.200939333>

Received: 28/1/2010

Accepted: 4/2/2010