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Review

A vital role for complement in heart disease☆

Knut T. Lappegård[a,b], Peter Garred[c], Lena Jonasson[d], Terje Espevik[e], Pål Aukrust[f,g], Arne Yndestad[f,g], Tom E. Mollnes[b,e,g,h,i], Anders Hovland[a,b,*]

[a] Coronary Care Unit, Division of Internal Medicine, Nordland Hospital, Bodø, Norway
[b] Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway
[c] Laboratory of Molecular Medicine, Department of Clinical Immunology, Section 7631 Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[d] Department of Medical and Health Sciences, Division of Cardiovascular Medicine, Linköping University, Linköping, Sweden
[e] Centre of Molecular Inflammation Research, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[f] Research Institute of Internal Medicine, Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital Rikshospitalet, Oslo, Norway
[g] K.J. Jebsen Inflammation Research Centre, University of Oslo, Oslo, Norway
[h] Research Laboratory, Nordland Hospital, Bodø, Norway
[i] Department of Immunology, Oslo University Hospital Rikshospitalet, Oslo, Norway

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ABSTRACT

Heart diseases are common and significant contributors to worldwide mortality and morbidity. During recent years complement mediated inflammation has been shown to be an important player in a variety of heart diseases. Despite some negative results from clinical trials using complement inhibitors, emerging evidence points to an association between the complement system and heart diseases. Thus, complement seems to be important in coronary heart disease as well as in heart failure, where several studies underscore the prognostic importance of complement activation. Furthermore, patients with atrial fibrillation often share risk factors both with coronary heart disease and heart failure, and there is some evidence implicating complement activation in atrial fibrillation. Moreover, Chagas heart disease, a protozoal infection, is an important cause of heart failure in Latin America, and the complement system is crucial for the protozoa–host interaction. Thus, complement activation appears to be involved in the pathophysiology of a diverse range of cardiac conditions. Determination of the exact role of complement in the various heart diseases will hopefully help to identify patients that might benefit from therapeutic complement intervention.

1. Introduction

Heart diseases are significant contributors to worldwide morbidity and mortality (Moran et al., 2014a). However, while mortality rates from coronary heart disease have declined over the last 30 years, the identification and treatment of unstable coronary lesions is still a challenge. Moreover, due to the growing and aging population, there is an increase in the global burden of coronary heart disease (Moran et al., 2014b). There is also an increase in heart failure as a result of coronary heart disease, dilated cardiomyopathy, hypertension and type 2 diabetes (Moran et al., 2014b). Another cause of heart failure is Chagas disease, predominantly found in Latin America where it is caused by a parasitic infection (Bocchi et al., 2013). In 2012, the global cost of heart failure worldwide was estimated to 108 billion US dollars (Cook et al., 2014). Due to the elderly population, and paradoxically, the improved survival in coronary heart disease, the prevalence and mortality rates of atrial fibrillation are increasing as well (Chugh et al., 2014).

1.1. The complement system

The complement system consists of more than 40 soluble and membrane bound proteins. A substantial number are inhibitors, which are crucially important to keep the system under control during normal conditions. The system can be activated through three main pathways: classical-, lectin- and alternative pathway. In addition, a direct activation of C5 without prior activation of C3 has been described (Huber-Lang et al., 2006). The different

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* Corresponding author at: Coronary Care Unit, Division of Internal Medicine, Nordland Hospital, N-8092 Bodø, Norway. Tel.: +47 75534000; fax: +47 75534742.
E-mail address: anders.w.hovland@gmail.com (A. Hovland).

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activation pathways converge in the common pathway with activation of C3 and C5 continuing to the terminal pathway with release of the biologically highly potent anaphylatoxin C5a and formation of the terminal C5b-9 complement complex (TCC). The terminal complement complex can appear as a soluble complex in the fluid phase (sC5b-9) or attack cell membranes as the membrane attack complex (MAC). The latter may either lead to lysis of bacteria and cells, or, if formed in sub-lytic amounts, to stimulation of the cell with subsequent release of inflammatory mediators. Recent studies suggest that complement also can be regarded as a surveillance system that quickly can be activated by sensing danger signals, both sterile and non-sterile, to the host and thereby contribute to maintain tissue homeostasis and promote tissue repair (Ricklin et al., 2010). On the other hand, undesired or uncontrolled complement activation can induce tissue damage and organ dysfunction in the host such as can be seen during septicemia and various autoimmune disorders (Barratt-Due et al., 2012).

1.2. Inflammation and cardiovascular disease

Atherosclerosis is a common chronic inflammatory disease of the arterial vasculature that is associated with lipid accumulation in the arterial wall with the bidirectional interaction between lipid and inflammation as a phenotypical hallmark. This process is the underlying pathology of major cardiovascular diseases, including coronary heart disease and heart failure (Hansson and Libby, 2006; Hansson and Hermansson, 2011). Modified lipoproteins and cholesterol crystals in the arterial wall are potentially dangerous stressors. The innate immune system initiates and orchestrates the immune response to these particles. In this "first line of defence" a variety of pattern recognition receptors are used, including cellular pattern recognition receptors such as scavenger receptors and Toll-like receptors (TLRs), and soluble pattern recognition receptors such as complement components. Oxidized low-density lipoprotein (LDL) is endocytosed by CD36 that among others coordinates the intracellular conversion of this ligand to cholesterol crystals (Sheedy et al., 2013). Phagocytosis of cholesterol crystals induces lysosomal damage that results in the activation of the NLRP3 inflammasome, with subsequent activation of caspase-1 and secretion of IL-1β and IL-18 (Duewell et al., 2010). Recent data have demonstrated that the complement system can control several cellular processes involved in cholesterol crystal-induced inflammasome activation (Samstad et al., 2014).

Hence, there is considerable crosstalk between the different parts of the innate immune system in the atherosclerotic process. This opens the possibility of identifying therapeutic targets, with subsequent inhibition of the innate immune response at different levels. So far, no such inhibition has proven clinical efficacy, and more research in this area is warranted. There is also an intensive crosstalk between the coagulation and the complement systems, and if uncontrolled this "immunothrombosis" may lead to thrombotic complications including myocardial infarction and stroke (Engelmann and Massberg, 2013). Inflammatory responses are also involved in the development and progression of heart failure, and again, innate immune responses and complement seem to participate in these responses.

In the current review we address the latest research on the importance of the complement system for the evolvement of different heart diseases with focus on coronary heart disease, heart failure, arrhythmias and Chagas disease (Fig. 1).

2. Coronary heart diseases and the complement system

Coronary heart disease is, in the great majority of cases, caused by atherosclerosis in the coronary arteries, and spans from silent ischemia, effort-induced angina pectoris, acute coronary syndromes (unstable angina and myocardial infarction) to sudden cardiac death. There is an important distinction both prognostically and therapeutically, between ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction. Innate immunity, including the complement system, is important in the formation of atherosclerotic plaques (Haskard et al., 2008; Hansson and Hermansson, 2011; Weber and Noels, 2011; Torzewski and Bhakdi, 2013). These plaques may be stable, characterized by a large fibrous cap, or unstable, where inflammatory cells and lipids dominate. While the former lesion may be associated with a narrow lumen giving rise to stable ischemic symptoms, the latter lesion is associated with plaque rupture and thrombus formation with subsequent development of an acute coronary syndrome.

2.1. Genetic studies on the complement system and risk of coronary heart disease

The C4A and C4B genes code for C4, important in both the classical and the lectin pathways. Low C4B numbers are associated with increased short-term mortality in smoking myocardial infection patients (Blaskó et al., 2008). The mannose-binding lectin (MBL) 2 gene codes for MBL in the lectin pathway. Øhlenschlaeger et al. and Siezenga et al. found that the O/O genotype of MBL2, was associated with future risk of coronary heart disease in patients with systemic lupus erytmatosus and type 2 diabetes, respectively (Øhlenschlaeger et al., 2004; Siezenga et al., 2011). Alipour et al. did not find any association between MBL2 haplotypes and the progression of coronary heart disease in statin treated patients (Alipour et al., 2011). Vengen et al. have found that MBL2 gene variants with functional MBL deficiency were associated with increased risk for myocardial infarction in a population-based cohort of young individuals followed for 10 years (Vengen et al., 2012). Leban et al. recently described a strong relationship between the C3F allele of the C3 gene, coding for complement factor C3 of the common pathway, and risk of myocardial infarction (Leban et al., 2013). Factor H is a complement regulator, and polymorphisms, especially Y402H, in the Factor H-gene is extensively studied and associated with age-related macular degeneration (Gehrs et al., 2010). There are conflicting results about the Y402H polymorphisms and cardiovascular disease including myocardial infarction, but most studies find no association, so the importance of factor H variants in cardiovascular disease at present is unclear (Zee et al., 2006; Kardys et al., 2006; Nicaud et al., 2007; Stark et al., 2007; Sofat et al., 2010). Thus, some variants in genes encoding proteins of the complement system including MBL and C3 are associated with risk for coronary heart disease, whereas the association with variants in others like factor H is less well defined.

2.2. The complement system and myocardial ischemia–reperfusion injury

The treatment of acute coronary heart disease has been substantially improved with the introduction of reperfusion strategies including fibrinolysis and percutaneous coronary intervention. However, reperfusion of the ischemic myocardium may itself cause damage to the heart. This ischemia–reperfusion injury involves direct cardiomyocyte death and also myocardial stunning, arrhythmias and the "no reflow" phenomenon (Gerczuk and Kloner, 2012; Jennings, 2013; Ovize et al., 2013). Several approaches including pre-, post-, and remote-ischemic conditioning and several pharmacological therapies including immune modulation have been promising in both pre-clinical and clinical models. However, there is currently no widely accepted therapy that addresses this important clinical problem (Heusch, 2013; Kloner, 2013; Frangogiannis, 2014). Experimental studies strongly implicate the complement