Pharmacology & Therapeutics 172 (2017) 63–72

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: M. Belvisi

Complement: A primer for the coming therapeutic revolution

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ARTICLE INFO

Available online 1 December 2016

Keywords:
Complement
Innate immunity
Inflammation
Host defense

ABSTRACT

The complement system is an important part of the innate and adaptive immune systems. Originally characterized as a single serum component contributing to the killing of bacteria, we now know that there are close to sixty complement proteins, multiple activation pathways and a wide range of effector functions mediated by complement. The system plays a critical role in host defense against bacteria, viruses, fungi and other pathogens. However, inappropriate complement activation contributes to the pathophysiology of autoimmune diseases and many inflammatory syndromes. Over the last several decades, therapeutic approaches to inhibit complement activation at various steps in the pathways have met with initial success, particularly at the level of the terminal pathway. This success, combined with insight from animal model studies, has lead to an unprecedented effort by biotech and pharmaceutical companies to begin developing complement inhibitors. As a result, complement has been brought for the first time to the attention of pharmacologists, toxicologists, project managers and others in the drug development industry, as well as those in the investment world. The purpose of this primer is to provide a broad overview of complement immunobiology to help those new to complement understand the rationale behind the current therapeutic directions and the investment potential of these new therapeutics.

Contents

1. Introduction

Complement is one of the oldest components of the innate immune system. Over time it has integrated itself into multiple host defense mechanisms such as phagocytosis, chemoattraction of leukocytes,

Abbreviations: MAC, membrane attack complex; CD, cluster of differentiation; MBL, mannose binding protein; CR1, complement receptor type 1; CR3, complement receptor type 3; PAMPs, pattern associated molecular patterns; DAMPS, damage associated molecular patterns; MASP, MBL associated serine protease.

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http://dx.doi.org/10.1016/j.pharmthera.2016.11.014
0163-7258/

pathogen lysis, coagulation and intracellular innate/adaptive signaling pathways (Ricklin, Hajishengallis, Yang, & Lambris, 2010). Inappropriate activation and targeting of complement leads to the pathophysiology of many autoimmune diseases including rheumatoid arthritis, glomerulonephritis and others. Similarly, over-exuberant activation of complement in the setting of infectious disease or injury can contribute to a poor clinical outcome due to non-specific tissue damage and heightened inflammatory responses (Ricklin & Lambris, 2013). Therapeutic inhibition of complement to minimize complement-mediated damage in these clinical settings is now a highly active area of research. Although initial efforts in the 80′s and 90′s were hampered by the poor specificity of small molecule inhibitors and problems with expression of large and complex complement biologics (such as soluble complement receptor type 1 and derivatives thereof, (Mulligan et al., 1999; Rittershaus et al., 1999; Weisman et al., 1990), the last few years have seen a new generation of pharmaceutical and biotech companies revisiting complement inhibition using multiple approaches, including small molecules, siRNA inhibitors and antibodies (Holers et al., 2016; Morgan & Harris, 2015; Reis et al., 2015). These advances have the potential to benefit millions of patients worldwide with acute and chronic conditions driven by complement-mediated mechanisms. In the next five to ten years, as complement inhibitors move their way through clinical trials, FDA approval and reach the marketplace, many drug development teams, pharmaceutical management and investors will encounter to the complexity of complement biology and biochemistry for the first time and in greater detail than ever before. Unfortunately, complement is frequently viewed as overwhelming and bewildering because of the large number of proteins in its multiple activation pathways, the pleotropic functions of the activation fragments and the complex regulatory mechanisms that modulate its activity. The purpose of this primer is to demystify complement to facilitate discussions around the safety, efficacy and ultimately, the investment value of these inhibitors.

2. Complement and innate immunity

Complement is a critical part of the innate immune response, serving as a first line of defense to eliminate a diverse range of pathogens, including bacteria, viruses and parasites. Unlike the adaptive immunity, which requires several days to a week or more to mount an effective immune response, complement acts immediately upon infection or injury. Similar to other components of the innate immune system, complement neither "remembers" pathogens nor responds more rapidly and vigorously on subsequent encounters. Thus, complement does not exhibit memory, a key feature of the adaptive immune system. Complement is a major contributor to the acute phase response, a systemic response to infection and injury that serves to eliminate invading pathogens, limit innate immune-mediated damage to host tissues and aid in the return to homeostasis (de Jong, van der Poll, & Wiersinga, 2010).

From an evolutionary perspective, complement is an ancient part of the immune system whose origins are thought to extend back some 800 million years. Simple organisms (cnidaria and protostomes) including sea anemones, jellyfish, segmented worms, mollusks and, arthropods have one or more complement-like genes but not all of these organisms have a functional primitive complement system. The sea urchin (a representative deuterostome) has a primitive complement system with components of two of the activation pathways (lectin and alternative), but limited functionality compared to complement in higher species. Further up the evolutionary tree and concomitant with the development of the earliest elements of the adaptive immune system, components of the lytic and classical pathways appear, unifying the system into the tightly inter-related pathways found in humans (Cerenius, Kawabata, Lee, Nonaka, & Soderhall, 2010; Dodds, 2002; Fujita, Matsushita, & Endo, 2004; Nonaka, 2014; Sekiguchi & Nonaka, 2015).

Complement was initially discovered in the late 1880s by Nuttall and Buchner who observed that blood depleted of white blood cells was still capable of killing bacteria (Buchner, 1894; Nuttall, 1988). At that time complement was termed "alexin" from the Greek meaning to "ward off", in this case to ward off infection. Thus, along with phagocytic cells, complement was one of the first components identified in the innate immune system. Within a few years of its discovery, the term alexin was changed to *complement* when it was shown that it could "complement" the bactericidal activity of serum antibodies (Bordet, 1899, 1900). Nonetheless, at the turn of the last century, there was no understanding that complement was composed of a large group of proteins that generated host defense functions through activation of one or more pathways. The complexity of complement from a single serum component to many proteins and pathways was slowly unraveled over the next several decades with the advancement of protein chemistry techniques and the development of hemolytic assays (to measure complement activity in vitro). The advent of molecular biology extended our understanding of the system and provided insight into the role of complement in adaptive immunity and in biological functions outside the immune system (Lachmann, 2006; Mastellos, Deangelis, & Lambris, 2013; Morgan, 2015b; Muller-Eberhard, 1988; Phieler, Garcia-Martin, Lambris, & Chavakis, 2013; Sim, Schwaeble, & Fujita, 2016).

3. Complement – working definition/principles

From a host defense point of view, complement can be defined as follows: a group of sequentially reacting proteins, that upon activation, mediate a number of biological reactions important in host defense. This simple definition has several points worth exploring in greater detail:

a) a group of sequentially reacting proteins – that is, complement activation is a cascade of cleavage events similar to that of the coagulation system. Once complement has been activated through any of the three main pathways (classical, lectin and alternative), the proenzyme form of the initiating protein is cleaved to its active form and subsequently activates the next protein in the pathway and so on. The cleavage events occur until two forms of multi-molecular enzyme complexes called convertases are generated. The convertases cleave either C3 or C5, the two main proteins of the complement system.
b) Complement requires activation to provide host defense against pathogens. Complement is generally thought of as inactive in blood and tissues but this is not entirely true. It is well established that there are baseline blood levels for essentially all the complement activation fragments (Bergseth et al., 2013; Nilsson & Ekdahl, 2012a; Oppermann & Wurzner, 2010). Thus complement is active to a small degree all the time: it is primed to take off quickly in the event of infection or injury. As will be discussed later, we know that the basal activation of complement occurs through the alternative pathway and dysregulation of this pathway leads to the pathophysiology that underlies many complement-mediated disease syndromes (Thurman & Holers, 2006).
c) Complement mediates a number of biological reactions important in host defense. Once activated, complement targets pathogens for removal by covalent attachment of activation fragments to the cell membrane, chemoattracts and helps activate phagocytic cells such as neutrophils and macrophages to engulf pathogens and lyses susceptible pathogens through the formation of the membrane attack complex (MAC).

These operational points underlie much of what will be covered in subsequent sections.

4. Complement nomenclature

As might be expected with a system of proteins whose complexity has continued to evolve since its discovery over 100 years ago, the