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Material properties in complement activation ☆

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ABSTRACT

Uncontrolled complement activation can induce many inflammatory and life threatening conditions. Accordingly, the role of complement in initiation of adverse reactions to polymers and nanoparticulate drug carriers is receiving increasing attention and has prompted extensive 'structure-immune performance' relationship studies in nanomedicine research at many fronts. The interaction between nanomaterials and the complement system is complex and regulated by inter-related factors that include nanoscale size, morphology and surface characteristics. Each of these parameters may affect complement activation differently and through different sensing molecules and initiation pathways. The importance of material properties in triggering complement is considered and mechanistic aspects discussed. Mechanistic understanding of complement events could provide rational approaches for improved material design and nanoengineering strategies for clinical medicine.

Contents

1. Introduction

Acute allergic reactions with symptoms that fit in Coombs and Gell's Type I category but, which are not initiated or mediated by pre-existing IgE antibodies have been reported to occur in a high percentage (up to 45%) of patients within minutes of radio-contrast media, therapeutic antibodies, micellar drug formulations and regulatory approved particulate nanomedicine (e.g., liposomes) infusion [1–5]. The haemodynamic, respiratory, cutaneous and subjective manifestations include hypertension or hypotension, dyspnea, flushing, rash and feeling of choking. Symptoms vary from light to severe and may be lethal depending on the individuals' sensitivity [1]. However, unlike type I allergy, responses arise at the first exposure without prior sensitization and may lessen or disappear on later treatments. Acute allergic reactions to the same medicines/nanomedicines are very common in pigs and dogs [1,6–8]. Haemodynamic responses in pigs include a massive rise in pulmonary arterial pressure and a decline in systemic arterial pressure, cardiac output and left ventricular end-diastolic pressure. These changes are further associated with massive but transient electrocardiogram alterations, including tachycardia, bradycardia, ST-segment depression and T-wave changes, ventricular fibrillation or cardiac arrest, depending on the formulation's composition and dose [6,7]. In dogs

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nanomedicine infusion may initiate neuro-psychosomatic and vegetative responses [1,8].

Experimental and clinical evidence strongly suggests that the infusion of the abovementioned medicines, nanomaterials and nanomedicines is associated with activation of the complement system (Fig. 1), which is one of the most ancient defence strategies in the body [1–8]. The complement system plays a central role in the fight against intruders and in the modulation of immune and inflammatory responses [9,10]. It has been argued that complement may be a key contributing, but not a rate limiting factor in eliciting acute allergic responses to nanomaterials and nanomedicines, Fig. 2 [1]. Therefore, understanding of the molecular basis of material properties in complement activation could provide rational approaches to better material design and nanoengineering strategies for eliminating or minimizing acute allergic responses to future nanomedicines and are discussed here.

2. The complement system

The complement system is a network of over thirty different soluble and membrane-bound proteins that can be activated via three different initiation pathways (classical, alternative and lectin pathways), Fig. 1, that all converge at the step where the central complement protein C3 is cleaved, Fig. 3 [9–12]. A detailed description of complement pathways is covered elsewhere [9,10]. Nevertheless, these pathways use different recognition molecules to sense a foreign particle (e.g., antibodies for the classical pathway and mannose-binding lectin and ficolin for the lectin pathway), but use similar activation mechanisms to generate enzymes that cleave C3 (known as C3 convertases).

The prime consequence of nanoparticle-mediated complement activation is surface opsonization (by the opsonic fragments of C3 cleavage such as C3b and iC3b), Fig. 3 [9,10,12,13]. This aids material recognition and rapid clearance by macrophages of the reticuloendothelial system bearing complement receptors (e.g., hepatic Kupffer cells, splenic marginal zone and red-pulp macrophages, blood monocytes, etc.). However, surface opsonization may not necessarily induce particle clearance by these macrophages; the process is further modulated by surface topology and notably by the presence of elements that generate steric constraints (e.g., projected surface polymers) to particle–macrophage interaction [14,15]. This has been demonstrated with poly(ethylene glycol)-conjugated liposomes,

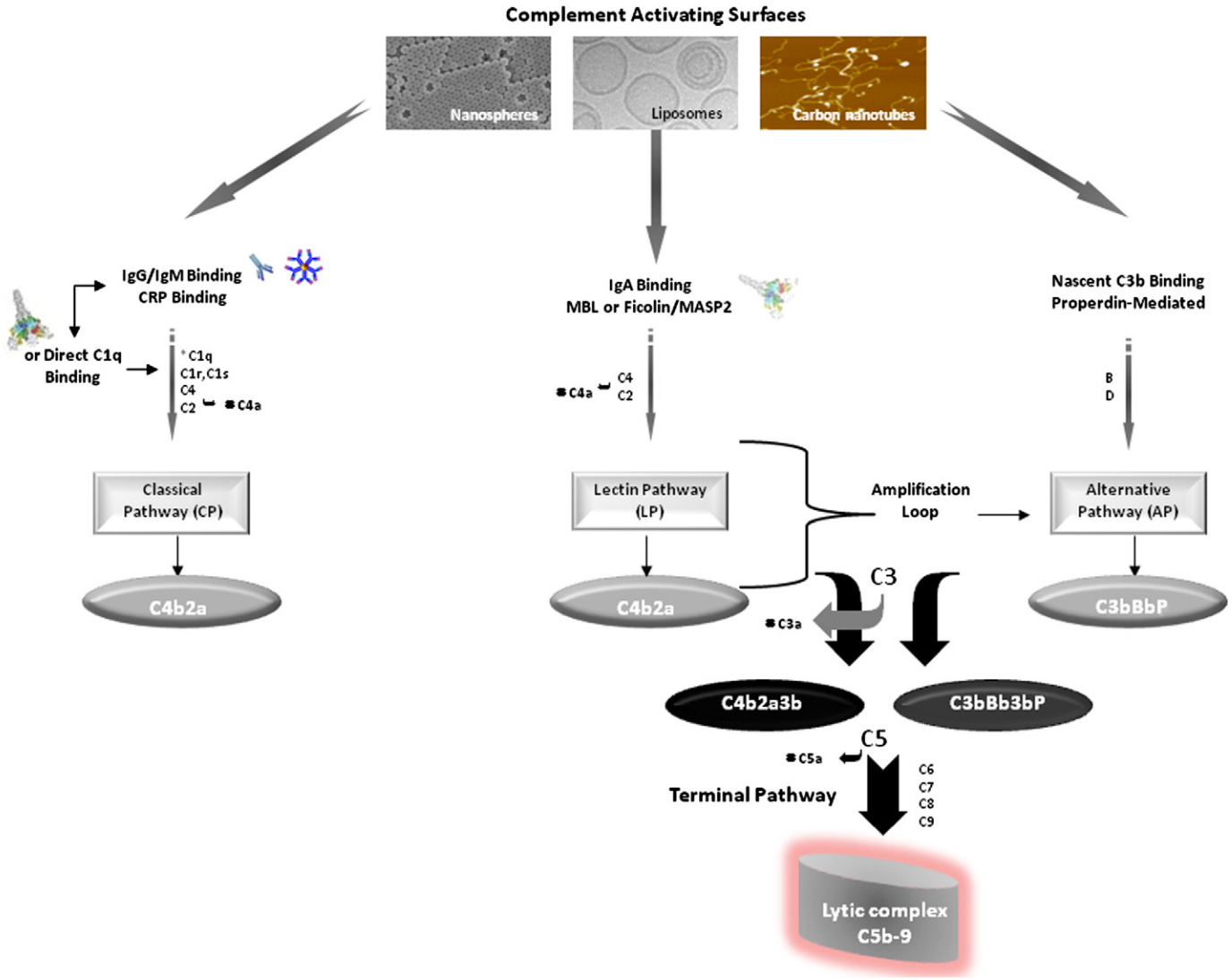

Fig. 1. Complement activation pathways. Sequential addition and activation of complement proteins for each pathway as well as anaphylatoxin C4a, C3a and C5a releases are shown. C4b2a and C3bBbP are C3-convertases, and C4b2a3b and C3bBb3bP are C5 convertases, respectively. CRP = C-reactive protein; MBL = mannose-binding lectin; MASP-2 = MBL-associated serine protease-2.