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Complement in stem cells and development

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ABSTRACT

From its discovery in the late nineteenth century, as a 'complement' to the cellular immune response, the complement system has been widely affirmed as a powerful controller of innate and adaptive immune responses. In recent decades however, new roles for complement have been discovered, with multiple complement proteins now known to function in a broad array of non-immune systems. This includes during development, where complement exerts control over stem cell populations from fertilization and implantation throughout embryogenesis and beyond post-natal development. It is involved in processes as diverse as cell localisation, tissue morphogenesis, and the growth and refinement of the brain. Such physiological actions of complement have also been described in adult stem cell populations, with roles in proliferation, differentiation, survival, and regeneration. With such a broad range of complement functions now described, it is likely that current research only describes a fraction of the full reach of complement proteins. Here, we review how complement control of physiological cell processes has been harnessed in stem cell populations throughout both development and in adult physiology.

1. Introduction

The complement system has long stood as a powerful controller of immunity. Initially identified as the heat-labile effector of antibody-mediated immunity, a continuum of discovery has revealed complement to be a complex family of proteins which also has functions outside of immunity. This family orchestrates innate immunity through the activation and recruitment of immune cells, tagging of pathogens for destruction, and direct lysis of bacterial pathogens [1,2]. Traditionally, these functions are achieved through the initiation of an activating cleavage cascade via three main pathways; the C1 antibody-antigen complex of the classical pathway, spontaneous C3 hydrolysis of the alternative pathway, or recognition of damaged or pathogenic surfaces by mannose-binding lectin (MBL) through the lectin pathway. Successful progression of the complement cascade results in the cleavage of factors C3, to C3a and C3b, and C5, to C5a and C5b, with these core fragments representing the foundation of the complement immune response (for a comprehensive review, see [3,4]). C3a and C5a can activate specific receptors to recruit immune cells to sites of inflammation, whilst C3b acts as a powerful opsonin to directly tag pathogens for destruction. Additionally, C5b facilitates the formation of the membrane attack complex (MAC) along with further complement factors, C6-9, to disrupt bacterial membranes causing cell lysis [5]. C3 and C5 can also be cleaved in the absence of cascade activation by a number of serine proteases [6–8]. This 'extrinsic' pathway provides a mechanism for local complement activation in the absence of inflammation, to potentially facilitate a number of non-immune cell processes under complement control.

The theory that complement acts solely as a controller of innate immunity was maintained for almost a century. In the early 1990s, the discovery of seminal complement proteins and the actions of complement C3b and CD46 in facilitating sperm-oocyte interactions, broadened the scientific perspectives of complement beyond the boundaries of the immune system towards roles in development [9]. From here, the biological niche of the complement proteins has rapidly widened, with the complement system now accepted as a multi-faceted family of proteins, capable of not only innate and adaptive immune regulation, but of facilitating an extensive number of non-immune actions including the control of tissue morphogenesis, wound healing, and synaptic pruning [10–12]. Even with the monumental steps of the past two decades in the understanding of complement, it is apparent that the full array of functions under the influence of complement family

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members is yet to be described. Recent examples of the continued surprises include the discovery of novel modes for autocrine complement activation and signalling. This recent discovery, termed the complosome, has demonstrated independent intracellular cleavage of C3 and C5 to activate autocrine intracellular signalling [13,14].

We have previously reviewed the evidence for complement control in fundamental cell processes such as cellular proliferation, differentiation, migration, and survival [15]. Here, we focus on how complement control of these processes has been harnessed in stem cell populations in both development and in adult physiology.

2. Complement during early developmental processes

2.1. Gametes and fertilization

One of the earliest discoveries demonstrating a clear non-immune function for complement was in its role in fertilization [9]. Complement factors have been identified on both sperm and oocyte, as well as being secreted into the female reproductive tract by the epithelial lining [16,17]. Given the potential for exposure to pathogens, such expression of complement factors in the female reproductive tract would not be unexpected. However, in addition to immune functions, complement has been shown to act in areas such as the selection and protection of healthy spermatozoa, oocyte maturation, and in facilitating sperm-oocyte interactions (refer to Fig. 1 for overview).

In the male reproductive tract, complement cascade proteins, such as C3 and C4, are present in the seminal plasma ejaculate that accompanies spermatozoa [18]. In addition, seminal plasma contains specific 'prostasome' complexes which concentrate complement regulators CD55, CD59, and CD46 [19]. Overall, this leads to an inhibitory effect on complement activation, with prostasomes hypothesized to provide anti-complement protection for spermatozoa deposited in the female reproductive tract. Upon migration through the female tract, the sperm will leave the seminal plasma and prostasomes, rendering them vulnerable to complement exposure. As such, sperm have been shown to express their own complement regulators, with a number of complement proteins identified on mammalian spermatozoa, including CD55, CD59a, CD46, C1-INH, C1qR [20,21]. Factors CD55 and CD59a are localized to the plasma membranes of spermatozoa, providing a functional defense against MAC-mediated lysis [20]. The expression of these factors aids in the preservation of healthy spermatozoa to protect from MAC formation and lysis, and elimination of dysfunctional spermatozoa lacking in such complement regulators [20]. Additionally, a complement 1 inhibitor-like protein (C1-INH) has been shown to have similar spermatozoa-protective effects. A shift in the balance of this protein can alter fertility, with C1-INH dysfunction, or the presence of C1-INH autoantibodies in human populations linked to male infertility [22,23].

Whilst complement factors have been shown to protect sperm from complement mediated attack, a number of complement proteins have been shown to have more unique expression and function in sperm, with isoforms specific to the testes demonstrated to be involved in facilitating fertilization via effects on sperm motility, activation, and sperm interactions with the egg. Here, the complement regulator, CD46, has garnered the most interest. CD46 is abundantly expressed on the membranes of all human nucleated cells, to confer host protection from autoimmune attack [24]. However, on sperm, CD46 displays a unique localization and isotype expression. Sperm localization is restricted to the inner acrosomal membrane where it is unable to be exposed to complement until after the acrosome reaction [25,26]. Furthermore, murine expression of CD46 is testis specific, with Crry performing the systemic functions that CD46 performs in humans [27]. This unique expression of CD46 has been postulated to be for the formation of a C3b-CD46 bridge between spermatozoa and oocyte receptors following the acrosome reaction, facilitating attachment and penetration. In support of this, acrosome reacted spermatozoa have been demonstrated to be able to activate the classical complement cascade, resulting in the cleavage of C3 without C5 cleavage or MAC formation [25]. The C3 fragment, C3b, can then deposit on the inner acrosomal membrane leading to increased adherence of sperm and penetration of oocytes [9]. Interestingly, whilst this may suggest a potential for deficits in fertility and embryonic development, C3 knockout mice show no alterations in fertility [28]. This observation suggests either a potential redundancy in this C3b-CD46 interaction, compensation by other factors, or that there is an alternative function of CD46 in fertilization.

Support for alternative functions of CD46, outside of C3b-CD46 interaction, has been demonstrated in a study utilizing new world monkeys. Protein structure profiling of CD46 in these animals found a loss of expression of an extracellular domain, CCP1, in all tissue except the testis where CCP1 expression was preserved [29]. This site is a preferential binding site for a number of viruses, with evolutionary pressure for pathogen resistance hypothesized as the cause for the loss of CCP1 expression [29]. CCP1 does not interact with C3b, therefore loss of expression of this domain would not affect the canonical function of CD46. The preservation of the CCP1 domain in the testis of these animals suggests an importance for this region in reproduction, and an action of CD46 on sperm outside of C3b binding, explaining the continued fertility of C3 knockout mice. In support of this, antibodies directed against CCP1 are able to reduce human spermatozoa-egg binding, whereas an antibody blocking the C3b binding site of CD46 had no effect [29,30]. In studies of fertility, abnormalities in CD46 have been associated with human infertility [31], whilst CD46 knockout mice have been reported to have increased fertilization rates due to increased spontaneous acrosome reaction [32], suggesting primate-rodent variations in CD46 function, or multiple actions of this protein. The full function and interactions of CD46 in development remains enigmatic.

As with CD46, C1q receptors have also been implicated in sperm-oocyte interactions. Receptors for the collagen-like and globular head regions of C1q, cC1qR and gC1qR respectively, have been detected on human spermatozoa [21], with C1q itself present in follicular fluid [33]. Following capacitation, membrane localization of gC1qR increases with exogenous C1q increasing sperm agglutination and adhesion to C1q receptor expressing zona-free hamster eggs [34,35].

The complement regulators, CD55 and CD59, display isoform

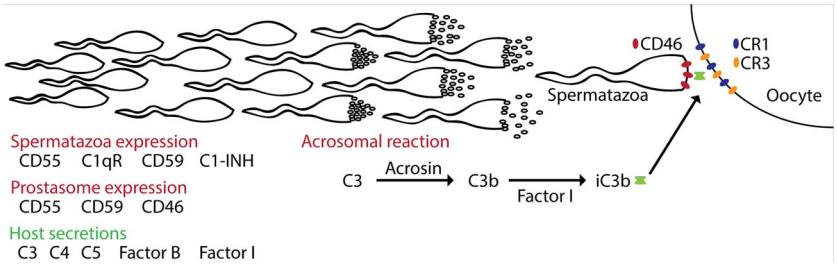

Fig. 1. Complement in the interaction of sperm and oocyte. Multiple complement factors are secreted into the female reproductive tract under hormonal control. To counteract this threat of complement-mediated lysis, there is expression of complement regulatory proteins by spermatozoa, and regulators concentrated into 'prostasomes' contained within the seminal fluid. On approach to the oocyte, spermatozoa undergo the acrosomal reaction, exposing the inner acrosomal membrane. The enzyme responsible for this reaction, acrosin, also cleaves local C3 to C3b, which can be further reduced to iC3b though factor I activity. This locally produces iC3b forms a linkage molecule between CD46 on the inner acrosomal membrane and complement receptors (CR1, CR3) on the oocyte, thus bringing the membranes into close proximity for fertilization.