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Alternative Pathway Activation: Ever Ancient and Ever New

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SUMMARY

Primitive underpinnings of the alternative pathway (AP), namely a C3-like protein, likely arose more than a billion years ago. Development of an AP amplification loop, while greatly enhancing speed and potency, also presents a double-edged sword. Although critical to combat an infectious disease, it is also potentially destructive particularly in a chronic disease process involving vital organs where scarring and reduction of regulatory function can occur. Further, new knowledge is pointing to genetic factors involved in an increasing number of complement-related diseases such as age-related macular degeneration (AMD). However, even a normal functioning repertoire of complement components can drive cellular damage as a result of low-level complement activation over time. Thus, the modern human AP now faces a new challenge: cumulatively-driven tissue damage from chronic inflammatory processes that mediate cellular injury. The impact of ongoing low-level AP-enhanced complement activation in disease processes is just beginning to be appreciated and studied. However, the sheer numbers of individuals affected by chronic diseases emphasize the need for novel therapeutic agents capable of modulating the AP. The more we learn about this ancient system, the greater is the likelihood of developing fresh perspectives that could contribute to improved human health.

Keywords

alternative pathway; feedback loop; complement regulation; age-related macular degeneration; atherosclerosis

1. INTRODUCTION

As an ancient component of immunity, the complement system likely arose for protection of single-cell organisms and gradually expanded to become the guardian of the intravascular space[1]. A primeval C3-like protein originated at least a billion years ago[2]. This protein and others provided individual cells with a mechanism for constant surveillance against microbes as well as a means to engage intracellular metabolic processes[3]. While the complement system retains some of these ancient functions, it has grown in players as well as sophistication.

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C3b-opsonized pathogens that enter the cytoplasm are marked for destruction and engage pathways for inflammasome-type responses[4]. One can envision the storage of C3 in intracellular vesicles capable of quick release to serve in recognition of foreign particles. With the increasing specialization afforded by continuing evolution of multicellularity, C3 likely evolved a secretory capability for guarding the interstitial space and ultimately to protect the vasculature[3].

Primitive underpinnings for a "pumped circulation" emerged approximately 650 million years ago in vertebrates[5]. During the evolution of a circulatory system two critical issues needed to be addressed. The first was clot formation and the second was to prevent intravascular infections. Attention to these issues commonly had to occur in parallel. Likely, at this earlier time, these two "terrible C's" ("clotting" and "complement," as appreciated by many a medical student) may have been more closely related than they are in contemporary humans. In either case, if coagulation or host defense were not functioning properly, death could be imminent. A key factor in the evolution of these two systems was speed. While blood loss was an obvious immediate threat for death, so was sepsis and meningitis. Prevention of these potentially catastrophic events had to be as quick and fool-proof as possible. Thus, absolute necessities for survival were to promptly form a clot and to clear pathogens from the blood stream by phagocytosis (immune adherence followed by ingestion) or lysis (intravascularly or extravascularly). These two pathways largely solved this issue by developing amplification loops. The latter served survival by being constantly on guard ("idling" or "turning over") and able to be heavily engaged within a few seconds[6,7].

2. EARLY AP AND AN AMPLIFICATION LOOP

Thus, innate immunity became a remarkable means to deal with life-threatening local and intravascular infectious disease challenges. Assaults by bacteria and viruses had to be quickly identified and then neutralized. Primitive elements of an ancestral complement system likely organized around an intracellular C3-like protein that featured opsonic capabilities and at a later time developed an amplification loop [1]. Activation to protect an organism (single or multicellular) required not only a rapidly acting intracellular complement-like system but also likely one on the membrane of a host cell as well as in its surrounding environment. Thus, organisms developed an intracellular defense system that could be transferred at least in part via secretion to the cell membrane and into the interstitial space to hopefully trap an invader locally and/or, even better, to attack it prior to cellular invasion. Because of the potency of this growing arsenal of protective proteins, regulators must have soon followed to guard uninfected nearby host cells.

It makes evolutionary sense for such a defensive "identification and damaging pathway" to reside and function in three locations – intracellular milieu – cell membrane – and extracellular space. Consequently, as organisms developed sophisticated circulatory pathways, such as the lymphatic and blood systems, the key players in the other more "ancient intracellular systems" were likely retained and continued to expand to even more efficiently interact in the circulation. The recent identification of an intracellular complement system supports this overview [3,8-10].

Further, a primitive C3-like protein evolved into a mosaic protein characterized by homologous and independent modules. One such module is the thioester domain that includes a rather unique feature: a labile thioester bond that transiently activates (i.e., the "tickover phenomenon") to promote its covalent attachment to particles. C3's instability also enabled its continual turnover as well as generating a feedback loop mechanism to rapidly identify, amplify and destroy pathogens. Likely then, the alternative pathway (AP) and its powerful amplification loop became a key player in vertebrate survival as it evolved from a primitive intracellular sentry to a refined circulating innate host defense pathway. It is now continuously "on guard" in the plasma and capable of binding to infectious agents and debris[11-13].

3. DEVASTATING DEFICIENCIES

Perhaps the most instructive examples of the importance of the AP are the anomalies of nature: complement component deficiency states[14]. For example, complete C3 deficiency was 100% lethal because of virulent encapsulated bacteria like streptococcus and staphylococcus. Deficiencies of properdin (P) or a member of the membrane attack complex (C5, C6, C7, C8 and C9) were usually also a high mortality event for a host secondary in this case most commonly to a meningococcal infection. The AP's amplification loop which can amazingly deposit millions of C3b molecules in a few minutes on a single bacterium was designed to prevent these lethal infections. Until the development of antibiotics and vaccines, survival of a baby with a deficiency of an AP component was unlikely.

The attachment of C3b to an organism (bacterial or viral) in blood led to immune adherence in which the erythrocyte via its C3 receptor served as a sump and a taxi in the circulation[15]. Shuttling was followed by a transfer of the cargo to a phagocytic cell in the liver or spleen or, in the case of gram-negative bacteria, lysis of the organism within the blood stream. In summary, the modern AP represents a robust system to carry out the destruction of invading pathogens via immune adherence leading to ingestion or membrane perturbation resulting in death of the infectious agent.

4. THE CHALLENGE OF DEBRIS CLEARANCE

Concomitant with the destruction of infectious organisms is another critical requirement: removal/clearance of biological debris. In this regard, even single cell organisms, let alone multicellular ones, must deal with such debris on a minute-by-minute basis. Because of this issue, a host evolved specialized mechanisms to handle cells and tissues damaged by an infection. However, the increasing longevity of humans also necessitates processes to ensure the effective handling of non-infectious debris so as to avoid undesirable tissue damage. Unfortunately, the immune system is better designed to deal with an acute process or, if it becomes chronic, to wall-it-off rather than handle continuous low-level generation of biological debris. Thus, in modern times, clearance systems in this scenario can be overwhelmed as apparently evolution has not yet caught up with human longevity.

Earlier in our history, infant mortality tragically resulted in a high death rate of young children, usually from infections, commonly before one year of life. This is evident from

"old" cemetery family burial plots where graves are dominated by infant deaths. It was not until antibiotics, vaccines and sterile surgical procedures began to arrive on the scene that this situation started to improve. While this early death problem has been largely solved (a phenomenal contribution of modern science), a new situation has begun to emerge. Earlier for the survival of the species, the major goal of our immune system was to protect individuals until they arrived at a reproductive age. Albeit a century or more ago, living up to the age of 50 was considered lucky, with contemporary medicine, most individuals now reach 70 to 90 years of age.

5. LONGEVITY AND THE CONTEMPORARY ALTERNATIVE PATHWAY

The AP now faces a new challenge – that of longevity. Having evolved to help individuals survive and reproduce, the AP must deal with milder (low grade) but chronic activation that amplifies and accumulates over time. Examples of such diseases in which AP activation may lead to chronic types of tissue injury include atherosclerosis, osteoarthritis, hypertension, diabetes mellitus, age-related macular degeneration (AMD)[16] and Alzheimer's disease (AD)[17] .

Longer life amplifies the likelihood of acquiring low level, but continuous, injury states that humans are ill-prepared to handle, in particular, for those involving the brain or the vasculature. This is contrasted with the capability to handle assaults in the skin, kidney, liver and lung. Evolution has designed a selective repair system for "hardy" humans in that one can lose up to 50%, even 75% of kidney, lung and liver function and yet survive! This is generally not the case, however, in the white matter of the brain, retina of the eye or vasculature to the heart. Thus, the current challenge is trying to define/resolve/inhibit the complement system in chronic, low grade, inflammatory processes of aging. In these now all too common clinical situations, the complement system is a dual-edged sword in being helpful in some cases but, more likely, creating harm as it fires and contributes to tissue damage. This is a case of 'too much of a good thing'[18].

Another poignant example in the setting of an AP amplification process is AMD. In this chronic disease of the retina, being haploinsufficient secondary to a rare variant for a regulator of the AP's feedback loop – namely factor H (FH) or factor I (FI) – is highly predisposing[16-21]. For example, instead of having a plasma level of ~40 μg/ml of FI, patients carrying a rare variant have ~20 μg/ml and, as a result, experience an increased frequency, earlier age of onset and a more severe form of AMD[19,21]. Further, earlier studies identified a FH single nucleotype polymorphism (SNP) that resulted in a histidine residue replacing a tyrosine at residue 402 (reviewed in[16]). A potential explanation for the high prevalence of Y402H is that the minor allele provides a survival advantage against streptococcal infections in early life (reviewed in [20]). The streptococcal FH binding protein has a much lower affinity for 402H. Moreover, a similar hypothesis to explain the positive selection for 402H suggests that this common polymorphism may have conferred protection against the Black Death (i.e., the plague caused by the bacterium *Yersinia pestis*) that was responsible for the death of 30-60% of the European population during the middle ages[20,22]. However, in older age, the 402H variant has a negative effect on handling drusen, thus contributing to retinal inflammation and AMD pathology[23].

For these and other reasons, one hypothesis is that excessive complement activation could be contributing to tissue damage in many chronic diseases. In addition to the continuous turnover of C3 to C3(H_2O) that generates deposition of C3b on a damaged tissue[24,25], there are lectins and natural antibodies in blood that could acutely and chronically directly deposit C3b on injured self. They represent natural mechanisms to activate the complement system in primitive species that lack an adaptive immune system. In these species and humans, hundreds to thousands of natural antibodies and lectins could provide both target selection and, especially, the initial C3b deposition to trigger the system, which is then amplified by the AP[26] . Thus, this mechanistic paradigm for engaging the complement system (as well as others to be identified) likely play a role in many chronic diseases of ever-aging humans.

6. CONCLUSION

To summarize, an amplification loop is a double-edged sword – highly desirable from an infectious disease point of view but potentially deleterious in a chronic destructive disease process, especially in vital organs in which repair processes lead to permanent scarring and minimal return of function. Also, aside from genetic factors exacerbating a disease such as AMD, even a normal functioning complement repertoire can ultimately drive cellular damage as a result of low-level complement activation. Thus, contemporary humans now face a new challenge: cumulatively-driven tissue damage from chronic inflammatory processes that may mediate cellular injury. The impact of ongoing low level complement activation in a chronic disease process is just beginning to be appreciated and studied.

With new and expanding genetic and pathologic evidence highlighting the role complement plays in chronic conditions, we await further development of novel therapeutic agents capable of modulating the AP. Emerging drug trials should ultimately reveal how to therapeutically modulate the debris-driven AP. It is an exciting time to be a “complementologist” – namely, associations with new and unexpected diseases and availability of therapeutic agents to alter complement activation! Thus, the more we learn about how our ancient amplification activation loop “works” and is regulated, the greater the likelihood of developing fresh perspectives that will hopefully contribute to improved knowledge of human health.

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