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Age to End Dreadful Diseases (HIV, Malaria, TB, Cancer and More): A Theory of Intact or Protected Complement (IPC) Immunity

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Abstract

After enormous efforts to fight for a successful HIV vaccine, the movement ended with frustration. While people are celebrating the victories of disease prophylaxis and healthy improvement, millions of them are still struggling on numerous unsettled dreadful illnesses, i.e., HIV, malaria, TB, cancer and autoimmune disorders. A theory of Intact or Protected Complement (IPC) immunity proposed in this review is to focus on hijacked complement system, the powerful leverage weapon restrained by many pathogens or cancer cells. The theory is to stimulate more investigations to discover the key block in continuous achievement in successful vaccine development and immune therapy.

Keywords: Intact complement system; Protected immunity; H factor; Vaccine; Cancer therapy

Introduction

In 2001, a bent syringe was showed on the front cover of a published book titled Big Shot: Passion, Politics and the Struggle for an AIDS Vaccine [1]. People had to admit that after enormous efforts to develop an efficacious HIV vaccine ended with frustration. Today we are in the similar situation. The current status of HIV, TB and malaria research seems wandering around in a forest with a long and arduous path of the disease control and vaccine development [2-4]. A representative cancer treatment vaccine is sipuleucel-T (Provenge®), which was approved by the U.S. Food and Drug Administration (FDA) in 2010. Patients receiving sipuleucel-T had a median overall survival of 25.8 months compared with 21.7 months for patients receiving the placebo, with an extension in median survival of only 4.1 months was observed [5,6]. Malignant cancers remain incurable in the vast majority of cases. Patients will eventually relapse rapidly, with their death less likely to be at home but rather in an intensive care unit or hospice referral [7]. Although many preclinical and clinical studies have shown the important role of monoclonal antibodies (mAbs) for the treatment of various solid tumors, many mAbs, such as bevacizumab, cetuximab, or panitumumab, have unfortunately failed to improve the survival of cancer patients. These tumors, in particular the aggressive forms, are highly sensitive at early stage to both chemotherapy and radiotherapy. However, relapse and resistance prevent the ultimate goal of achieving a cure in all patients [8,9]. Based on tumor-specific antigens and the direct killing of the tumor cells by tumor-specific T-cells, immune checkpoint blockade therapies have offered some improvements in cancer therapy; however, the immunotherapy was not approved as standard cancer therapy because the clinical effects were limited [10].

HIV continues to present a major global health problem. Most of the HIV research emphasis in the field is devoted toward the development of a preventive HIV vaccine. Nevertheless, such a vaccine is still elusive. The vaccine approach overall is still far from reaching the protective efficacy desired. Compared with healthy individuals, HIV-infected patients often have reduced immune responses to various immunizations (e.g. influenza, hepatitis B virus and pneumococcal vaccinations) [11,12]. Early initiation of antiretroviral therapy (ART) is critical to reduce HIV transmission [13]. However, ART is expensive as illustrated by costs in the US (more than $30,000 per year, per patient) [2]. It is observed that the side effects of ART medication exist increasing challenges in its course of treatment, ART can induce immune reconstitution inflammatory syndrome upon initiation, a tendency for HIV positive patients on ART to show increased kidney damage in addition to HIV associated nephropathy and cardiovascular disease. At the end of ART treatment, resistance rate in HIV patients can reach up to 30%, showing the urgent need not only for new method of therapy but also effective HIV vaccines [2]. However, with disappointing results from the vaccine based on the envelope protein gp120 and cytotoxic T lymphocytes (CTL) directed vaccines, pessimism and frustration have grown among HIV research field. It was even suggested that vaccine-related immune activation might have led to increased susceptibility to infection. The future prospect for HIV vaccinology seems grim. But HIV is not the only vaccine to experience difficulties.

Tuberculosis (TB) remains a global emergency despite widespread inoculation of BCG, the only licensed vaccine to prevent TB. While BCG has some efficacy on certain forms of childhood TB, the vaccine is not recommended for use in HIV-infected infants due to safety concerns, and lack of protection to the most common form of the disease which is adult pulmonary TB. Since the failure of the clinical trial of MVA85A vaccine three years ago, there have been no new tuberculosis vaccine candidates entering clinical testing. To date, no vaccine has been shown to be clinically safer and more effective than the presently licensed BCG vaccine [3].

According to the latest world health organization (WHO) estimates, released in December 2015, there were 214 million cases of malaria in 2015 and 438,000 deaths [4]. Impediments to successful vaccination are represented by the fact that malaria is a parasitic disease and the fact is that no vaccine against any parasitic disease exists so far. Almost all scientific reviews about the currently most advanced vaccine candidate RTS, S come to a clear consensus: the formidable task of

malaria disease eradication will not be accomplished with this vaccine [4,14].

What lessons can we glean from prior vaccine development? Most of the easy diseases have been successfully addressed, leaving only the most intractable targets like HIV, TB, and malaria to be solved. In the past decades, the concept of cell immunity has generated more confusing than reliable and consistent clinical results. Discovery of the most earnest vaccines, i.e., HIV, TB and malaria, and effective treatment for cancers seem being plagued by more uncertainty. Global scientific recognition or even a Nobel Prize presumably awaits scientists that eventually develop any of those long-desired vaccines or an efficient treatment for cancer disaster.

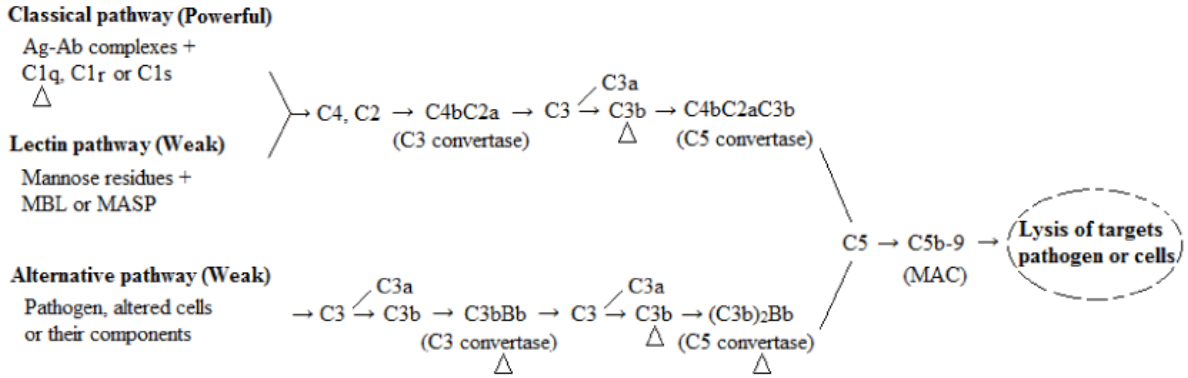

Figure 1: The critical roles of down-regulator Factor H (FH) in complement pathways. FH inhibits the formation of the C3 and C5 convertases, accelerates the disassembly of already formed convertases, and acts as cofactor for the inactivation of C3b, or directly competes with C1q.

Phenomena of the hijacked complement system

The immune system has been classified into two categories: innate and adaptive. The innate immunity provides an immediate, short-term and non-antigen-specific response against a variety of organisms. The adaptive immunity needs a lag time to develop, however the antigen-specific protection it provides can last in long-term, and the immune responses being induced are much faster and stronger than the innate immunity. The essential components of the innate immune system include epithelial/surface barriers, dendritic cells (DC), phagocytic leukocytes, natural killer (NK) cells, and plasma proteins (e.g., complement system proteins). The adaptive immune system has its own two functional categories: humoral immunity mediated by antibodies (generated by B-lymphocytes), which are powered by the complement system, and cellular immunity mediated by T-lymphocytes. The complement system is a central element of both innate and adaptive immunities. It acts as a vital defence system initiating and coordinating both immediate and long-term immune reactions, which are extremely toxic to microbes, foreign particles, and altered self-cells [11]. Complement cascade reactions are triggered by the binding molecules of C1q (classical pathway) and lectin (MBL, lectin pathway), or by spontaneous C3 hydrolysis (alternative pathway) [15-18]. All three activations elicit the assembly of C3 convertases (C4bC2a or C3bBb), which cleave and activate the central C3 molecule, creating C3a and C3b. C3b binds to target surfaces and, if not inactivated, leads to accumulate additional C3 convertases (amplification loop) [15,17]. The binding of C3b to a C3 convertase produces a C5 convertase that cleaves C5 into C5a and C5b. C5b attaches to target surface following by rapid binding C6, C7, C8 and several C9 molecules, a terminal membrane attack complex (MAC) is assembled that leads to target pathogen/cell lysis [15,16]. The cascade reactions of the complement system are rapid and powerful, and present a battle of life and death. Unrestricted activation of the complement cascade occurs at the surfaces of foreign particles - most microbes and altered self-cells, as these cells either lack endogenous regulators or at lower numbers. As a result, the fully unrestricted, uncontrolled activation generates a battery of damaging products, leading to the elimination of the target. However, the host cells and tissues are protected from the potentially deleterious effects of complement activation by fluid-phase regulators (Factor H, FHL1, properdin, C1q, C1INH, C4BP, clusterin, vitronectin and FHR1) and membrane-bound regulators (CR1, MCP/CD46, DAF/CD55 and MCP-IP/CD59). Compared to membrane-bound regulators, factor H (FH) is the central and critical down-regulator for all three complement pathways. It acts as cofactor for the inactivation of key complement molecule C3b, inhibits the formation of the C3 and C5 convertases, accelerates the disassembly of already formed convertases, or directly competes with C1q [15,17,18] (Figure 1). FH has the highest plasma concentration (approximately 500 μg/ml) among the complement related regulators or proteins, suggesting that cells which are in direct contact with plasma are completely covered with FH regulator. FH, factor H-related proteins (FHRs), and factor H-like protein 1 (FHL-1) belong to a family of complement regulatory proteins which are genetically designed to a locus on chromosome 1 [19,20]. These proteins are structurally and immunologically related, all members of this family possess a highly conserved motif, termed the short consensus repeat (SCR) [19]. FH is made up of 20 unique SCR domains arranged in an extended head to tail fashion and flexible chain, which permits a variety of functional sites to interact with complement proteins and surface molecules in a biological example of single-molecule regulatory chemistry [19,20]. In addition to the complement regulatory site located in its N-terminal four SCR domains, two other sites bind complement protein C3b, and three sites appear to recognize a variety of polyanions that serve as host markers [19]. It has been found that the multiple C3b and polyanion sites arrayed along the flexible structure of FH form a sophisticated recognition system [15,17,19-21]. This flexibility and the length of FH allow it to use its 20 domains to search for and interact with many ligands on a given target. A simple combinatorial math is calculated for

the possible recognition patterns of SCR domain on FH if the binding sites of FH work cooperatively in groups twos, threes, fours, etc, which would have the ability to discriminate among over 10^6 target surfaces [15].

Pathogens / altered cells	FH/FHL-1/ FHR1	Binding protein(s)/ substrate(s)	References
A. actinomycetemcomitans	FH	Omp100	[22]
B. afzelii (Lyme)	FH/FHL-1	BAPKO_0422, BaCRASP-1,-2,-3,-4,-5	[23]
B. hermsii (Lyme)	FH	FHBP19/FhbA, FHBP28	[24]
B. burgdorferi (Lyme)	FH, FHL-1	CspZ (BbCRASP-2 or BBH06), CspA, ErpA, ErpC, ErpP, BbCRASP-1 (BBA68), BbCRASP-3,-4,-5, BhRASP1, OspE, p21, 35kDa protein	[24,25]
C. albican	FH, FHL-1	CaCRASP1, Gpm1p	[26]
Cancer cells	FH	BSP, OPN, DMP-1, GAGs, Sialic acid	[27-29]
H. influenza type b, type f	FH	PH	[30]
H. influenza, non-type	FH	OmpP5	[31]
HIV	FH	gp41, gp120	[32]
Hepatitis B virus	FH	HBx	[33]
Leptospira species	FH	LcpA	[34]
M. meningitidis	FH	fHbp, PorB3, NspA	[35]
M. catarrhalis	FH	OlpA	[36]
Malaria parasite	FH	PfGAP50	[37]
M. tuberculosis	FH	Lipid?	[38]
N. gonorrhoeae	FH	Los, Sia, Por1A	[24]
P. aeruginosa	FH/ FHR1	PaCRASP/Tuf	[21]
S. agalactiae	FH	ß protein	[24]
S. enterica	FH	PgtE	[39]
S. pneumoniae	FH/FHL-1	PspC, Fba, Hic	[21,24]
S. pyrogenes	FH/FHL-1	M, Fba, emm5, emm6, emm18	[21,24,26]
T. denticola	FH	FhbB	[40]
Y. enterocolitica	FH	YadA	[24]
Y. pestis	FH	Pla	[39]
West Nile virus	FH	NS1	[41]

Table 1: The protein(s) or substrate(s) of pathogens or altered cells utilized to bind FH/FHL-1/CFHR1 to escape effective complement reactions.

In the course of pathogen-host or mutated cell-host combat, numerous human pathogenic microbes or cancerous cells have abilities to inhibit or control complement recognition. During the past decades, more discoveries of evasion mechanisms of pathogens or tumor cells through hi-jacking the host complement system have been reported (Table 1). Although the binding site of FH for all these pathogens appears to be SCR, no common similarities on the invaders' side have been found, pointing to distinct mechanisms for immune evasion have evolved for the different cancerous cells or pathogen species. The strategies used by those alien invaders to prevail our immune system through hijacking the complement regulators are summarized here:

1) Binding of host fluid-phase complement system inhibitors. A wide variety of pathogens including HIV, malaria parasite, Yersinia pestis, and malignant cells subvert complement attack by binding host complement inhibitors such as FH, C4BP or vitronectin, which results in diminished opsonophagocytosis and inhibited complement-induced lysis [21]. The receptor proteins of these microbes and uncontrolled cells take advantage of binding of FH/FHL/FHR1 to their surface protein receptor(s) to escape initiation of complement reactions are showed in Table 1.

Most pathogens plunder host FH by binding it via two separate SCRs, one within the domains 6-7 and the other in the C-terminal SCR 19-20 [22-41]. Attached to the surface of the pathogen, the host-resourced complement regulators FH, FHL-1 and C4BP maintain cofactor activity for inactivating C3b and C4b, and thus restrict complement activation. The critical role of FH for the survival of HIV virus is obvious, since incubation of HIV with FH-depleted sera ends up to 80% complement-system-mediated virus lysis in the presence of HIV-specific antibodies [32]. It suggests that FH is bound to pathogen surface proteins, an initiation of FH-dependent interaction with C3b activates, and thus efficient FH mediated inhibition of complement lysis becomes a powerful scheme for the survival of invaded pathogens. Furthermore, the bacterially captured FH becomes functionally enhanced and achieves at a structural level. The N-terminal domain of *S. pneumoniae* protein PspC not only binds FH in an extremely tight manner, but also manipulates it in a conformational change. This structural change of FH doubles its affinity for C3b molecular and transfers a 5-fold increase in its capability to accelerate decay of the C3b convertase responsible for cleaving more C3 to C3b in an amplification loop [42].

2) Incorporation of host cell membrane complement inhibitors or components into their own surface or envelope. Viruses such as HIV, human cytomegalovirus and vaccinia incorporate host cell CD59 into their own viral envelope to prevent lysis by complement [32]. The essential mechanism of viral escape being destroyed is due at least in part to the presence of membrane regulators such as CD59 and CD55 in the viral envelope, which are exclusively from the host cell during the budding process [43,44]. In addition to binding of the more efficient fluid phase complement regulator FH, incorporation of host cell membrane complement inhibitors provides HIV-1 more stronger protection from complement attack. It shows that the presence of complement regulators of FH and CD59 on the exterior surface of the viral envelop provides vigorous resistance to complement-mediated lytic killings, which proves why certain human pathogenic viruses are not deactivated by complement cascade reactions in human fluids even when they elicit a strong and specific antibody response [32]. This similar evasion strategy is also found with pathogens like *N. gonorrhoeae* which scavenge sialic acids (Sias, such as Neu5Ac or Neu5Gc, or the cytidine-monophospho (CMP)–activated form CMP-

Neu5Ac) from the host [45]. Surface-bound Sias increase the affinity of FH for C3b which is deposited on these or other host cells or microbial surfaces upon inactivation of complement reactions.

3) Expression of factor H or membrane-anchored regulatory proteins. Soluble complement inhibitors, such as C1 inhibitor, FH, FHLs, factor I, and C4BP are secreted by tumor cells into the local microenvirionment. Secretion of soluble complement regulators FH and FHL-1 by tumor cells could help them to evade humoral immune attack and significantly reduce the effective outcomes of monoclonal antibody therapies [46,47]. Actually, the increased FH or related proteins were widely accepted as diagnostic marker for many cancers, such as transitional cell cancer of the bladder [46-48]. By Northern blot analysis, a high expression of factor H and FHL-1 was demonstrated to occur in most non-small cell lung cancer cell lines [46]. FH was discovered to express in various malignant cell lines, including colon, ovarian, liver, bladder, and lung cancer cell lines [46-48]. The strategy of tumor cells to express and bind FH to their surface reveals their malicious persistence to prevent C3b accumulation upon their cell membranes. Therefore, high expression of FH leads to more aggressive tumors with a worse clinical outcome. Patients with lung adenocarcinoma who have positive expression of FH have a shorter survival time [47]. HER2-positive breast cancer patients with CD55 and CD59 overexpression have a higher relapse rate than those with low expression of CD55 and CD59 [48]. Similarly, the mean disease-free survival of patients with CD55 or CD59 overexpression was significantly shorter than those with a low expression of CD55 or CD59 [48].

4) Degradation of complement components. A prostate-specific antigen (PSA) was found to continually express in high-level among the majority of men with both high- and low-grade prostate cancer [49]. It could not be confirmed that PSA had a role in the pathogenesis of this disease until a C3 cleavage site was discovered by biochemical analysis with tryrosine-1348. Furthermore, purified PSA was able to cleave iC3b and the associated complement protein C5 [49]. These results revealed that PSA as an immune inhibition protease could assist to create a micro-environment beneficial to malignancy through degradation of the complement components.

5) Increased expression of factor H binding proteins. For cancerous cells, the increased expression of FH binding proteins: bone sialoprotein (BSP), osteopontin (OPN) and dentin matrix protein-1 indicates enhanced protection from complement lysis [50]. It revealed that BSP and OPN first bound to a cell surface receptor, then to complement Factor H, thereby blocking the lytic activity of the alternative pathway of complement (APC) [50].

6) Over-presenting of variant FH genotypes (Tyr/His and His/His). Variant FH genotypes (Tyr/His and His/His) were over-presented among lung cancer patients compared to controls, a single nucleotide polymorphism (SNP) located in exon 9 of the FH gene [51]. It contains a tyrosine to histidine change at amino acid position 402 in the FH that re-directs the complement reactions. Tyr402His has been showed to be related with lung cancer and as a marker for lung adenocarcinoma [51]. The over-presentation of variant FH contributes to tumor growth by suppressing the anti-tumor cell and antibody mediated-responses was observed in the cell lines of several malignancies [51].

Critical role of FH in pathogenesis of several dreadful diseases

AIDS: The term "immunodeficiency", or maybe the more accurate term "immune-malfunction", expresses exactly what people observed in AIDS patients. HIV-1 virus escapes complement-mediated immune protection and remain highly infective, even though both the HIV-1 envelope antigens and anti-HIV specific antibodies in the serum of HIV-1 infected patients are able to active the complement cascade reactions as discussed above [32,52]. It is confirmed that HIV-1 virions isolated from infected individuals have accumulated C3 on their surface, a signal of the initiation of complement reactions, but HIV-1 virions are still very resistant to complement mediated killing, which is a different phenomenon of humoral immune responses induced from the most invaded pathogens [32]. More and more experimental and clinical evidences indicate that MAC pores supposed to be seen on the surface of invaded pathogen are not effectively formed in the case of HIV infection, leading to the escape of virus and all over spreading through the blood and lymph systems in HIV patients [53,54].

HIV escaping from complement-mediated killing is mainly by binding soluble FH through surface proteins gp120 and gp41. In the presence of HIV-specific antibodies, sera devoid of FH (total genetic deficiency or normal human serum depleted of FH by affinity chromatography) can return its normal lysis ability both to free virus and HIV-infected cells [32,53]. On the contrary, with the involvement of FH, HIV and HIV-infected cells are not lysed by human complement; even in the presence of HIV-specific antibodies [32]. This intrinsic resistance is not due to a failure of HIV surface glycoproteins to interact with complement proteins since HIV, HIV-infected cells, and purified HIV envelope proteins bind complement proteins with activating functions like C1q or mannan binding protein and trigger complement fixation. HIV manipulates complement regulators to its advantage to facilitate early invasion steps leading to infection following mucosal transmission of HIV. Subsequent to virus capture by immature dendritic cells (iDCs), infectious HIV particles are transported to the draining lymph nodes [53]. Therefore, the complement system is designed to undertake crucial roles in neutralizing and clearing HIV-1 virions, but unfortunately, HIV-1 virions hijack the critical complement regulators, the complement system itself becomes is a tool for the spread and maintenance of the virus in the infected host.

In general, HIV virions and infected cells could be specifically killed *in vitro* by complement and HIV-specific antibodies in genetically FH-deficient sera. The complement-mediated lysis could be further enhanced through the addition of a blocking antibody against CD55; however, FH binding was shown to be responsible for most of the resistance mechanism in both cases. It has been confirmed that resistance to human complement can be completely overcome if Decay accelerating factor (DAF)/CD55 and FH are set out of function [32,53,54].

Malaria: A surprise discovery reported in recent year is that the gamete surface protein PfGAP50 from the malaria parasite P. falciparum is used to inactive the host complement regulator FH following transmission to the mosquito body to protect from it complement-mediated killing by fresh blood meal [37]. The human complement proteins present in the blood meal are active in the mosquito midgut for approximately one hour post-feeding. During this time window, PfGAP50 immediately seizes FH and uses it to inactivate the central complement component C3b [37]. The critical role of PfGAP50 in assisting malaria parasite infection was confirmed

after the neutralization of FH or blockade of PfGA50, the gametogenesis was significantly impaired. Furthermore, mAbs directed against FH were able to fully block transmission of Plasmodium to the mosquitoes [37]. Although it shows that both FH and FHL-1 bind to activated gametocytes, FHL-1 is present in the blood in a much lower concentration (30 μg/mL) than FH, malaria parasites appear to preferentially co-opt FH for protection against the human powerful complement lysis [55].

Bacteria: The three most common pathogens causing human acute otitis media are S. pneumoniae, H. influenzae, and M. catarrhalis, all of them have previously been reported to interact with FH, resulting in enhanced survival in serum [26,36,56]. Clinical isolated M. catarrhalis is highly resistant in relative bactericidal test. This is accomplished mainly by hijacking complement regulators in order to inhibit the formation of the MAC [36]. For example, M. catarrhalis not only recruits vitronectin from serum and ultimately inhibits the assembly of the C5b-C7 complex and polymerization of C9, and utilizes C4BP for inhibition of the classical pathway of complement activation, it also binds factor H to directly interact with the complement system [36]. Those strategies exploited by *M. catarrhalis* greatly increase its survival by combating our immune system. A selection of FH19-20 point mutants reveals that all studied microbes (*H. influenza, B. pertussis, P. aeruginosa, S. pneumonia, C. albicans, B. burgdorferi, and B. hermsii*) utilize the same binding site located on one side of SCR 20 [57]. Binding via this site not only mimics the glycosaminoglycans of the host cells, but also improves function of FH bound on the microbial surfaces via the new structural formation of tripartite complex [57].

Cancer: Like the threatening pathogens mentioned above, cancer cells are especially skilled at protecting themselves from complement-mediated immune responses. FH and FHL-1 expressions are discovered in up-regulated manner in many cancers and inhibition of their expression decreases the growth rate of the cells *in vivo* [27,28,58]. The presence of factor H in samples from all lung cancer stages suggests that plasma protein exudation is an early change in the bronchial epithelium and can be used for early detection. Quantification of markers such as factor H was suggested to be used in the future as a sensitive and reliable molecular diagnostic technique to implement cytologic examination in the diagnosis of lung cancer. There is a significantly higher concentration of FH in bronchoalveolar lavage fluid and sputum from patients with lung cancer [27]. In the context of lymphocytic leukemia, the efficacy of complement-dependent cytolysis or cytotoxicity (CDC) is significantly inhibited due to the expression and hijacking of regulators (CD20, CD55, CD59 and FH) by cancer cells [58-61]. Abrogating of FH with factor H-derived SCR 18-20 greatly increased the susceptibility of primary chronic lymphocytic leukemia cells to ofatumumab-induced CDC [58]. It is a reasonable conclusion that factor H-derived SCR 18-20 is likely to extend the turnover time of active C3b fragments accumulated on the target cells following antibody-induced complement activation, thereby, improving specific killing of cancer cells by CDC [58].

Many cancer cells are also altered to increase sialic acid synthesis [62], possibly by up-regulating sialytransferases [63], to maintain a state that has been fabricated "super-self" [29,64]. The strategy used by cancer cells to increase surface expressions of sialic acid provides efficient protection against complement cytotoxicity is found by applying the same strategy of recruiting FH, because when sialic acid is removed from malignancy cells their complement-mediated killing is greatly enhanced [63,65,66].

Theory of intact or protected complement (IPC) immunity

In the past decades, the concept of cell immunity has misled the majority of scientists: they stepped into a huge forest; paved hard, searched in dignity with little success (Figure 2). On the highway of pursuing efficacious vaccines or treatments for HIV, TB, Malaria and numerous malignant cancers, most investigators strode in sideways, including those studying T cell-medicated CTL immunity with equivocal and perplexing results. Investigations of alternative and MBL lectin pathways, applications of DNA/gene and mAbs, and others seem have not reached the essential portion of the problem. Among those sideways approaches, only pharmaceutical companies were pleased with the business of antibody therapy. The success highway to the most efficacious vaccines or treatments was greatly neglected or misinterpreted.

Almost all the effective vaccines having been licensed and improved are based on antigen-antibody-complement based B-cell immunity, not T-cell responses from adaptive immunity or the alternative pathway, nor on phagocytic response from innate immunity (including macrophage or natural killer cell strategies). The integrity of adaptive and innate immunities of our immune defending system is critical to maintain the healthy status of our body. However the limited clinical effects of antigen-specific T-cell responses, the immediate, short-term, non-specific and partial effectiveness of innate immunity, none of them are comparable to the specialized and powerful antigen-antibody-complement immune response in combating invaded pathogens or malignant tumor cells. A theory of Intact or Protected Complement (IPC) immunity is proposed here to hypothesize that the most dreadful diseases could be cured or prevented if our complement system is intact or protected, which not only provides direct or non-direct, non-specific immune responses generated from innate immunity, but also prepares powerful and prevailing cascade reactions in acquired immunity. Of course, to make the fully functional acquired immunity available, the complement system has to partner with specific antibody induced by invading pathogens or altered cells. Based on the accumulated findings on our complement system, the proposed IPC theory is try to put back the missing puzzle piece in human immune prevention and therapy mechanisms, the powerful leverage weapon hijacked and restrained by many pathogens or cancerous cells. The more effort applied to the functions of intact or protected complement system, the earlier the gap of continuous achievement in successful vaccine development or disease treatment could be closed. Then, the mysterious channel between adaptive and innate immunities may be unveiled.

Therapeutic and prophylactic strategies for dreadful diseases

The new therapeutic strategies based on the concept of an inhibited complement system include:

1) Development of monoclonal antibodies specifically directed to FH-binding sites of pathogen proteins to compete with the binding of human FH. Such as antibodies directed against plasmodial FH receptor protein, PfGA50, are capable to functionally block malaria transmission to the mosquito. Receptor PfGA50 antigen utilized by the malaria parasite for protection against the human complement lysis after a blood meal may provide ideal candidate for transmission blocking vaccines [37];

2) Synthetic peptides reproducing the FH region interaction with target pathogen or cell, which can be directly used in patients to block the binding with our serum FH;

3) Constructs consisting of recombinant bifunctional single-chain variable fragment (scFv) based on a monoclonal antibody against pathogen proteins, which are coupled to specific binding domains of FH (scFv-SCR), to enhance lysis by complement [67];

4) Chimeric proteins that comprised human FH domains 6 and 7 fused to human IgG1 Fc (FH6.7/HuFc) as an immunotherapeutic against pathogens by binding FH through domains 6 and 7 [68]. In the case of meningococcal bacteremia, FH6.7/HuFc can enhance human C3 and C4 deposition, mediate direct killing through complement, and protect infant rats against meningococcal bacteremia. This shows that the complement activation and killing is classical pathway dependent;

5) Targeted inhibition of factor H overexpression to enhance sensitivity to complement-mediated lysis of altered cells.

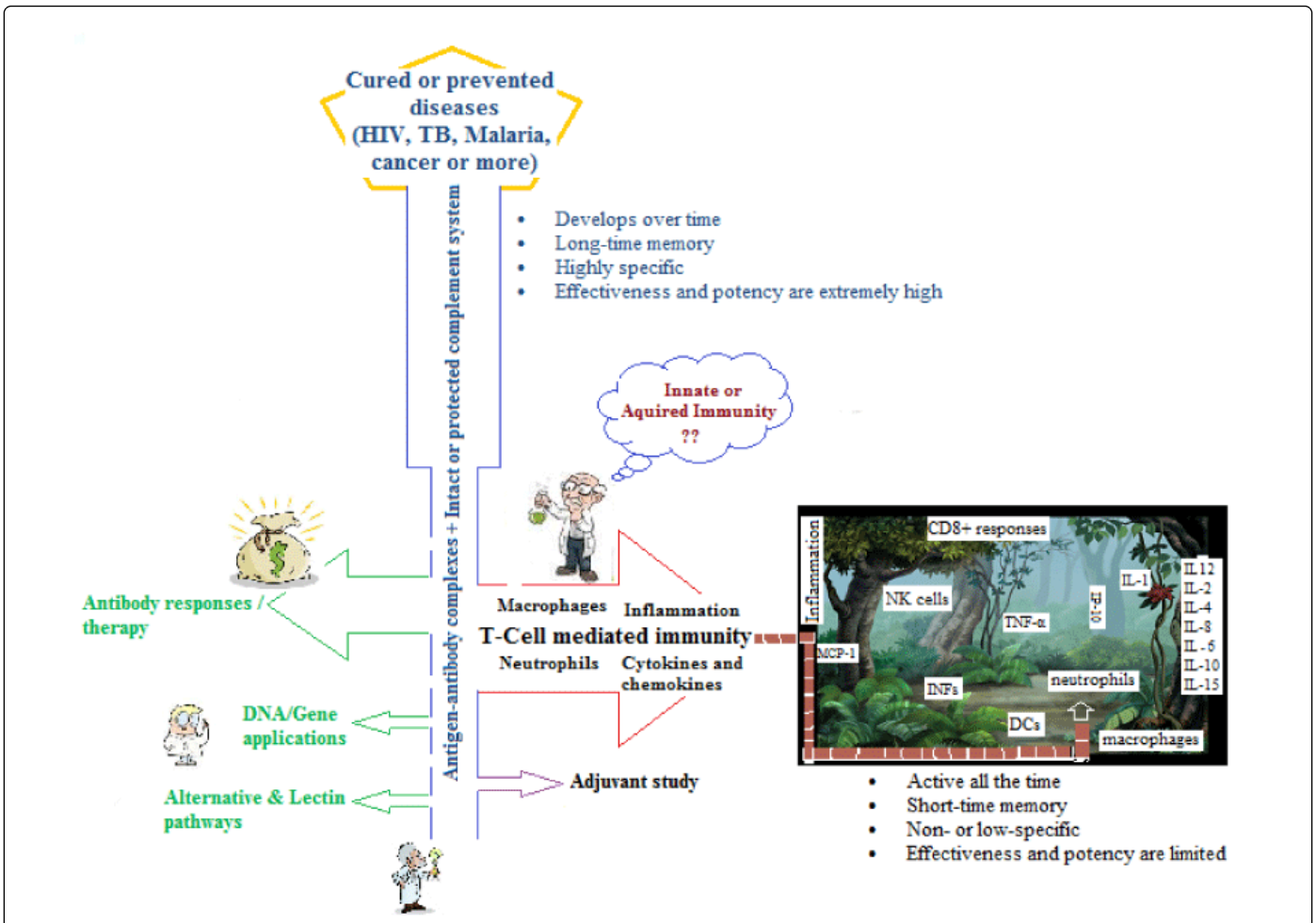

Figure 2: Path to end dreadful diseases: a theory of intact or protected complements (IPC) immunity. The sizes of arrows represent the research efforts in the past.

One of the benefits of introducing the IPC theory is to turn our attention to developing more efficient prophylactic strategies for the dreadful diseases we are facing. The unintentional discovery of FH binding antigen FHbp has been marked as a key component in recently licensed N. meningococcal group B (MenB) vaccines. It filled the final gap of decade-long search for a meningococcal meningitis vaccine comprising five serogroups (A, B, C, W-135, and Y) utilized to prevent this deadly and devastating disease. The success in developing the MenB vaccine has opened a door of vaccine design for many other preventable diseases. FH has at least four binding sites for C3b and pathogen target antigens, each with a different binding specificity, affinity, and functional significance. Although the binding sites of FH for all these pathogens or tumor cells appear to be SCRs, no common similar binding features on the pathogen or altered cell side are displayed (Table 1), pointing to distinct mechanisms for immune evasion, and specific antigen from different pathogen or altered cell can be utilized in their prophylactic vaccine development. Regarding a concern that FHbp vaccines may bind human FH, thereby eliciting FH autoantibodies, the flexibility and the length of factor H allow the protein to use its 20 domains to search for and interact with many ligands on a given target, in addition to specific binding antigen and pattern from pathogen or cancer cell side, it is less likely to generate a significant autoantibodies to interfere our normal function of human FH. Two FHbp MenB vaccines have recently been licensed by the U.S. FDA. However, no confirmed MenB vaccination-related autoimmune conditions have been observed in clinical trials or vaccination campaigns [69,70].

Finally, the HIV study suggests that virus membrane DAF, robbed from the host cell during the budding process, and exogenous FH

secondarily attached to the HIV envelope proteins, together are necessary for the efficient, crucial resistance of HIV to human complement reactions. Overcoming these two barriers should be an appropriate strategy for new vaccine designs, and would give us a hint that through inhibiting complement system, multiple antigens from pathogens or tumor cells may be used to overcome our immune system.

Conclusions

The complement system plays critical roles in killing or neutralizing pathogens. However, various pathogens and cancerous cells hijack our complement system by exploiting regulator proteins which are supposed to protect host cells from complement activation. As the chief soluble complement regulator, FH is a prime target for microbial and cancerous cell in hijackings. More and more evidence suggests that enormous FH circulates with its C3b-binding capabilities is deliberately abused, which restricts the complement system in regulating C3b amplification in fluid phase or on the surfaces when the FH being passively captured by bacteria or malignant cells.

The similar SCR binding sites on FH utilized by those of dreadful pathogens or tumor cells to invade our immune system appear to be the similar strategies. However, no commonality of binding substrate antigens on the pathogen or altered cell side have been found, which provides a unique opportunity in corresponding vaccine development, as showed in the successful campaign battle against MenB disease.

More than a century after the significance of the human complement system was recognized, people still do not fully realize that its versatile functions extend far beyond the elimination of dangerous pathogens. However, complement-dependent cytotoxicity induced by specific antibody acts as a central defending element in our immune systems can no longer be ignored. By eliminating cellular debris and infectious microbes, sending 'danger' signals, and coordinating immune responses, the uncompromised complement system contributes substantially to homeostasis of our healthy cells and efficient immunity within our bodies.

The FH-centered development strategy and the solution of how to sustain highly potent and effective antibody-based prevention/cure immunity may accelerate many vaccine development and cancer treatment programs and ultimately initiate a new age that might possibly eliminate the major diseases from the future of our humanity.

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