Perspective

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Complement Factor H: Function and Dysfunction

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Perspective

Due to the constant monitoring of its alternate channel, the complement system reacts promptly to threat (AP). Protective membrane-bound and soluble regulators keep an always-on positive-feedback C3b-amplification loop at "tick-over" level on autologous surfaces in the AP. Invading microorganisms exposed surfaces, on the other hand, are quickly opsonized by AP-generated C3b, which tags them for clearance, activates the cytolytic terminal pathway, and releases the anaphylatoxins C3a and C5a. Pathogenic microorganisms, on the other hand, frequently resist complement assault and so escape destruction. Complement factor H is a soluble AP suppressor that recognizes self-surfaces on autologous surfaces, either directly via particular glycosaminoglycan and sialic acid or indirectly via C-reactive protein (CRP), and operates in fluid phase. FH also helps to eliminate damaged cells and cell debris in a non-inflammatory manner. Binding sites, especially for complement receptor (CR3), malondialdehyde (MDA)-modified proteins, and apolipoprotein E (apoE), are dispersed throughout its 20 CCP modules (CCPs), also known as short consensus repeats, to facilitate additional "non-canonical" FH activities. FH-like 1 (FHL-1) is a smaller AP-regulating splice variation that does not discriminate between self and non-self. The family is completed by six FH-related proteins (FHRs-1-3, 4A and 4B, and 5). These products of genomic duplication events are encoded by a gene cluster located 3' of CFH (CFHR3;CFHR1;CFHR4;CFHR2;CFHR5) and may work against FH.

Single-nucleotide polymorphisms, copy number changes, exon duplications, deletions, and rearrangements are all prevalent in CFH and CFHRs. Atypical Haemolytic Uraemic Syndrome (aHUS), C3 glomerulopathy (C3G), and age-related macular degeneration (AMD) are only a few of the disorders that can be affected by these. The interaction between members of the FH family is unpicked. The self-surface-recognition and C3b-binding CCPs 19-20 of FHRs are similar to, and may compete with, the self-surface-recognition and C3b-binding CCPs 19-20 of FH. FHRs, on the other hand, lack CCPs that are similar to FH's C3b-binding CCPs 1-4, which are required for AP regulation. FHRs-1, 2 and 5 have N-terminal CCPs that stabilize homo/hetero-dimerization. FHL-1, on the other hand, has the CCPs 1-4 of FH, as well as CCPs 5-7 that enhance their function, but lacks FH's C-terminal CCPs, which explains its lack of self/non-self-discriminating. Because FHL-1 is smaller than FH, it can get to places where FH can't, such as crossing Bruch's membrane in the eye. These two studies emphasize the difficulties of working on FHRs and FHL-1, such as a lack of particular antibodies and appropriate animal models. FH is thought to be caused by the simultaneous engagement of CCPs 1-4 and CCPs 19-20 of FH with the same C3b molecule, which is aided by 14 connecting CCPs. Dunne et al. discovered a low-affinity dimerization location in CCPs 17-18, which might help explain disease-related mutations. FH molecules might be helped to assemble in locations that require strong AP suppression via dimerization. The function of FH's sialylated N-glycans is yet unknown. In instances of Streptococcus pneumonia-precipitated aHUS, Delgado et al. describe desalination of FH by bacterial neuraminidase (Sp-aHUS). FH was less efficient at preventing complement-mediated hemolysis after in-vitro enzymatic desalination, suggesting a pathogenic mechanism underlying Sp-aHUS. Rare genetic variants in the CFH/CFHR cluster, which were found in a large number of patients in our study, may also have a role in illness.

Knowledge of the implications of individual mutations informs standard genetic variant screening in aHUS management. Within the AP-regulating CCPs 1-4 of FH, researchers outline a methodology for characterizing "variants of unknown importance" seen in aHUS, C3G, and AMD patients. Q81P was discovered to be a dysfunctional, likely causal mutation in aHUS out of six novel SNPs evaluated. Less affected variations (such as D130N in our study) may have a role in AMD, which is a disease that progresses more slowly. The number of biochemically defined FH N-terminal variations now stands at 16, which is a useful figure.

Autoantibodies that bind CCPs 19-20 of FH and inhibit C3b binding were also found in four of 45 cases of neuromyelitis optica spectrum disorder, a rare inflammatory disease of the CNS that responds to therapeutic complement suppression and is also

associated with other autoantibodies. These FH-AAs responded with FHR-1, but none of the people tested had CFHR3; CFHR1, and none of them had renal disease. Larger cohort studies will be conducted to discover how FH-AAs are produced and contribute to underlying pathophysiology. Beyond its normal complement functions, surface-bound FH attaches to neutrophils and monocytes and impacts their behavior. Extending this feature to surface-immobilized FHL-1, FHR-1, and FHR-5, researchers describe how these proteins may alter extravasation and pathogen death by influencing adherence and migration, as well as the production of IL-8, IL-1, TNF, and anti-inflammatory IL-10. The identification of the cell-surface FH/FHR receptor(s), of which CR3 is the leading candidate, is a major issue. Use of engineered FH to suppress the cytokine storm generated by C3a/C5a binding to receptors on peripheral blood mononuclear cells in a similar study. A "mini"- FH, consisting of CCPs 1-4 connected to CCPs 19-20, modestly inhibited IL-6 production while stimulating IL-10 production in cells grown with autologous serum and exposed to artificial immune activation.

FH-mediated protection is critical for the survival and health of our cells and tissues. FH's position as the "master regulator" of the complement system is evidenced by the large number of pathogenic microorganisms that rely on it for survival in human tissues. The rising number of disorders connected to variations or mutations in the CFH and CFHRs cluster highlights the need for improved tools and animal models to help research, as well as the formation of complement diagnostics sections inside hospital laboratories.