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Eye Diseases Direct Interest to Complement Pathway and Macrophages as Regulators of Inflammation in COVID-19

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Abstract: Many of the risk factors for developing severe coronavirus disease 2019 (COVID-19) are also risk factors for eye diseases such as age-related macular degeneration (AMD). During the past decades, macrophages and the complement pathway (as a part of the innate immune system) have been identified as important contributors to the development of AMD, and we suggest that these mechanisms are of similar importance for the clinical course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Based on the experience with AMD, we discuss how behavioral factors such as diet, smoking and higher body mass index, as well as genetic determinants such as the complement and immune pathway genes may lead to the overactive inflammatory phenotypes seen in some patients with COVID-19, and may in part explain the heterogeneity of disease manifestations and outcomes. Based on this experience, we discuss potential genetic research projects and elaborate on preventive and treatment approaches related to COVID-19.

Key Words: complement, COVID-19, inflammation, lifestyles, macrophages, macular degeneration

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According to the World Health Organization (website WHO), people who have an increased risk of developing severe *coronavirus disease 2019* (COVID-19) are "older persons and persons with preexisting conditions such as lung disease, high blood pressure, cancer, heart disease, or diabetes."[1] Elderly age, being overweight, and smoking are important risk factors for dying from an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Younger individuals can carry the virus, but are less likely to develop similar signs and symptoms as older adults. We noticed that several of the risk factors are related not only to cardiovascular disease, but also to age-related macular degeneration (AMD). Aging, smoking, and abdominal and overall obesity have all been identified as important risk factors for this potentially blinding eye disease. One of the great advantages of studying AMD is the visibility of the different stages: detailed analysis of the fundus and precise visual follow-up provide direct staging information. This has enhanced many studies that have reported the role of genetic and immune factors such as complement and macrophages in various subtypes of AMD, and have shown the importance of preventive measures. The similarity in risk factors called our attention to the potential role of macrophages and the complement pathway in the development of severe COVID-19. This knowledge may help to understand heterogeneity of disease manifestations and outcomes, why some people develop severe inflammation after contracting SARS-CoV-2 and others do not, and why especially older persons and those with preexisting cardiovascular and pulmonary conditions are more likely to develop severe COVID-19 than others. Patients with AMD are also more at risk. We will describe the role of behavioral risk factors, macrophages, and complement in AMD, and then discuss their potential impact on preventive and treatment strategies for COVID-19.

RISK FACTORS AND MECHANISMS OF SEVERE COVID-19

COVID-19 patients admitted to intensive care units frequently show signs of cardiovascular disease and are often found to be overweight.[2] A study of 221 COVID-19 patients admitted to the Shanghai Public Health Clinical Center, China, reported that those older than 60 years more often developed a severe or critical disease course.[3] The group was separated according to age: 136 cases were younger than 60 years, and 85 patients were $\geq$60 years old. At admission, symptoms did not differ significantly, but the older group showed higher levels of blood urea nitrogen, lactate dehydrogenase, and inflammatory blood markers. The patients in the older group had more severe pulmonary disease and more often needed assisted ventilation. Among 300 cases with COVID-19 admitted to the intensive care units at the Montefiore Medical Center, Bronx, New York, United States of America, overall 30-day mortality was 52%.[4] A higher mortality was associated with increasing age, male sex, hypertension, obesity, smoking, the number of comorbidities, and the presence of acute kidney injury at admission. The overrepresentation of men among severe cases has been attributed in part to the greater percentage of smokers among men compared to women.[2] A recent meta-analysis that included 11,590 COVID-19 patients indicated that 30% of ever smokers experienced disease progression, versus 18% of non-smokers.[5]

After the initial upper airway infection with SARS-CoV-2, pulmonary disease may develop, leading to low oxygen saturation levels, necessitating intubation and extracorporal oxygenation. Kidney disease and thrombosis may complicate the infection. These latter effects may all develop from an overactive inflammatory response, as reviewed by Tay et al.[6] A severe cytokine storm may occur and is associated with multiorgan failure, but the extraordinary

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inflammatory infiltration and subsequent fibrosis of the lungs is the most important reason for being placed on a ventilator. Patients are now being treated with antiviral therapy (ritonavir, lopinavir, and remdesivir) and trials have started with anakira (Spain, Clinicaltrials.gov NCT04443881, and multiple others) and tocilizumab (Spain, ClinicalTrials.gov NCT04445272, and multiple studies); anakira and tocilizumab are drugs that are being used to treat autoimmune disease such as rheumatoid arthritis and lupus, and which interfere with the immune system (anakira is a human interleukin-1 receptor antagonist and tocilizumab is a monoclonal antibody against interleukin-1). It may sound contradictory, but the approach in which the immune system is blocked in the phase of pulmonary problems may be essential to limit the severity of COVID-19. This theory has already found support in practice, as the addition of dexamethasone to treat severe pulmonary disease has been found to decrease the mortality.[7] This is understandable as the secondary response with the cytokine storm and pulmonary infiltration is predominantly caused by the body's immune system (see below).

Complement and immune factors have been suggested to play an important role in the enhancement of inflammation in COVID-19.[8] It is well known that complement genes are involved in the susceptibility to develop AMD as noted below. Ramlall et al recently reported that in New York, patients with COVID-19 who already had macular degeneration showed a much higher mortality rate than those without, after correction for age and sex.[9] Among the 6,393 admitted patients who were COVID-19-positive, the mortality rate was 9.7%. Eighty-eight patients were identified as having macular degeneration, and among these, the mortality rate was 25%. This was higher than for type 2 diabetes mellitus (21%) or obesity (13.8%). The same article looked at complement-related polymorphisms in a British database of hospitalized SARS-CoV-2 positive patients; genes that occurred more often in these patients included four variants previously associated with AMD, two of which were related to CD55 (complement decay-accelerating factor). [9,10] A look at the epidemiology and genetics of AMD suggests some comparisons with the occurrence and development of COVID-19, the consequences of which we will describe below.

RISK FACTORS FOR AMD

AMD is a leading cause of irreversible blindness, visual impairment and reduced quality of life in older populations despite recent advances in treatments.[11,12] In AMD, the retinal photoreceptors are damaged or die most likely due to underlying diseases in the choroidal vasculature and retinal pigment epithelium (RPE), leading to loss of vision. Even with optimal treatment with intravitreal injections (bevacizumab, ranibizumab, aflibercept), many patients with advanced wet or neovascular disease have residual visual impairment, due to varying degrees of retinal and choroidal atrophy and scarring. The advanced dry form with macular atrophy has no known treatment, but many clinical trials are underway.

The prevalence of AMD is increasing as the proportion of elderly people rises worldwide, and the number of people with AMD is expected to be 196 million in 2020, increasing to 288 million in 2040.[13] Environmental and genetic risk factors can lead to inflammation and dysfunction in the macula, with subsequent development of advanced stages of AMD which include neovascularization and geographic atrophy that result in loss of vision. The established demographic risk factors are increasing age, white race, and a family history of the disease; these factors are not modifiable. Lower levels of education confer risk of AMD in many studies as well, which could reflect a wide range of health care disparities.[14]

Cigarette smoking is the most consistently identified modifiable risk factor.[12,15] The relationship between cigarette smoking and the incidence of AMD was evaluated in a prospective cohort study of a total of 31,843 nurses, followed for 12 years. Women who were current smokers of $\geq$25 cigarettes per day had a relative risk (RR) of AMD of 2.4 (95% confidence interval [CI] 1.4–4.0), compared to women who never smoked. Past smokers of this amount also had a 2-fold increased risk (RR = 2.0, 95% CI 1.2–3.4). The risk of developing AMD increased with an increasing number of pack-years.

In a clinic-based prospective cohort study, higher abdominal and overall obesity increased AMD incidence and progression from nonadvanced to advanced disease, whereas exercise reduced the risk.[16] Relative risk was 2.35 (95% CI, 1.27–4.34) for a body mass index (BMI) of at least 30, and 2.32 (95% CI, 1.32–4.07) for a BMI of 25 to 29, relative to the lowest category (<25) after controlling for other factors ($P = 0.007$ for trend). There was also about a 2-fold increased risk for progression to advanced AMD for abdominal obesity as measured by both waist circumference and waist-hip ratio. Diet and nutrition also play a role in AMD, as confirmed by many studies, and play a significant role in prevention (see below).

INFLAMMATORY FACTORS

Associations of AMD with diet, obesity, and smoking point toward similar predisposing factors with those seen in COVID-19 patients, where obesity, smoking, and chronic diseases lead to increased systemic inflammation. Analyses with regard to associations between AMD and other diseases have shown some associations with cardiovascular diseases, high blood pressure, and high cholesterol.[17,18] Such analyses may be hampered by the fact that patients with diabetic retinopathy are excluded from studies of AMD.

AMD is associated with systemic inflammation, as has been shown with regard to serum levels of a systemic inflammatory marker, high sensitivity C-reactive protein (CRP). A study of 930 individuals showed that serum levels of high-sensitivity CRP were significantly elevated in individuals with advanced AMD. After adjusting for variables including age, sex, BMI, and smoking, the odds of having AMD were 65% higher for the highest quartile of CRP compared with the lowest quartile.[19] Higher levels of other proinflammatory cytokines, like interleukin-6 (IL-6) and tumor necrosis factor (TNF)-alpha receptor 2, were evaluated for their effect on progression to advanced stages of AMD.[20] In this prospective study of 251 participants aged 60 years and older, the relative risk for progression to advanced stages of AMD was 2.10 (95% CI 1.06–41.18) for the highest quartile of CRP, and 1.81 (95% CI 0.97–3.36) for higher IL-6 serum levels.[20] Interestingly, both CRP and IL-6 levels were significantly related to a higher BMI and current smoking.[21] These elevated levels suggest that reducing inflammation may slow the progression of AMD. Some studies raise the possibility that medications with anti-inflammatory properties, such as statins and triamcinolone, may be beneficial.[22]

GENETIC RISK FACTORS IN AMD

In addition to modifiable factors, AMD also has a strong genetic component. AMD aggregates in families and is highly heritable. Great progress has been made in identifying the genes that underlie this genetic and familial risk.[12,23–26] Many genes associated with AMD are in the complement pathway, such as *complement factor H* (*CFH*), *complement factor B (CFB*), *complement component 3* (*C3*), *complement factor I* (*CFI*), and *complement component 9* (*C9*). Several common variants in these genes confer low to moderate levels of risk, and rare variants in *CFH, C3,* and *C9* confer higher risk. For example, the rare variant *CFH* R1210C has the highest impact with a 20-fold higher risk, and leads to earlier age of onset, familial occurrence, and a more severe phenotype.[27] The combination of genetic risk factors and smoking greatly increases the risk of developing AMD.[28,29] Ramlall et al observed an association between admission to a hospital because of COVID-19 and complement genes for *CFH*, *C4BPB*, *C4BPA,* and regulators of a complement suppressor, CD55.[9] Further support for involvement of the complement pathway is derived from the occurrence of thrombotic angiopathies and hypercoagulability in patients with COVID-19. Complement and coagulation systems work together biologically and complement can activate or interfere with coagulation.[30,31]

Plasma complement components and activation fragments are increased in AMD.[32] Since there is uncontrolled alternative complement pathway activation as a result of some of these variants, complement-modulating agents are currently in clinical trials for the treatment of AMD. COVID-19 patients who required continuous positive airway pressure or mechanical ventilation showed increased plasma levels of activated complement C5a.[33]

With regard to ethnicity, the white population accounts for most AMD cases, followed by Hispanic.[34] The worldwide prevalence estimates suggest that higher levels of pigmentation are related to a lower incidence of AMD. These ethnic differences could also be explained by differences in allele frequencies for some of the AMD susceptibility genes.[35] One study found no substantial difference between white and African American populations for the common variant in the gene *CFH* in the complement pathway.[36]

When looking at COVID-19, African-Americans in the United States are disproportionally affected. However, the outcomes (receiving mechanical ventilation or death as endpoint) among hospitalized patients in Georgia, USA, did not differ between patients with a different racial background.[37]

MACROPHAGES ARE RELATED TO AMD AND AGING

Inflammation is strongly interwoven into AMD and drusen pathogenesis. Drusen are an early sign of the development of AMD. Evaluation of tissue samples has shown that "cellular debris" from RPE cells becomes trapped in the RPE basal lamina and Bruch's membrane, potentially causing a chronic inflammatory response that could prompt drusen formation. Drusen contain proteins that are associated with chronic and acute inflammatory responses and age-related diseases, including amyloid P component and complement proteins. Histologic analysis of eyes with drusen showed not only the presence of complement deposits but also of macrophages.[38,39] Macrophages come from the bone marrow and circulate as monocytes in the blood stream, till they are recruited into tissues in response to local chemokine production. One factor may be hypoxia, which is known to lead to monocyte migration. Hypoxia stimulates the production of many factors, including hypoxia-inducible factors (HIFs). HIF1 stimulates the production of a wide range of proangiogenic factors, including vascular endothelial growth factor-A (VEGF-A), and of modifiers of the immune system, such as monocyte chemoattractant protein-1 (MCP-1) and TNF-alpha, each capable of attracting myeloid cells to hypoxic areas. Late AMD is characterized by blood vessel ingrowth and fibrosis.

There are two types of macrophages, M1 and M2. M1 macrophages are considered the classically activated macrophages, which can stimulate immune responses and have antibacterial and anti-angiogenic activity.[40] M1 macrophages are known for their phagocytic activity and promote local immunity by secreting a variety of cytokines, such as IL-2, interferon (IFN) gamma, and TNF-alpha. The so-called alternatively-activated or M2 macrophages play a role in blood vessel formation. They secrete cytokines such as IL-10 and transforming growth factor beta (TGF-beta). During aging, a relative decrease in M1 macrophages and increase in M2 macrophages occurs, changing the M1/M2 balance, which may affect diseases such as cancer of the eye (uveal melanoma) and AMD.[41-43]

That not only aging but also genetics determine the activity of macrophages was analyzed in post-mortem eyes.[44] Studies on macrophages illustrated the relation between complement polymorphisms in *CFH* Y402H and choroidal inflammation: postmortem eyes with the C allele (either CC or CT genotype), which is associated with an increased risk of AMD, contained higher levels of macrophages in the choroid, and increased levels of a growth factor that activates macrophages and microglia, granulocyte macrophage-colony stimulating factor (GM-CSF). Studies in murine models for AMD similarly showed a great influence of macrophages in the development of experimental laser-induced ocular disease.[45,46] An additional factor was smoking: animal studies showed that exposure of mice to nicotine or to cigarette smoke led to an increase in size and severity of experimental choroidal neovascularization, with more inflammation. This effect was enhanced in old mice.[47] It will be very interesting to see how smoking and possibly BMI interact with putative genetic factors in the development of COVID-19 disease.

One may ask the question whether anything can be done to modulate the effect of old macrophages, as this may decrease their effect on disease development. When aged mice were transfused with bone marrow from young mice of the same strain, the ocular repair system in a laser-induced macular degeneration model became more similar to that of young mice.[48] This shows the importance of changing macrophage function. Several drugs have been reported to modulate macrophage polarization. An anti-cancer drug for high-grade serous ovarian cancer, AZD5153 that inhibits bromodomain-containing protein 4 (BRD4), was found to reset tumor-infiltrating M2 macrophages to the M1 type.[49] It furthermore suppressed the production of IL-6, IL-10, and TGF-beta, but stimulated the production of IL-12 and IL-23, and helped to stimulate CD8 T cell activity, which may help in the fight against the virus.

MACROPHAGES AND LUNG DISEASE

As described above, inflammation (including the complement system) and macrophage activity have proven to be of great

importance for the development of AMD. We hypothesize that these mechanisms will be seen in COVID-19 as well, and could explain in part the varying degree of inflammation among carriers of the SARS-CoV-2 virus. Analysis of alveolar macrophages obtained by lavage during anesthesia demonstrated that macrophages from smokers showed a reduction in phagocytic and antimicrobial activity, indicating a loss of M1 capacity.[50] Macrophage polarization was studied in surgically obtained lung specimens: Kaku et al and Bassan et al noticed that smoking and the presence of chronic obstructive pulmonary disease both led to highly increased numbers of alveolar macrophages.[51,52] This may parallel the situation in early AMD where people at risk show macrophage-containing drusen. The presence of increased numbers of macrophages may stimulate a severe inflammatory response after an infection with SARS-CoV-2 among smokers and individuals with chronic obstructive pulmonary disease. This was recently similarly suggested by Merad, but without drawing a similarity to AMD.[53]

PREVENTIVE MEASURES

As the case description for severe COVID-19 corresponds to some extent with the risk factors for developing AMD and cardiovascular disease, we propose that the lifestyle changes indicated above for AMD may be important to prevent severe COVID-19. A healthy diet rich in foods containing antioxidants, particularly lutein and zeaxanthin, and supplements containing these types of nutrients, can decrease the risk of progression from early or intermediate AMD to the advanced atrophic or neovascular stages. Prevention of AMD is now a key public health strategy: avoiding smoking, along with getting adequate exercise to maintain a normal weight and eating a healthy diet rich in fruits, vegetables, and fish, as in the Mediterranean type diet, can prevent a significant amount of visual loss due to AMD.[12,54,55]

In 1994, in a study based on a food frequency questionnaire, individuals reporting the highest quintile of carotenoid intake had a 43% lower risk for AMD compared with those in the lowest quintile (odds ratio = 0.57, P for trend = 0.02). Among the carotenoids, lutein and zeaxanthin, which were primarily obtained from dark green, leafy vegetables, were most strongly associated with a reduced risk for advanced exudative AMD (P for trend = 0.001). The median intake in the highest quintile was 6 mg/day,[55] which is now a dose recommended for supplement use. Later, the Age-Related Eye Disease Study recommended antioxidant supplements[56] and supported the use of lutein and zeaxanthin carotenoid supplements for AMD.[57] A healthy dietary pattern, such as the Mediterranean diet, can reduce the rate of progression from non-advanced to advanced AMD. A high Mediterranean diet score was associated with a reduced risk of progression to advanced AMD after adjustment for demographic, behavioral, ocular, and genetic covariates.[54] Dietary fat intake is also important in AMD prevention, with increased risk for trans-fats and lower risk for higher intake of omega-3 fatty acids.[58] Exercise reduces the risk of getting AMD as well. In a prospective cohort study, more physical activity tended to be associated with reduced risk of progression to advanced AMD (25% reduction for 3 times per week vigorous activity vs none, $P = 0.05$).[16]

Higher vitamin D intake may be beneficial for AMD: in a study of risk factors for progression to advanced stages of AMD, there was a lower risk of progression in the highest versus lowest quintile of dietary vitamin D intake after adjustment for demographic, behavioral, ocular, and nutritional factors (hazard ratio 0.60, 95% CI 0.43–0.83; P trend = 0.0007).[59] In European population studies of COVID-19, a correlation was observed between low vitamin D levels and high CRP levels in elderly people.[60]

Because of the similarity in risk factors for severe COVID-19 and developing AMD, many of the lifestyle risk factors for AMD may also relate to COVID-19. This may also have relevance for elderly individuals, as can be illustrated for vitamin D. A cross-sectional analysis on 235 COVID-19 patients admitted to Sina Hospital, Tehran, Iran, observed that patients with sufficient vitamin D developed less severe COVID-19. A cut-off of 30 ng/mL was used for vitamin D levels. Lower vitamin D levels were associated with increased severity of COVID-19: of the 206 patients who were 40 years or older, 67 had high vitamin D levels, and 9.7% died, whereas of the 139 patients with low levels, 20% died ($P = 0.04$).[61] Although it sounds logical that nutrition may be relevant for prevention of COVID-19 and its clinical course, the current literature is not definitive and this area is worthy of increased investigation.[62]

Inflammation and macrophage function may not only be related to lifestyle and genetic factors, such as the complement pathway genes, but also to age-related changes. The question is whether one has to block all macrophage activity or module M2 macrophages toward an M1 phenotype. As mentioned, several cancer therapies are being investigated for their capacity to reset macrophages. However, as elderly individuals have mainly M2 macrophages, one may have to direct treatment against all macrophages. One could investigate whether individuals receiving treatment with macrophage-blocking clodronate homologs that are clinically allowed in humans, such as zodronate and bisphosphonate, are less likely to develop the severe symptoms of COVID-19.

CONSIDERATIONS FOR TREATMENT OF SEVERE COVID-19 DISEASE

With regard to clinical care, one needs to consider the two phases in viral diseases: the first is the infectious stage, where the presence of the angiotensin-converting enzyme-2 (ACE-2) receptor has been implicated in the susceptibility to infection with SARS-CoV-2.[63] Antiviral therapies are being used in this phase.[64] The major problem with inhibiting macrophages is that they help in battling the virus in the early stages of the infection. M1 macrophages in young people may be very useful in this phase, explaining why not only fewer young people develop clinical signs of infection in the first place, but also why few develop severe pulmonary disease. The finding that younger individuals with a genetic defect in toll-like receptor 7 (TLR7), a pattern recognition receptor, develop much more severe disease may be an indicator of the dual role of macrophages.[65] Peripheral blood mononuclear cells of these youngsters did not produce interferon after stimulation with imiquimod. The authors suggested that TLR7 deficiency led to impaired viral clearance with a high viral load, thereby increasing inflammation: the second phase of a COVID-19 infection is the overactive inflammatory response, which leads to the deadly systemic response. The secondary response leads to pulmonary inflammation with lack of oxygen, necessitating hospital admission and ventilation. The two phases are also well known in another viral disease, herpes simplex

disciformis of the cornea, where early during the infection, the virus is the main cause of corneal disease, but a secondary inflammatory response subsequently damages the cornea and causes blindness, once the specific immune response has kicked in. Depletion of macrophages before corneal infection with HSV-1 in mice led to a reduction of inflammation in the trigeminal ganglion, with, however, an increase of virus in the same ganglion.[66] In herpetic disease, one has to time the moment of intervention in the immune response with corticosteroids well. Interestingly, in a model of SARS-CoV-1 infection, macrophage depletion helped to reduce the virus-induced inflammation.[67] Aggressive therapy with blockers of the innate immune response such as corticosteroids is therefore important as soon as the pulmonary infiltration becomes the major problem, although it is occasionally given earlier.

Complement inhibitors may be useful in the early phase of inflammation (not infection). Useful drugs may be conestat alfa (Ruconest, Pharming), a recombinant human C1 esterase inhibitor, and eculizumab, a C5 inhibitor, originally developed for the treatment of atypical hemolytic uremic syndrome.[68,69] This drug is now being used in a trial for patients infected with SARS-CoV-2.[6] Other complement modulators are also being tested for COVID-19 patients. When the fibrotic stage of the COVID-19-associated pneumonia is developing, specific inhibitors of inflammation and fibrosis, such as methotrexate, may be considered. Although methotrexate has been reported to stimulate lung fibrosis, a new preparation, ADX-2191, is currently under investigation to inhibit fibrosis after ocular surgery following penetrating trauma.[70]

RESEARCH TOPICS FOR COVID-19

Systematic study of which behaviors and medical conditions enhance inflammation and endothelial damage in COVID-19 will be informative and may reveal the impact of smoking, higher BMI, unhealthy diets and lower levels of exercise as seen in AMD. As mentioned above, in AMD, prevention is a key public health strategy: avoiding smoking, along with getting adequate exercise to maintain a normal weight and eating a healthy diet. Vitamins may also be important for COVID-19: vitamin C, lutein/zeaxanthin, and fish consumption are associated with lower serum CRP levels.[19–21]

Genetic factors should be explored to determine which variants are associated with different levels of inflammation and the spectrum of severity of outcomes of COVID-19. It would be very interesting to determine whether there is a correlation between occurrence and severity of COVID-19 and AMD, and when patients with AMD get infected with SARS-CoV-2, do they have a more serious disease course. That complement pathway genes may play a role in epidemics has been suggested with regard to the ancient Plague.[71] Persons with complement system gene variants in the regulatory protein Factor H, that predispose to AMD, may have been protected due to reduced interaction of the bacterial factor H binding protein, rendering the pathogen more sensitive to complement-mediated damage. The hypothesis is that the *CFH* polymorphism may have provided a selective advantage for surviving an infection by the Plague bacillus and then resulted in an increased incidence of AMD in those who survived.

With regard to COVID-19, genetic susceptibilities in the complement, immune, or other pathways could confer varying degrees of risk or protection, and this remains to be sorted out. Furthermore, one has to differentiate between the susceptibility to getting the virus, the severity of the first stage of viral replication and distribution, and the secondary inflammatory response that has been the focus of the current paper. For all of these stages, researchers can study the interaction between genes and environment—such as smoking, as in AMD, where knowledge of genetic variants for AMD coupled with identification of the non-genetic risk factors has improved our ability to predict which patients will develop advanced forms of this disease associated with visual impairment. Similar to the development of a prediction model for macular degeneration,[14] one may develop a prediction model for developing severe COVID-19. When more is known, differences in genetic susceptibilities including complement pathway dysregulation may help to explain why severe COVID-19 strikes some individuals and families more than others, leading to an inflammatory phenotype, and such a model should also include aging, medical conditions, and individual lifestyle factors.

CONCLUSIONS

Given that three decades ago we only knew that AMD was associated with aging, much progress has been made. AMD is a complex interplay between individual characteristics, behaviors, medical conditions, and genetics. Challenges remain to develop better therapies. For COVID-19, searching for behavioral, medical, and genetic determinants of the onset and variable severity and subsequent outcomes of COVID-19, and the role of complement and macrophage activity, will identify higher risk individuals. This could lead to new insights into prevention and personalized treatment to reduce the growing medical and economic burden of this disease.

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