in disease models and human specimens. However, we are not quite there yet. A principal challenge for any automated image analysis is robustness. Biologic morphology variability is extensive, and performance suffers when algorithms encounter features not seen before, such as artifacts or uncharacterized diseased conditions. Experimentation can often lead to unexpected histology, and if improperly trained, even the most advanced recognition algorithms will fail. Therefore, extension of these techniques to other specific applications will require detailed validation as evidenced by the more limited success of the algorithm trained on rat glomeruli when applied to human specimens. Notably, Bukowy *et al.*[2] show how training by simpler "region-based" classification of images (quick and easy) rather than detailed manual segmentation (harder and more time consuming) can yield useful results. Also, they show a general approach by which well defined image pattern recognition problems in renal research can already be adequately addressed with machine learning tools.

CNN and other pattern recognition techniques will undoubtedly be further potentiated by the continuing adoption of whole-slide imaging and rapid advancements in other digital histology techniques. Routine digitization of microscopic data that can be readily correlated with electronically recorded interpretations or objective outcomes, when properly organized and collated, will help provide critically lacking training sets for more massive application of pattern recognition, even if it will take some time and effort for specific tasks to be individually trained and tested. In the interim, whether you are in the dystopic camp or the utopic camp on the future of artificial intelligence, consider that there are avenues to explore today that can make your counting and classifying of glomeruli more accurate, more informative, and much easier!

DISCLOSURES

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See related article, "Region-Based Convolutional Neural Nets for Localization of Glomeruli in Trichrome-Stained Whole Kidney Sections," on pages 2081–2088.

Novel Approaches to Control of the Alternative Complement Pathway for the Treatment of C3 Glomerulopathies

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The complement system is an important pillar of our innate and acquired immune system, and it is essential for host defense against foreign pathogens. Activation of complement has important functions that, in general, are beneficial to the host, but when adverse complement activation occurs by or near our own tissue and cells, the same functions can become detrimental to the host. In general, complement activation is under strict control by a number of fluid phase– and tissue-associated complement regulators. Complement can be activated by three known pathways, namely the classic pathway, the lectin pathway, and the alternative pathway. After initial complement activation by any of these pathways, further amplification is essential for efficient elimination of foreign pathogens, unwanted cell debris, and soluble immune complexes and for triggering of the common effector pathway with activation of C5 and generation of the membrane attack complex (MAC) C5b-9.

The degree of amplification of C3 activation in the fluid phase is controlled to an important degree by complement factor H (CFH). CFH is a 155-kD glycoprotein that consists of 20 short consensus repeats. Short consensus repeats 18–20 bind to cell surfaces and recognize C3b. CFH controls complement activation in both the fluid- and tissue-associated phases; because it can bind to cells (for instance, endothelial

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cells), it conveys extra protection to complement-mediated injury.

Uncontrolled C3 activation occurs in C3 glomerulopathy (C3G), and treatment options for C3G are limited. Some progress has been made with the treatment of C3G with eculuzimab, an mAb against C5 that prevents the generation of the phlogistic fragment C5a from C5 and the formation of the MAC; however, the success of treatment is often uncertain.

In this issue of the *Journal of the American Society of Nephrology*, Wang *et al.*[1] explored the potential efficacy of an Fc fusion protein of complement receptor of the Ig superfamily (CRIg-Fc) in the treatment of mice with an experimental form of C3G, namely mice with a common CFH and properdin double deficiency. These mice develop an early onset of C3G with increased C3 catabolism, increased proteinuria, and lethal crescentic GN. Treatment of the double-deficient mice with CRIg-Fc but not the control Fc fusion protein reduced proteinuria, hematuria, BUN, C3 deposition, and GN scores. Additionally, treatment with CRIg-Fc improved complement pathology and survival. Treatment of these mice was started at 4 weeks of age, at which time the mice have a mild form of C3G. The question remains whether CRIg-Fc will prove to be efficient in reversal of a fully active disease. The findings, however, are promising, and combined with the fact that it down modulates the degree of C3 amplification, it adds a potential new approach to the treatment of C3G in patients.

Other promising approaches are being explored. Like the approach of using CRIg-Fc as a down modulator of C3 amplification, two other inhibitors have been developed. Both are on the basis of the regulatory domains of CFH itself.

Yang *et al.*[2] engineered two CFH miniconstructs consisting of specific domains of CFH, with a higher retention of the drug in the kidneys of mice. These mini-CFH constructs were fully able to regulate complement amplification in mice, and they were shown to be very effective in prevention of glomerular C3 deposition in CFH-deficient mice. The advantage of using these CFH miniconstructs is that they block complement activation in the affected organ directly, whereas the CRIg-Fc mainly down modulates circulating complement activation.

Another very promising agent to block the alternative pathway convertase was reported recently by Michelfelder *et al.*[3] They synthesized a fusion protein MFHR1 that contains the regulatory domains of CFH and the C5 convertase/C5b-9 inhibitory fragment of FH-related protein 1. MFHR1 has cofactor and decay accelerating activity and inhibits C5 convertase activation and MAC assembly, which prevent C3b deposition. Administration of MFHR1 to CFH−/− mice resulted in inhibition of C3 activation *in vivo* and reduced abnormal C3 deposition in the kidneys. The advantage of MFHR1 is that it not only controls alternative pathway C3 activation but that it also affects the C5 convertase and generation of MAC.

The idea to down modulate complement activation at the C3 level was introduced quite a number of years ago by the research group of Lambris and colleagues.[4] They developed a drug called Compstatin that prevents C3 activation by binding to C3 itself. Continuous development of the Compstatin scaffold for increased target affinity, inhibitory efficacy, and advantageous pharmacokinetic properties has resulted in the analog CP40, which also looks very promising in preclinical models of C3G and other complement-mediated diseases.

In summary, several potentially very promising drugs that control the degree of the activity of the alternative pathway are now in the pipeline. Most of these drugs are still in the preclinical stage, and much more work is ahead to bring these drugs to implementation in the clinic.

DISCLOSURES

None.

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Now or Later? Understanding Timing of Dialysis Initiation beyond IDEAL

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"When will I need dialysis?" For older patients with advanced CKD, the decision to start dialysis is one that is often fraught

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