biologists, pathologists, nephrologists, genetic counselors, and genome scientists to interpret the significance of AS-causing mutations on an individual’s clinical course, the underlying pathology, and potential interventions will provide better patient management and understanding of this disease.

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DISCLOSURES

None.

REFERENCES


MicroRNA-155 a New Therapeutic Target in Crescentic GN

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Crescentic GN is characterized by severe and aggressive glomerular and interstitial inflammation with a poor prognosis but is potentially amenable to appropriate therapies. There have been several recent advances in our understanding and treatment of this disease. This form of GN occurs in several different systemic diseases, and it is now recognized that most are autoimmune in origin (antiglomerular basement membrane GN, SLE, ANCA-associated vasculitis [AAV], and IgA GN). The introduction of cyclophosphamide radically improved outcomes but brought considerable morbidity. In parallel with better understanding of the immunopathogenesis of crescentic GN, the introduction of potentially less toxic biologic therapies with B cell CD20-targeted antibodies shows considerable promise. Our understanding of gene expression and regulation through microRNAs (miRNAs) is another potential approach that may lead to new less toxic therapies.

This issue of JASN contains a report providing proof of concept that targeting an individual critical miRNA with a major regulatory role in autoimmune inflammation (miR-155) can significantly immunomodulate an animal model of crescentic GN, thereby opening the way for a new era of therapeutic intervention.

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miRNA-based treatments for this important renal disease. MicroRNAs, first described in 1993, are endogenous noncoding single-stranded small RNA molecules (approximately 22 nucleotides) that silence gene expression. They play key roles in physiology, growth, and biologic homeostasis, and they also regulate function of the innate and adaptive immune systems. MicroRNAs are expressed (and likely pathologically overexpressed) in affected diseased tissues, and there is good evidence of their functional pathologic role in cancer and autoimmunity. MicroRNAs act at the posttranscriptional level by binding to the 3′ untranslated regions of specific mRNAs, leading to their degradation and hence suppression of protein expression. More than 1000 miRNAs have been described that can target at least 60% of our genes. Furthermore, miRNAs may be involved in positive gene regulation (transcriptional and translational activation). MicroRNAs are encoded by genomic DNA and are commonly translated by polymerase II to form pri-miRNAs that are then cleaved in the nucleus by Drosha (ribonuclease III) and its cofactor DGC8R to pre-miRNAs. Exportation into the cytoplasm then occurs (via exportin 5) and further cleavage by Dicer results in the formation of miRNA duplexes. These are further processed and guided into the RNA-induced silencing complex, through which they target specific mRNA.

More than 100 different miRNAs are expressed in the immune system with individual cell lineages having unique expression patterns. miR-155 was one of the first miRNAs associated with inflammation because Toll-like receptor ligands upregulate miR-155 in macrophages during inflammation. In addition to innate immune cells, miR-155 is prominently expressed in most adaptive immune cells, including B cells, CD4+ T helper (Th) cell subsets, and T regulatory cells (Tregs). Research shows that inflammatory cytokines and specific antigens upregulate miR-155 in many different immune cells. miR-155 is encoded within the B cell integration complex cluster gene and stem cell overexpression can induce malignancy (myelodysplastic syndrome). Experimentally, miR-155−/− mice have significantly reduced functional B cell capacities with reduced numbers and responses of germinal centers. Furthermore, B cells show reduced class switching and somatic hypermutation and consequently produce reduced IgG1 responses, which are deficient in high-affinity antibodies. Cellular immunity is also affected and miR-155−/− mice have altered Th cell function. They show Th2 bias with enhanced IL-4 production. Although Th1 capacity is not affected, Th17 responses are considerably reduced with diminished IL-17 and IL-22 production. On a cell for cell basis, Tregs are not functionally impaired but aspects of their behavior, including migration, may be disturbed. Interestingly, Tregs in both the thymus and periphery are decreased in miR-155−/− mice, whereas CD4+ T cells treated with a miR-155 antagonist demonstrate increased Treg-mediated suppression.

In the context of autoimmunity, miR-155 has been extensively studied and reviewed where the collective data suggest that its pathologic overexpression generates autoimmunity. In a clinical setting, miR-155 is detectable in several important human diseases, including multiple sclerosis, rheumatoid arthritis, and SLE. Moreover, miR-155 is prominent in murine models of these diseases, in which deletion and targeted antagonist use suggest that miR-155 plays an important functional role in mediating disease pathogenesis. In both experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA), miR-155−/− mice were strongly resistant to the development of autoimmunity and demonstrated diminished Th17 and B cell responses. Successful outcomes of strategies attempting suppression of miR-155 in established disease have not yet been reported. It is worth noting that both of these models are heavily IL-17 dependent. The effects of miR-155 suppression, or antagonism, of Th1 directed autoimmunity are still awaited.

In this edition of JASN, Krebs et al. use a well characterized model of crescentic GN, induced by sheep globulin, to demonstrate that miR-155 drives renal injury through the recruitment of nephritogenic Th17 cells. They found that miR-155−/− mice had attenuated renal injury, diminished renal Th17 leukocyte recruitment, and reduced kidney expression of Th17-associated chemokines. Using an elegant adoptive transfer model, they demonstrated that miR-155 was an important requirement for Th17 cell stability in experimental nephritis. The therapeutic promise of this approach was highlighted when Krebs et al. demonstrated that preemptive treatment of wild-type mice with a miR-155 antagonist successfully decreased renal Th17 cell recruitment and by implication renal injury. These are exciting findings and suggest that targeting miR-155 in crescentic GN could represent a novel therapeutic approach.

Interestingly, the protection afforded to miR-155−/− mice in the model of crescentic GN was not as pronounced as that described previously in EAE and CIA. Although nephritic miR-155−/− mice showed decreased histologic injury, functional injury was only marginally decreased. Conversely, there was a pronounced improvement in clinical scores in EAE in miR-155−/− mice, whereas arthritis was completely abrogated in miR-155−/− deficient mice. One potential explanation for this discrepancy is the heightened Th1 responses observed in nephritic miR-155−/− mice. Experimental evidence strongly supports a role for both Th1-related cytokines and Th1 cells in driving nephritogenic immunity and crescentic GN. Using this same model of crescentic GN, the authors previously demonstrated an important role for Th1 cells in driving crescentic GN later in disease. In this article, Krebs et al. assessed renal injury in nephritic wild-type and miR-155−/− mice on day 10, when both Th17 and Th1 immune responses were likely to be active. It would be interesting to see whether the protection afforded by miR-155 deletion would be observed later in the disease model, which is more clinically relevant.

To provide clinical perspective, the authors examined histologic tissue from patients with AAV and found that miR-155 expression was elevated and correlated with renal injury. It is difficult to predict whether miR-155 inhibition would be useful in AAV. Although the model of crescentic GN used in this article...
is not a model of AAV, both Th17 and Th1 cells have been implicated in human and experimental AAV. However, significant experimental work supports a role for B cells in driving renal injury in AAV. The use of B cell-depleting agents has significantly improved the outcomes of patients with AAV, implicating B cells in the pathogenesis of AAV. The authors found that miR-155 was required for the complete development of humoral immunity, although humoral immunity has a limited role in this model. The therapeutic potential of miR-155 inhibition could extend to renal diseases in which B cells promote renal injury.

In summary, silencing miRNA has exciting clinical potential and this study has extended the potential benefits to include treatment of crescentic GN. Although the authors used antagonists, several other strategies have been trialed experimentally, including the use of decoy technologies with the transgenic introduction of tandem miRNA binding site repeats. Targeting miRNAs could potentially form part of the therapeutic armamentarium available to nephrologists.

DISCLOSURES

None.

REFERENCES


Cloudy Peritoneal Dialysate: In Search of a Clear Cause?

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Peritoneal dialysis–associated peritonitis is usually caused by infection. It is characterized by abdominal pain and cloudy peritoneal effluent caused by an increased peritoneal leukocyte count (>100 million cells/L, more than 50% of which are neutrophils), as well as positive effluent microbiological cultures. Empirical treatment with antibiotics is promptly started with antibiotics that cover both gram-positive and gram-negative infections before the results of the cultures become available.

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