ulation. CHGA induction of endothelin from human umbilical vein endothelial cells, which are derived from a large vessel, is consistent with release from storage granules; however, fenestrated glomerular endothelial cells are not known for their Weibel-Palade bodies, and the study does not specifically establish Weibel-Palade bodies in these cells or report whether cultured glomerular endothelial cells produce von Willebrand factor or angiopoietin upon exposure to CHGA. Because the constitutive pathway is regulated principally at the level of gene transcription and previous studies showed catecholamines increase endothelin gene expression, additional studies will have to be performed to clarify whether CHGA stimulation of endothelin in each of these cell types occurs through distinct mechanisms.

In summary, the study by Chen et al. illustrates both the promise of a novel approach to an established vasoactive pathway and the remaining gaps in our understanding of the regulation and prediction of GFR.

DISCLOSURES

None.

REFERENCES


Do Genes Allow Inflammation to Kill or Not to Kill?

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Cardiovascular disease is principally responsible for the high mortality in patients with ESRD. Extending to dialysis patients therapies proven successful in the general population has thus far been of limited success, indicating the critical need for alternative interventions in this patient population. The metabolic complexity of renal failure encourages a variety of processes that increase cardiovascular complications and mortality. One such mechanism is enhanced chronic inflammation brought on, in part, by low GFR and, of course, various dialysis-specific proinflammatory signals.

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Inflammation initiates and propagates atherosclerosis through chemokines that mobilize inflammatory cell influx and proliferation during atherosclerotic plaque formation. Chemoattractant cytokines—such as CXC, CX3C, and CXC3C—are small (8 to 14 kD) proteins that regulate leukocyte trafficking, cell adhesion, phagocytosis, cytokine secretion, cell activation, proliferation, apoptosis, and angiogenesis during inflammation. Chemokines are classified into four groups on the basis of the number and position of conserved cysteine residues in their amino acid structure (CC, XC, CXC, and CX3C), and their receptors are accordingly designated as CCR, XCR, CXCR, or CX3CR followed by a number corresponding to the chronological order in which they were identified. One chemokine receptor attracting substantial interest is CCR5, because it also serves as a co-receptor to HIV1 and 2. A nonfunctional allele of CCR5 resulting from a 32-bp deletion in exon 4 (CCR5Δ32), in certain white populations, renders them more resistant to infection by these viruses. Further research into CCR5, which is localized on macrophages, T cells, coronary endothelial cells, and aortic smooth muscle cells and in atherosclerotic plaques, also indicates it plays an important role in the inflammation surrounding atherosclerosis. The presence of a well-described nonfunctional allele of CCR5, CCR5Δ32, has allowed the identification of various confounders affecting the inflammatory process. Such so-called Mendelian randomization studies in the general population indicate that people with the CCR5Δ32 allele have fewer cardiovascular events.

In this issue of the JASN, Muntinghe et al. performed an observational study in Dutch and Swedish dialysis patients, describing a statistical interaction between CCR5 genotype and all-cause and cardiovascular mortality associated with elevated levels of C-reactive protein (CRP). Dialysis patients with CCR5Δ32 seem unaffected by the higher cardiovascular mortality seen in association with elevated CRP and can be interpreted as a potential protective effect of the nonfunctioning gene. Noncardiovascular mortality increases in dialysis patients with higher CRP levels, irrespective of their CCR5 polymorphism, consistent with the hypothesis that CCR5 is involved in the process of atherosclerosis but also the effects of inflammation that reach beyond the process of atherosclerosis and affect both cardiovascular and noncardiovascular mortality.

This observational study, however, has some limitations. First, the most critical subgroup in the study, those with concurrent high CRP and the deletion allele, include only 25 patients with small numbers of outcomes, allowing almost no reliable statistical inference by multivariate regression modeling for this group. Second, the stated conclusions for this subgroup are based on NS P values and without adequate statistical power. Lower cardiovascular mortality in these patients would be better substantiated if they had significantly lower hazard ratios for death compared with those with the wild genotype and concurrent high CRP levels. Third, CRP measurements were done at baseline, ignoring CRP fluctuations over time. Time-averaged or time-dependent models with repeated CRP measures would be more appropriate. Fourth, other more reliable inflammatory markers such as IL-6 were not studied. Finally, examining similar interactions between hypoalbuminemia, the strongest predictor of dialysis patient mortality and a combined surrogate of inflammation and wasting, and CCR5 polymorphism was not examined.

What are the implications of the inferences by Muntinghe et al.? Establishing a parallel between patients with ESRD and the general population is important, because we cannot assume disease processes will follow identical patterns in these two different groups. Although it is plausible that CCR5 activation may be causally involved in cardiovascular morbidity and mortality in ESRD, it is unclear which phases of atherogenesis are affected by CCR5 activation, given the complex nature of this process and the multiplicity of sites expressing CCR5. On the basis of data from animal studies, it is likely that CCR5 exerts its effects in late stages of atherosclerosis, which would offer a therapeutic strategy based on this mechanism of action more applicable to dialysis patients, most of whom have experienced long-standing cardiovascular disease and in whom primary prevention is probably not feasible. This is even more important considering that Mendelian randomization studies such as the one by Muntinghe et al. examine the consequences of lifetime exposure— or lack thereof—related to a genetic polymorphism, and their results do not necessarily mean that pharmacologic interventions aimed at exposure later in life can have a similar effect. It is also necessary to clarify the importance of CCR5 relative to other chemokine receptors, because it is possible that the process of atherogenesis represents a more complex mechanism with more than one participating chemokine receptor. The concomitant blocking of various chemokine receptors, including CCR5, in an animal model results in almost complete abrogation of atherosclerotic plaque formation, raising the possibility that the application of several agents to block various chemokine receptors could have an additive benefit.

The growing body of evidence on the role of chemokines and their receptors in atherogenesis may lead to the development of novel therapeutic agents to prevent or improve cardiovascular complications. The study by Muntinghe et al., despite its aforementioned limitations, offers hope that such agents may be useful in patients with ESRD. The most difficult part on the road to finding such new therapies still lies ahead because we desperately need prospective proof of efficacy and safety from clinical treatment trials.

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See related article, “CCR5 Deletion Protects Against Inflammation-Associated Mortality in Dialysis Patients,” on pages 1641–1649.