4. Keevil BG, Kilpatrick ES, Nichols SP *et al.* Biological variation of cystatin C: implications for the assessment of glomerular filtration rate. *Clin Chem* 1998; **44**: 1535–1539.

Michael Zappitelli[1] and Chirag R. Parikh[2,3]
[1]*Division of Nephrology, Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada;* [2]*Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA and* [3]*Clinical Epidemiology Research Center, Veterans Affairs Medical Center, West Haven, Connecticut, USA*
Correspondence: *Chirag R. Parikh, Section of Nephrology, Yale University and Veterans Affairs Medical Center, 950 Campbell Avenue, Mail Code 151B, Building 35 A, Room 219, West Haven, Connecticut 06516, USA. E-mail: chirag.parikh@yale.edu*

Kidney International (2012) **81,** 598–599; doi:10.1038/ki.2011.441

CKD-associated atherosclerosis and monocyte heterogeneity

To the Editor: We noticed with great interest the mini review 'Novel inflammatory mechanisms of accelerated atherosclerosis in kidney disease' by Swaminathan and Shah.[1]

Although we commend the authors for their efforts to highlight the substantial impact of monocyte heterogeneity in chronic kidney disease-associated atherosclerosis, we are surprised that the authors exclusively relied on data obtained from murine experiments, ignoring the limits of homology between murine and human monocyte heterogeneity.

Notably, in mice, $Gr1^+/Ly6C^{high}$ monocytes (the putative homologs of human $CD14^{++}CD16^-$ monocytes) are proinflammatory, and they are more prone to enter the atherosclerotic plaque than $Gr1^-/Ly6C^{low}$ monocytes.[1] In contrast, in humans, CD16-positive monocytes ($CD14^{++}CD16^+$ and $CD14^+CD16^{++}$ cells, which are counterparts of murine $Gr1^-/Ly6C^{low}$ monocytes) are considered proinflammatory cells by most groups (as reviewed in Ziegler-Heitbrock[2]). Moreover, ample circumstantial evidence (as discussed in Rogacev *et al.*[3]) and clinical data demonstrate that $CD14^{++}CD16^+$ monocytes[3,4]—but not $CD14^{++}CD16^-$ monocytes—are the relevant monocytes in human atherosclerosis. The importance of the $CD14^{++}CD16^+$ monocyte subsets in nephrology is underscored by the profoundly elevated counts of these cells in dialysis patients[4] and their activation during dialysis (referenced in Rogacev *et al.*[3]).

Taken together, we agree with the authors that knowledge of monocyte heterogeneity is of major relevance to both clinicians and researchers in nephrology. We kindly disagree with the uncritical transfer of murine data to human (patho)physiology.

1. Swaminathan S, Shah SV. Novel inflammatory mechanisms of accelerated atherosclerosis in kidney disease. *Kidney Int* 2011; **80**: 453–463.
2. Ziegler-Heitbrock L. The CD14+ CD16+ blood monocytes: their role in infection and inflammation. *J Leukoc Biol* 2007; **81**: 584–592.
3. Rogacev KS, Seiler S, Zawada AM *et al.* CD14++CD16+ monocytes and cardiovascular outcome in patients with chronic kidney disease. *Eur Heart J* 2011; **32**: 84–92.
4. Heine GH, Ulrich C, Seibert E *et al.* CD14(++)CD16+ monocytes but not total monocyte numbers predict cardiovascular events in dialysis patients. *Kidney Int* 2008; **73**: 622–629.

Kyrill S. Rogacev[1], Adam M. Zawada[1] and Gunnar H. Heine[1]
[1]*Department of Internal Medicine IV–Nephrology and Hypertension, Saarland University Hospital, Homburg (Saar), Germany*
Correspondence: *Gunnar H. Heine, Department of Internal Medicine IV–Nephrology and Hypertension, Saarland University Hospital, D-66421 Homburg (Saar), Germany. E-mail: Gunnar.heine@uks.eu*

Kidney International (2012) **81,** 599; doi:10.1038/ki.2011.433

The Authors Reply: We thank Rogacev *et al.*[1] for their interest in our mini review 'Novel Inflammatory Mechanisms of Accelerated Atherosclerosis in Kidney Disease.'[2] While we appreciate and acknowledge the important points raised by the authors regarding homology of monocyte heterogeneity between mice and humans, we suggest several additional aspects that are worth considering.

Although we agree that $Gr1^+/Ly6C^{hi}$ are pro-inflammatory monocytes and are putative homologs of human $CD14^+CD16^-$ monocytes, in many settings, depending on local and systemic cues, they can also differentiate into a variety of macrophage and dendritic cell (DC) subtypes that could inhibit immune response.[3]

Pertaining to atherosclerosis, although $Ly6C^{hi}$ monocytes more efficiently accumulate in atherosclerotic plaques, $Ly6C^{lo}$ anti-inflammatory monocytes were particularly prone to developing into plaque cells that express the DC marker CD11c.[4] Similarly, in human atheroma, macrophages express c-fms (macrophage colony-stimulating factor receptor) but not inflammatory cytokines such as interleukin-6,[5]and $CD14^+CD16^-$ rather than $CD16^+$ monocytes correlate with worse myocardial salvage after myocardial infarction.[6]

More recently, gene expression profiling has identified close similarities between murine and human monocyte subsets in more than 100 genes, suggesting similarity between $Ly6C^{hi}$ monocytes and human $CD14^+CD16^-$ monocytes, and between $Ly6C^{lo}$ anti-inflammatory mouse monocytes and $CD16^+$ human monocytes.[7] This has led the authors to refer to monocytes as $CD14^+CD16^-$ and $CD16^+$ subsets in both species. However, it is important to point out some notable differences that the authors observed between the homologous human and mouse monocyte subsets, especially in PPAR-γ and phagocytic receptor expression.

Thus, origin, differentiation, and plasticity of different monocyte subsets in mice, and the corresponding cell populations in humans and their independent role in health and disease, remain to be fully elucidated.

1. Rogacev KS, Zawada AM, Heine GH. CKD-associated atherosclerosis and moncyte heterogeneity. *Kidney Int* 2012; **81**: 599.
2. Swaminathan S, Shah SV. Novel inflammatory mechanisms of accelerated atherosclerosis in kidney disease. *Kidney Int* 2011; **80**: 453–463.

3. Geissmann F, Manz MG, Jung S *et al.* Development of monocytes, macrophages, and dendritic cells. *Science* 2010; **327**: 656–661.
4. Tacke F, Alvarez D, Kaplan TJ *et al.* Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J Clin Invest* 2007; **117**: 185–194.
5. Salomon RN, Underwood R, Doyle MV *et al.* Increased apolipoprotein E and c-fms gene expression without elevated interleukin 1 or 6 mRNA levels indicates selective activation of macrophage functions in advanced human atheroma. *Proc Natl Acad Sci USA* 1992; **89**: 2814–2818.
6. Tsujioka H, Imanishi T, Ikejima H *et al.* Impact of heterogeneity of human peripheral blood monocyte subsets on myocardial salvage in patients with primary acute myocardial infarction. *J Am Coll Cardiol* 2009; **54**: 130–138.
7. Ingersoll MA, Spanbroek R, Lottaz C *et al.* Comparison of gene expression profiles between human and mouse monocyte subsets. *Blood* 2010; **115**: e10–e19.

Sundararaman Swaminathan[1,2] and Sudhir V. Shah[1,2]

[1]Nephrology Department, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA and [2]Renal Section, Medicine Service, Central Arkansas Veterans Healthcare System, Little Rock, Arkansas, USA

Correspondence: *Sundararaman Swaminathan, Nephrology Department, University of Arkansas for Medical Sciences, 4301 W Markham Street #501, Little Rock, Arkansas 72205, USA. E-mail: sswaminathan@uams.edu*

Kidney International (2012) **81,** 599–600; doi:10.1038/ki.2011.436