Thermoneutrality Prevents Monocytosis and Reduces Atherosclerosis

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People with metabolic syndrome and obesity are at an increased risk of mortality from cardiovascular disease. Over the past decade, there has been intensive research into new ways to stimulate weight loss to lower this risk. One of the key tissues is the metabolically active brown adipose tissue (BAT). Given that this is a thermogenic tissue, it can be stimulated by cold and is suggested by some as a new frontier in weight loss and improvements in other aspects of human health. But what does this mean for the health of our arteries? In the current issue of Circulation Research, Williams et al,1 reveal that ambient cool temperature may not correlate to benefit in our blood vessels. By comparing atherosclerotic lesion development over a series of temperatures and in 2 athero-sclerotic prone models, they reveal stark differences in plaque size, such that larger lesions are found in animals under cold conditions. Their studies reveal a novel temperature-sensitive modulation of monocyte release from the bone marrow that ultimately impacts atherogenesis. Importantly, Williams et al1 have also uncoupled the metabolic protective role of the heat-generating UCP1 (uncoupling protein 1) from atherosclerosis.

Cooler temperatures have long been associated with an increased mortality because of cardiovascular disease; however, the causality has been indirect, rationalized by changes in traditional risk factors (eg, lipids and blood pressure).2 In line with this, Dong et al3 originally found that cold housing (4°C) compared with thermoneutrality (the temperature at which energy expenditure is not needed to maintain body temperature) stimulated BAT and the browning of white adipose tissue. Cold temperature through UCP1 caused lipolysis and resulted in elevated levels of atherogenic lipoproteins. However, the role of ambient temperature and cholesterol seems controversial, with the current study reporting no changes.1 To complicate matters, 2 other studies revealed an increase in atherosclerosis under thermoneutral settings (ie, 30°C) and, consistent with Williams et al, found evidence of increased lipolysis through elevated levels of nonesterified fatty acids.1,4,5 Nonetheless, the alterations in plasma lipids are unlikely to explain the changes in atherogenesis, suggesting that other mechanisms are more important.

Immune cells are major players in cardiovascular disease, particularly members of the mononuclear phagocyte system. The mononuclear phagocyte system comprises a heterogeneous population of cells,6 and atherosclerosis is a disease dominated by recruited blood monocytes.7 Thus, the abundance of circulating blood monocytes is a predictor of the severity of disease and has been shown through numerous studies to directly contribute to plaque progression and impaired regression.7,8 Williams et al discovered that ambient temperature has a direct effect on blood monocyte counts. They show that mice housed at 30°C have reduced monocyte counts. They also showed the direct translational relevance by examining leukocyte counts from >15,500 samples from Saint Louis, Missouri, over a year where temperatures oscillated between $4^\circ$C ($40^\circ$F) to $30^\circ$C ($85^\circ$F). While this cannot prove causation, it does confirm that temperature and monocyte counts are inversely correlated. In mice, using positron emission tomographic/computed tomographic imaging and intravital microscopy, they elegantly demonstrated increased monocyte retention in the bone marrow as temperature increased from 22°C to 30°C. Monocyte egress relies on the C–C chemokine receptor 2, while retention is regulated by C-X-chemokine receptor 4 (CXCR4).3,10 Using a probe that detects CXCR4, they found an accumulation of CXCR4+ monocytes in the mice housed at 30°C, which suggests a retention of an immature Ly6-C+ monocyte or alternatively a block in maturation.6 CXCR4 is famously known for its role in hematopoietic stem cell retention, but interestingly these cells were not altered by temperature, confirming a mechanism pertinent to monocytes (see Figure). Precisely, how temperature selectively regulates CXCR4+ monocytes and not other CXCR4-expressing cells in the bone marrow will be fascinating to unravel in more detail, particularly the flip-side by surveying for changes in the bone marrow microenvironment and the possible link with the sympathetic nervous system. Collectively, the changes in bone marrow egress results in fewer circulating Ly6-C+ monocytes, perturbed recruitment to atherosclerotic plaques, and ultimately reduced atherosclerosis.

Next, the authors dissected the role of the BAT in mediating enhanced atherogenesis and how this could modulate monocyte egress from the bone marrow. Through the generation of Ldlr−/−Ucp1+/− mice and comparing Ldlr−/− mice at 22°C (UCP1 high) and 30°C (UCP1 neg), they confirmed that loss of UCP1 was atheroprotective.5 Similar to Tian et al,1 they found an improvement in glucose metabolism in mice housed at 30°C. However, consistent with UCP1 playing a role in glucose metabolism, deletion of this gene rendered the mice glucose intolerant, but again, this was overcome with thermoneutral housing. This is an important

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(Circ Res. 2017;121:596-598.
DOI: 10.1161/CIRCRESAHA.117.311721.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.117.311721
finding, which uncouples atherogenesis from glucose metabolism. However, this should not be confused with accelerated atherogenesis in diabetes mellitus because the mice reported here were only glucose intolerant. Despite having impaired glucose metabolism, atherosclerosis was reduced in the Ldlr−/−Ucp1−/− mice, and this was likely driven by the significant reduction in the atherogenic lipoproteins, VLDL (very low-density lipoprotein) and LDL (low-density lipoprotein). The mechanism for lower lipoprotein levels in Ucp1-deficient mice remains to be determined, particularly given the differences between the data in this study and that of Dong et al1 on lipolysis and the recent discovery of the cold induced BAT–liver–intestine axis.11 In any case, thermoneutral housing rescues glucose metabolism and reduced atherogenesis independent of UCP1. Thus, in the context of atherosclerosis, stimulating UCP1 seems to be detrimental.

The effect of housing temperature on monocyte egress from the bone marrow is also not simply a product of UCP1 activation. Intriguingly, while the authors conclude that Ucp1 deficiency did not alter blood monocyte numbers, the data does show a significant increase in Ly6-C0 monocytes at ambient temperature. It may be appropriate to examine marginated Ly6-C0 patrolling monocytes17 in the Ucp1−/− mouse with or without thermoneutrality. This would enable us to understand if temperature alters the function of these cells, which cannot be investigated from blood draws as this monocyte subset is attached to the endothelium. Further, given the heterogeneity in human monocyte subsets,12 it would have been interesting to determine whether a particular monocyte subset was altered in donors from the Saint Louis cohort. This may be important because studies report that CD16-expressing monocytes are expanded in patients at risk of cardiovascular disease.7,8 Moreover, monocyte subsets clearly represent independent effector functions in terms of response to microbial, viral, or lipid cues.7,13 It would be relevant to begin looking at effects of thermoneutrality on these responses.

Finally, the authors investigated whether retention of monocytes in the bone marrow was linked to the known pathway of sympathetic activation through β3 adrenergic signaling and UCP1 expression in BAT.14 Based on their experiments at 22°C (ie, where UCP1 is stimulated), the hypothesis is that UCP1 stimulation would induce atherosclerosis. To test this, the β3 adrenergic receptor agonist (CL-316,243) was administrated over 4 weeks at 30°C. This showed little effect on plaque area, suggesting that activation of UCP1 expression in BAT does not reverse the atheroprotective effects of thermoneutrality. However, they still find that mice treated with CL-316,243 lost weight. Thus, an important take-home message from this study is that this may be a safer way to stimulate the BAT to burn energy without the vascular complications induced via UCP1 in the cold. Therefore, the question arises: should those investing in ‘cold’ procedures to stimulate BAT for weight loss proceed with caution, and should this extend to current trends, including cryotherapy in at-risk individuals?

In summary, Williams et al1 show using multiple approaches, including cutting-edge in vivo imaging, that thermoneutrality can mediate monocyte bone marrow retention associated with decreased atherosclerosis. The caveat for these studies, like many, is the difference between mouse and human biology. Some suggest thermoneutrality may matter less for humans than for mice,15 but Williams et al1 do show that decreased monocyte levels are associated with living in warmer average daily temperatures. But, before we all rush to chase the endless summer, or turn off our air-conditioning, much more human experimental and interventional data are required. It may be interesting to start exploring the thermoneutral effects during infection or other chronic inflammatory diseases associated with monocytosis.
Sources of Funding
A.J. Murphy is supported by the NHMRC (CDF; APP1085752) and a future leader fellowship from the NHF (100440). K.J. Woollard lab is funded from Kidney Research UK (RP01920160303), BHF (FS/14/50/30856), and MRC (MR/M003159/1).

Disclosures
None.

References

Key Words: Editorials ■ atherosclerosis ■ brown adipose tissue ■ monocytes ■ thermoneutrality ■ uncoupling protein 1
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Circ Res. 2017;121:596-598
doi: 10.1161/CIRCRESAHA.117.311721

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/121/6/596

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