Response to Letter by Loboda et al Regarding Article, “Bach1 Represses Wnt/β-Catenin Signaling and Angiogenesis”

We are grateful for the opportunity to respond to the comment\(^ 1\) on our article, “Bach1 Represses Wnt/β-catenin Signaling and Angiogenesis.”\(^ 2\) Loboda et al\(^ 3\) are correct that neither interleukin-8 (IL-8) nor an orthologue for IL-8 is present in the murine genome; however, as noted by the authors of the comment, mice express 3 chemokines that are considered functional homologues of IL-8. One of those functional homologues, keratinocyte-derived chemokine (KC/CXCL1),\(^ 4–5\) is highly expressed in the endothelial cells of mice\(^ 6\) and was the target of our mRNA analyses in the mouse hind-limb ischemia model and in mouse lung endothelial cells. Thus, the y axes and legends for Figures 1E and 2D of our article should indicate that we measured mRNA levels of KC, the functional homologue of IL-8, rather than IL-8 itself, and the forward (5′-AGCCACCGCGTCTCTTCCT-3′) and reverse (5′-TCGGTTTGGGTGCAGTGGGG-3′) primers used for these measurements should be included in the list of primers provided in Online Table I. We sincerely apologize for this omission to provide this detailed information in our article, and we thank the authors of the comment for calling attention to this omission.

Despite the absence of IL-8 in the murine genome, mice express a receptor that is homologous to the IL-8–targeted human receptor CXCR2.\(^ 6\) Both murine and human CXCR2 (mCXCR2 and hCXCR2, respectively) are endogenously expressed in endothelial cells, and interactions between KC and mCXCR2\(^ 7–11\) or between IL-8 and hCXCR2\(^ 12, 13\) promote angiogenesis. Furthermore, both IL-8 and KC can interact with mCXCR2 to mediate neutrophil chemotaxis,\(^ 14\) and antibodies against human IL-8 inhibit lung inflammation in rodents.\(^ 15\) Thus, IL-8 and KC exhibit numerous key similarities in physiological function.

Loboda et al\(^ 3\) also noted that vascular endothelial growth factor expression was lower in the ischemic limbs than in the nonischemic limbs of Bach1\(^ -/-\) mice and their wild-type littermates on day 7 after injury (Figure 1D). We acknowledge that this observation may seem counterintuitive, but it is consistent with our observations in saline-treated C57BL/6J mice (also shown in Figure 1D), so we do not think it diminishes the importance of our observation that the expression of vascular endothelial growth factor is inversely correlated with Bach1 levels in the ischemic limbs of mice. Nevertheless, we agree that additional experiments, such as those proposed by the authors of the comment (ie, administration of vascular endothelial growth factor– or KC-neutralizing antibodies to the ischemic limbs of Bach1\(^ +/+\) and WT) mice) are needed to conclusively show that the enhanced angiogenesis associated with the loss or silencing of Bach1 expression is mediated through increases in vascular endothelial growth factor and KC expression.

In summary, we acknowledge that we evaluated the expression of KC (a murine functional homologue of IL-8), rather than IL-8, in murine tissues and cells, and we apologize for this inaccuracy. Our misstatement applies to a subset of the data displayed in Figures 1E and 2D of our article, but does not alter our conclusion that Bach1 suppresses angiogenesis after ischemic injury and impairs Wnt/β-catenin signaling.

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Disclosures

None.

References


The authors have posted a Correction notice to their original article clarifying the issues discussed here. The Correction notice along with a link to the corrected online version of the article is available at http://circres.ahajournals.org/content/117/9/e79.full (Circ Res. 2015;117:e77-e78. DOI: 10.1161/CIRCRESAHA.115.307486.)

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