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Neutral Cholesterol Ester Hydrolases in Macrophages: Still a Matter of Debate

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To the Editor:

In a recent study, Igarashi et al[1] reported knockdown experiments using adenoviral short hairpin RNA constructs targeting human neutral cholesterol ester hydrolase-1 (NCEH1, originally named KIAA1363) and the potential cholesterol ester hydrolase CES1. The authors concluded that "NCEH1 is the only enzyme that requires attention when dealing with neutral cholesterol ester hydrolase activity in human macrophages," reinforcing similar observations by the same group on murine macrophages.[2] This created a controversy,[3] because our group demonstrated identical neutral cholesterol ester hydrolase activity in wild-type and Nceh1 knockout mice,[4] which argues against a critical role of NCEH1 as cholesterol ester hydrolase. The validity of our observations was questioned[5] by claiming that we failed to present "data demonstrating the clean knockout of KIAA1363 of this model by Western and/or Northern blot analyses." This is at variance with Figure 4F of our report,[4] which demonstrated the lack of NCEH1 in macrophages of Nceh1 knockout mice by Western blotting with a specific anti-NCEH1 antibody. Moreover, Figure 1 of the supplemental material of our study confirmed homologous recombination by Southern blot analysis and PCR. Thus, we provided comprehensive information on the generation of the Nceh1 knockout mice and compelling evidence that we used macrophages from a "complete and clean" Nceh1 knockout mouse model for our cholesterol ester hydrolase activity assays.

The major conclusion drawn by Igarashi et al[1] that "NCEH1 is quantitatively the most important neutral cholesterol ester hydrolase in human macrophages and atherosclerosis" is insufficiently supported by the data presented. Despite an almost complete knockdown of NCEH1 in human monocyte-derived macrophages, neutral cholesterol ester hydrolase activity was reduced by only 50%, which leads us to question the conclusion that "NCEH1 is the only enzyme that requires attention when dealing with neutral cholesterol ester hydrolase activity in human macrophages." In contrast to NCEH1, CES1 knockdown lacked any reduction in cholesterol ester hydrolase activity. Knockdown of CES1, however, was less efficient, and substantial amounts of CES1 protein were present in CES1-silenced macrophages.

The claim that NCEH1 (KIAA1363) is the neutral cholesterol ester hydrolase in human[1] and murine[2] macrophages, therefore, continues to be at variance with observations made by us[4] and others.[3]

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Disclosures
None.

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