
In our Circulation article,1 we stated that few studies have addressed the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the small intestine and in the metabolism of triglyceride-rich lipoproteins. In their letter, Drs Le May and Cariou point out the omission of 2 references. The first, published by Le May et al2 in 2009, reports that PCSK9−/− mice display reduced postprandial hypertriglyceridemia and apolipoprotein B levels after olive oil gavage and that adeno viral PCSK9 overexpression or targeted shRNA silencing of PCSK9 increased and reduced apolipoprotein B secretion, respectively. In that article, Le May et al acknowledge an earlier observation, published by 1 of us (S.R.) in 2005, that apolipoprotein B48 levels are reduced in PCSK9−/− mice.3 This notwithstanding, we consider the article by Le May et al important and central to our story, and its omission was unintentional. The work was mentioned in an earlier draft, but the section was left out during manuscript rewriting to adjust the size to journal specifications. We apologize for the oversight and have prepared the correction notice that appears in this issue of the journal.

The second publication, by Levy et al4 in 2013, reports a role for PCSK9 in cholesterol absorption by showing that the addition of exogenous PCSK9 to CaCo-2 cell media affects NPC1L1 expression, a finding we also report in our Circulation article.1 However, we focused on mechanisms that directly account for increased intestinal apolipoprotein B production by PCSK9 and showed for the first time that mRNA levels of proteins (FAS, SCD, and DGAT2) involved in chylomicron assembly are increased by the addition of exogenous PCSK9 to CaCo-2 cells, that these effects are low-density lipoprotein receptor dependent, and that they are reversed by acute siRNA silencing of PCSK9 gene expression.5 Because we placed no emphasis on NPC1L1, we felt that not mentioning the article by Levy et al was appropriate given the space limitations. Le May and Cariou then ask whether in our study exogenous PCSK9 was added at the apical or basolateral side of CaCo-2 cells. We presented data from PCSK9 added to the apical side but obtained similar results after adding it to the basolateral side. This is in line with previous work in which Levy et al5 show that CaCo-2 cells secrete PCSK9 mostly into the basolateral medium, whereas Le May et al6 state that enterocytes show “strong PCSK9 immunostaining mainly in the apical compartment” and that “PCSK9...accumulates at the subapical and basolateral compartments of the enterocyte.”

Finally, Le May and Cariou question our claim of having used a physiological dose of PCSK9 in the studies of CaCo-2 cells1 and suggest instead that the dose we chose is 2- to 3-fold higher than the highest physiological human PCSK9 concentration. We disagree with this statement because 10 μg/mL, the concentration we used to stimulate CaCo-2 cells, mimics the physiological effect of PCSK9 in vitro and is at the high end of the physiological PCSK9 concentration in humans.3

Disclosures

None.

References


DOI: 10.1161/CIRCULATIONAHA.114.013729

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_Circulation_. 2015;131:e428
doi: 10.1161/CIRCULATIONAHA.114.013729

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/131/18/e428

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