commentary

Location, location, location…again[1]

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Claude Bernard is referred to as the Father of Physiology and made profound contributions to the development of the scientific process (1). We all recognize readily his proposal of 'milieu intérieur'; this concept has become so much a part of our conceptual thinking that we interpret much of the biological data on this framework, many times subconsciously. This constancy of the environment, and more importantly, when perturbed by external forces (physiological or otherwise), the ability to return itself to this balance is one we apply to all manner of physiological processes, including the regulation of body temperature, blood glucose, electrolytes, etc. Yet one blood substance that continues to evade simple adherence to the homeostasis paradigm is blood cholesterol.

The net balance of synthesis, absorption/intake, and excretion/breakdown determines the pool of body cholesterol. At the cellular level, this concept works well; the elegance of this regulation, mediated by the sterol regulatory element binding protein (SREBP) pathway (2), by synchronizing synthesis with receptor-mediated uptake of cholesterol and pathways that break down or secrete cholesterol, leads to tight cellular cholesterol homeostasis. What is likely regulated is the level of plasma membrane 'free' (active) cholesterol, as proposed by Lange and Steck (3), rather than cholesterol in any other pool, though this remains controversial.

Many have extended the concept of cellular cholesterol homeostasis to include this level of balance at the organ and whole body level. Surely plasma cholesterol levels are controlled by mechanisms that can integrate dietary/intestinal cholesterol absorption, body synthesis, and excretion (as cholesterol or bile acid loss)? One corollary of this would be that if synthesis is decreased (e.g., via statin therapy), then this should result in a compensatory increase in dietary/intestinal absorption of cholesterol (and vice versa). Miettinen and his colleagues (4) have shown that markers of absorption are indeed increased in statin-treated subjects.

In this issue of the *Journal of Lipid Research*, Tremblay, Couture, and colleagues (5) report a well-designed human study to explore potential mechanisms to support this theory. The strengths of this study are that it is a well-powered, double-blind placebo controlled human study with both biochemical characterization, as well as mRNA expression analyses of duodenal biopsies obtained before and after treatment with 40 mg of atorvastatin for 3 months. Treatment resulted in reduced markers of cholesterol synthesis (lathosterol) and increased levels of sterol absorption (sitosterol and campesterol), with the expected lowering of plasma LDL-C. More importantly, mRNA analyses showed that NPC1L1 expression was increased, as were genes upregulated by the SREBP pathway. Thus, at the intestinal level, the homeostatic functions to maintain cholesterol levels seem to be fully operative. More interesting was the upregulation of PCSK9 in the intestinal cells, over and above that seen for the LDL receptor, suggesting that regulation of receptor activity via this molecule may be the more important consequence of statin therapy. ABCG5 and ABCG8 mediate the sterol secretory pathway and their expression was reduced, thus providing an explanation for the increased plant sterol levels in the blood, as well as a homeostatic function of reduced cholesterol secretion. Direct intestinal secretion of cholesterol and plant sterols was first identified in man (6), but this pathway has gained popularity and rediscovery after it was shown to occur in mice (7). The authors also compared the correlation between the levels of gene expression of the target genes and SREBP-2 or HNF-4 expression, and found that the latter also correlated well (if not better) with the levels of expression of LDL-R and HMG-CoA reductase. One disappointment of this otherwise excellent example of translational research is that the authors were not bold enough to have subjected the precious duodenal biopsies to microarray analyses, as this would have generated perhaps better ways of looking at the network changes, rather than focusing on a limited set of genes that can lead to observer bias. Nevertheless, this study confirms the predicted compensatory changes expected when cholesterol synthesis is inhibited in the enterocyte and highlights also the role of drug therapy on the intestine itself.

So, does this support the concept of blood homeostasis for plasma cholesterol? Sadly, no. To date, no mechanism has been described that integrates absorption, synthesis, and excretion of cholesterol to keep blood cholesterol

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levels in a homeostatic manner. In FH subjects, baseline markers of absorption did not correlate with the ability of ezetimibe/statin to predict LDL-C lowering (8), suggesting that these two pools of cholesterol are not directly linked. Had Bernard chosen blood cholesterol to study, it is doubtful he would have championed the milieu intérieur. Cholesterol regulation, like politics, seems all too parochial.

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