Are Restenosis Cells Containing Nonmuscle Myosin Really Vascular Smooth Muscle Cells?

As a contributor to the study of restenosis,1-3 I have read with great attention the article by Leclerc et al4 and the Editorial Comment by Williams and Meidell5 about the evidence implicating nonmuscle myosin in restenosis. I would like to ask the authors6 why they use the term “smooth muscle cells” for the cells containing nonmuscle myosin.

Unfortunately, Leclerc et al4 have not studied whether the cells containing nonmuscle myosin also possess smooth muscle myosin isoform. This question has been studied, however, by Zanellato et al6 in their outstanding experimental work concerning the myosin isoform expression in normal and atherosclerotic rabbit aortas. In the atherosclerotic plaque, which may be considered to be a model of the wound-healing reaction in the vascular wall, there are three populations of “vessel wall derived cells”: 1) the cells containing only nonmuscle myosin, 2) the cells containing only smooth muscle myosin, and 3) the cells containing both isoforms.6 This suggests that the cells containing only nonmuscle myosin differentiate into smooth muscle cells but leaves open the question of their origin. At variance with Zanellato et al,6 I believe that the atherosclerotic cells containing only nonmuscle myosin originate in nonmuscle myosin–positive vascular endothelial cells. For example, the horizontal structure visualized at the bottom of their Figure 11B is undoubtedly a hyperplastic capillary in the process of canalization and giving rise to interstitial fibroblastic cells.6,7 Indeed, from the “vessel wall derived cells,”7 only the undifferentiated vascular endothelial cells differentiating into smooth muscle cells are able to express macrophagic and smooth muscle cell markers concomitantly.8 At the same time, only this concept explains clearly why “blocking angiogenesis might block intimal hyperplasia, and vice versa.”9

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Reply

The data of Zanellato et al1 showing the induction of nonmuscle myosin expression in the proliferative rabbit atherosclerotic plaque are concordant with those of Kuro-o et al2 (cited in our article) and ours. Along with these two groups, we report that the vast majority of the cells expressing a nonmuscle myosin gene isoform (specifically the human nonmuscle myosin heavy chain-B isoform in our case3) can also be identified as expressing the α-actin protein, as evidenced by the immunostaining we performed on these lesions. The cell population described by Zanellato and referred to by Beranek (expressing only nonmuscle myosin) represented only the minority among all constituents of the rabbit plaque. Beranek’s suggestion regarding the origin of these cells is intriguing. To our knowledge, however, growth-related transition of myosin expression, including final reversal to smooth muscle myosin, has not been previously shown in cultured vascular endothelial cells. Pending such demonstration, the immunohistochemical findings that we and others have reported, as well as the well-documented transition in myosin expression observed in smooth muscle cells, suggest that cells expressing nonmuscle myosin identified in large numbers in restenotic lesions are of smooth muscle origin.

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