Prevention of Tissue Death by Killer Cells? 
The Role of the Immune System in Arteriogenesis

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Based on the observation that mouse strains differing in lymphocyte-mediated immune responses differed also markedly in collateral density, in their ability to develop a collateral circulation, in remodeling and the expression of VEGF-A after femoral artery occlusion, previously reported by Scholz et al,1 Chalothorn,2 and Helisch et al,3 van Weel et al had set out to test the role of lymphocytes in arteriogenesis.4 They found that NK-cells and CD4 cells are important for collateral vessel growth and that substitution in animals deficient for these cells accelerated collateral development. These elegant studies, using mouse genetics as well as antibody-based deletion experiments, provide a solution to a long smoldering discussion about the role of lymphocytes in arteriogenesis as well as in angiogenesis. As early as 1976 Klintworth and collaborators5 showed that angiogenesis in response to corneal injury was associated with an influx of leukocytes. The causal relationship was proven by irradiation to depress the bone marrow leading to impaired angiogenesis. The contribution of subsets of leukocytes was difficult to discern at the time because only morphological markers were available. Leukocytes were believed to play a lesser role compared with the unfractonated leukocyte population. We could show in 1971 that leukocytes played a role in arteriogenesis because they invaded the wall of developing coronary collaterals,6 and a systematic study published in 19767 identified these cells as monocytes. These findings were later supplemented by increased endothelial expression of monocyte chemoattractant protein 1 and by increased expression of adhesion molecules. The role of the monocyte in angiogenesis was reported by Polverini in 19778 and a few years later by Sunderkotter.9 Selective elimination of monocytes/macrophages by liposomes spiked with phosphonates inhibited arteriogenesis10 and targeted disruption of MCP-1 and its cognate receptor also impaired collateral growth.11 Extreme monocytopenia as in op/op mice markedly inhibited arteriogenesis.12

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In the studies by van Weel and colleagues the important role of lymphocytes is very convincingly demonstrated. However, their findings contrast with other previous reports that had come to different conclusions. Hoefer and colleagues13 found completely normal collateral blood flow after femoral occlusion in nude mice, suggesting that lymphocytes do not play a role. This may have been premature because the selection of mouse strains for controls is difficult in view of the wide variation in the arteriogenic potency of different mouse strains. Hoefer et al14 also infused chemokines that attracted either monocytes, leukocytes, or lymphocytes and found that only monocyte attractants stimulated arteriogenesis. These studies were carried out in rabbits and may be difficult to compare with van Weel's detailed genetic mouse studies. Studies by Hoefer et al in mouse strains with targeted disruption of tumor necrosis factor (TNF) alpha and its cognate receptors15 seemed also to imply that lymphocytes do not play a role. However, TNFalpha KO mouse strains in our hands were extremely sensitive to variations in the genetic background.

Van Weel's studies clearly showed the importance of lymphocytes but not their specific function in the process of arteriogenesis. We hypothesized earlier16 that lymphocytes may play an important role in the remodeling process: when collaterals grow, and this may be up to 20 times their original diameter, depending on the size of the species, additional space has to be provided. We had observed earlier nonspecific myocyte death bordering on the inflamed adventitia of collaterals and in close contact with lymphocytes. The pressure of the expanding vessel may have stimulated the myocytes to present MHC-II antigens invoking a deadly lymphocyte attack. Space for the expanding vessels is thus created by the loss of surrounding tissue. This proposed mechanism is imaginable especially in the tightly packed myocardium. It may not apply to the more loosely arranged peripheral collaterals of the mouse hind limb where some of the vessels are located subcutaneously. A more probable function may be the secretion of chemokines.

Thanks to the studies of van Weel and others we know now that lymphocytes as well as monocytes, well-known and well-specified bone marrow–derived cells, potently cooperate by creating collateral arteries. On the other hand we also know that the shear stressed collateral vessel wall activates other innate pathways important for growth, like the NO-pathway and the Rho pathway.15 What then would be the role of other circulating cells that are less well characterized, like endothelial progenitor cells? Is there a niche for them in this well-known and well-orchestrated cellular interaction that finally results in a fully functional artery originating from a preexisting arteriole? Originally it was assumed that EPCs are attracted to ischemic regions, attach to the collateral vessel wall, invade, undergo a metaplastic change, and become endothelial and smooth muscle cells that divide and proliferate.16 However, arteriogenesis proceeds in a normoxic envi-
vironment, and detailed confocal studies by Ziegelhoeffer et al.\(^{17}\) provided experimental proof that bone marrow–derived cells, found in the vicinity of growing collaterals, do not change into other cell types. Furthermore, EPCs are present in exceedingly low concentrations and the very high shear stress in collateral vessels may prevent their adhesion. Van Weel provided us with Ockham’s razor: among competing hypotheses, the simpler one is often closer to the truth. EPCs are most probably not needed for arteriogenesis that is so profoundly influenced by the innate immune system.

Disclosures

None.

References


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