This editorial refers to 'The constituents and mechanisms of generation of 'endothelial cell—colony forming units'' by G.J. Padfield et al., pp. 288–296, this issue.

Career switch for EC-CFU to modelling

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Online publish-ahead-of-print 20 September 2013

The opinions expressed in this article are not necessarily those of the Editors of Cardiovascular Research or of the European Society of Cardiology.

By thoroughly analysing the dynamics in the CFU, the CD14+ subtypes as well as a continuous expression of the leukocyte marker CD45 and an increase of the macrophage marker CD68 are seen. Moreover, when CD34+ cells are in vitro driven to express CD14, they also gain EC-CFU potential, illustrating the plasticity of the mononuclear cell fraction of blood.

The study by Padfield and co-workers also shows that monocytes and macrophages in the CFU are proliferative. Long considered terminally differentiated, non-proliferative cells, monocytes and macrophage counterparts can proliferate also when in a relevant environment as has recently been shown in atherosclerosis.4

Some of the features of EC CFUs are reminiscent of the described inflammatory events in vascular repair after injuries such as observed in percutaneous coronary intervention, transplant vasculopathy, and atherosclerosis. This suggested to the authors that the EC-CFU might be an in vitro correlate and perhaps a useful model or marker of local inflammation during vascular repair in vivo. They further suggest that EC-CFUs may be important in vascular repair by controlling local inflammation.

Indeed, the in vitro mechanisms in the CFU have also been established in neointima formation in vivo (Figure 1). CD14+ monocytes are recruited to sites of vascular injury,6–8 and so are CD3,8 CD8, and CD49 T-lymphocytes and B-lymphocytes.10 Monocytes are attracted to sites of injury by interaction with activated endothelium through increased expression of adhesion molecules, but also by tethering to activated platelets that cover the denuded injury site. Platelets subsequently activate monocytes, exemplified by the enhanced expression of VEGFR2.11 T-lymphocytes and B-lymphocytes serve primarily to limit neointima formation by inhibiting smooth muscle cell migration, a key mechanism in this process,9,10 whereas natural killer T-lymphocytes are required for controlled neointima formation.12 Although the in vivo conditions for these cells to function are obviously more complex than during in vitro CFU formation, the EC-CFU may serve as a model of local vascular inflammation (MOLVI).

The phenotypic change of monocytes when in contact with activated platelets suggests that circulating and surveying monocytes become activated or at least modified at the site of injury rather than being recruited in activated state.11 If true, the sought relationship between the level of circulating CD14+ monocytes and cardiovascular risk may not be as simple as desirable for a biomarker. In support of the hypothesis that a localized inflammation such as in vascular remodelling leads to a specialized activation of myeloid cells, Padfield et al.13 in an earlier study induced systemic inflammation with a salmonella typhus vaccine and found no change in circulating numbers of EC-CFUs. Likewise, using a lipopolysaccharide challenge to achieve systemic inflammation, recruitment of CD14 monocytes into the blood stream as well as neointima formation in a simultaneously injured artery depended on the dose,6 illustrating a complex relationship between circulating CD14+ monocytes and local vascular remodelling. In rheumatoid arthritis as an example of a chronic systemic inflammatory condition, CD14+ monocytes appear to be circulating in high numbers but dysfunctional in their capacity to induce neovascularization and vascular remodelling.14 From these studies, it is clear that simple phenotypic characterization of circulating monocytes as either CD14+ cells or as EC-CFUs does not cover the complex function of these cells in vascular remodelling. Although in a small-scale study, chronic cardiovascular risk status and vascular reactivity correlated well with circulating EC-CFU numbers,15 a more detailed phenotypic characterization of circulating myeloid cells...
will be required to define a meaningful biomarker of vascular remodelling and inflammation. If indeed the myeloid fraction becomes functionally activated at the site of injury, finding a circulating correlate that might serve as biomarker may even prove illusory.

EC-CFUs may thus go through a career-switch from biomarker to a model of local vascular inflammation.

Conflict of interest: none declared.

Funding
This research was partly performed within the framework of CTMM, the Center for Translational Molecular Medicine (www.ctmm.nl), project EMINENCE (grant 01C-204). N.v.d.A. is supported by the European Interreg IVa Flanders-The Netherlands grant VaRaA.

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