LETTER

Endothelial progenitor cells are cellular hubs essential for neoangiogenesis of certain aggressive adenocarcinomas and metastatic transition but not adenomas

Purhonen *et al.* (1) have refuted the data published in >50 reports (2, 3), neglecting to quote key articles or utilize relevant models, and have drawn unsubstantiated conclusions about the contribution of endothelial progenitor cells (EPCs) to tumor angiogenesis that are not supported by their nonquantitative data and superficially executed experiments. Their study (1) is flawed in experimental design and data interpretation. For example, they do not cite their own publication demonstrating the existence of $VEGFR2^+$ EPCs (4) and neglect mentioning clinical validation (5, 6) and acknowledging mouse genetic models (2, 3), which provide convincing evidence for functional incorporation of EPCs into neovessels. Every figure lacks stereoconfocal-microscopic quantification of vessels that are presented as poorly defined longitudinal–linear streaks. Plasma VEGF-A levels were not measured *in vivo* in mice treated with VEGF-A, questioning their low level of $VEGFR2^+$ EPC detection (3). Indeed, their FACS analysis is inaccurate because of (*i*) unconvincing CD31/VE-cadherin/VEGFR2 expression detected on MS-1 endothelium used as positive control and (*ii*) failure to show long-term marrow engraftment of donor-derived hematopoietic and authentic $VEGFR2^+LacZ^+$ colony-forming EPCs. APCmin mice develop only obstructive adenomas, rather than adenocarcinomas; therefore, it is an inappropriate model to study EPC incorporation, as Spring *et al.* (7) (not quoted) demonstrate that EPCs do not contribute to adenomas but contribute only to carcinomas/metastatic tumors. In the parabiotic model, wild-type EPCs compete with GPF^+ EPCs, which underestimates EPC recruitment. Finally, study of 6-month-old VEGF-A-loaded Matrigel plugs in mice is impossible because Matrigel plugs are degraded within 2 months, particularly when VEGF-A by itself does not induce neoangiogenesis. No quantification of patent vessels in Matrigel plugs was provided. This article fails to disprove the established role of EPCs in supporting neoangiogenesis in certain tumors (3, 5) and metastatic transition (2).

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