Diabetes and aging: a different phenotypic commitment of circulating and resident stem cells?

Amedeo Ferlosio & Augusto Orlandi

Acta Diabetologica

ISSN 0940-5429

Acta Diabetol
DOI 10.1007/s00592-012-0432-z

Springer

Acta Diabetol
DOI 10.1007/s00592-012-0432-z

LETTER TO THE EDITOR

Diabetes and aging: a different phenotypic commitment of circulating and resident stem cells?

Amedeo Ferlosio · Augusto Orlandi

Received: 12 September 2012 / Accepted: 13 September 2012

Atherosclerosis is a vascular disease largely attributed to chronic vascular injury, and its clinical manifestations appear more frequently in aged subjects. Accumulation of vascular smooth muscle cells in the tunica intima plays a major role in the pathogenesis of atherosclerosis. Arterial smooth muscle cells are heterogeneous even in the normal vessel wall and display more marked different phenotypes in pathological conditions. Smooth muscle cells in atherosclerotic plaques display a de-differentiated or "synthetic" phenotype compared to a "contractile" phenotype in the normal media. Aorta stiffens with age and other cardiovascular risk factors. In particular, diabetes-induced activation of the renin–angiotensin system increases the expression of angiotensin II, further increasing aortic calcification and stiffness. Thus, alterations of aortic and carotid walls in patients with diabetes were traditionally considered a sort of "accelerated aging." In the last years, the contribution of stem cells to atherosclerosis has been highlighted. Bone marrow and peripheral blood-derived endothelial and vascular smooth muscle cell resident progenitors both contribute to vascular remodeling during atherogenetic process and aging [1]. Both circulating and resident progenitor cells have been evocated to contribute to the response of the adult arterial wall to damage. Chronic treatment with bone marrow-derived progenitor cells from young non-atherosclerotic ApoE^{-}/$^{-}$ mice prevents atherosclerosis progression in ApoE^{-}/$^{-}$ recipients despite persistent hypercholesterolemia, whereas bone marrow-derived progenitor cells from older ApoE^{-}/$^{-}$ mice with atherosclerosis were much less effective [2]. These findings suggest that the progressive bone marrow-derived progenitor cells deficit may contribute to the development of atherosclerosis. Nevertheless, atherosclerotic lesions are characterized from the increase of stem cell marker-expressing cells, and macroscopically normal aortas from human and rat aged donors show an increased number of VEGFR-1^{+} and c-kit^{+} cells in the thickened intima [3]. Also, diabetes alters the function of circulating progenitor cells. Depletion of bone marrow-derived angiogenic cell populations may further promote atherogenesis and aortic calcification in patients with diabetes mellitus [4]. In multivariable analyses, the increase in colony-forming units from endothelial progenitor cells was associated with the decrease in coronary artery and abdominal aortic calcification [5]. These changes were not associated with changes in CD34^{+} expression, suggesting that a decreased angiogenic potential contributes to the development of human atherosclerosis. Moreover, decreasing colony-forming capacity associated with the progressive increase of calcification scores [5]. Recently, it has been reported that diabetes mellitus patients had significantly higher expression of osteocalcin and bone alkaline phosphatase on circulating VEGFR-2^{+}/CD34^{+} progenitor cells than control subjects [6]. Moreover, cultured VEGFR-2^{+}/CD34^{+} cells from diabetes mellitus patients formed structures highly suggestive of calcified nodules, strongly suggesting that circulating progenitor cells from diabetic patients show a drift toward a pro-calcific phenotype that may be driven by inflammatory signals in response to injury [6], similarly to that observed in non-vascular tissues [7]. Monocyte–macrophage recruitment is a crucial step for a correct angiogenesis, and this mechanism is mainly mediated by VEGFR-1, that favors the increase of vessel lumen, vessel

Communicated by Massimo Federici.

A. Ferlosio · A. Orlandi (✉)
Department of Biomedicine and Prevention, University of Rome, "Tor Vergata" Via Montpellier 1, 00133 Rome, Italy
e-mail: orlandi@uniroma2.it

Published online: 05 October 2012

stabilization and monocyte–macrophage infiltration and counteracts pathological angiogenesis stimulated from PlGF-mutated variants that not bind VEGFR-1 [8, 9]. These findings suggest that aging and diabetes share the decrease of circulating endothelial cells with potential angiogenic/reparative properties, but in addition, diabetes associates a conversion toward a pro-calcific phenotype, whereas with aging stem cells with a synthetic VEGFR-1^{+} myocitic phenotype prevail and contribute to aortic myo-intimal thickening and to vascular angiogenetic or healing processes [10, 11]. Although these findings support the divergent phenotypic conversion of circulating precursor cells, further studies are needed to verify whether also aortic resident stem cells are similarly modified in their differentiative capacities in diabetic patients.

References

1. Orlandi A, Bennett M (2010) Progenitor cell-derived smooth muscle cells in vascular disease. Biochem Pharmacol 79:1706–1713
2. Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, Wang T, Gregg D, Ramaswami P et al (2003) Aging, progenitor cell exhaustion, and atherosclerosis. Circulation 108:457–463
3. Ferlosio A, Arcuri G, Doldo E, Scioli MG, De Falco S, Spagnoli LG et al (2012) Age-related increase of stem marker expression influences vascular smooth muscle cell properties. Atherosclerosis 224:51–57
4. Jung CH, Lee WY, Kim SY, Jung JH, Rhee EJ, Park CY et al (2010) The relationship between coronary artery calcification score, plasma osteoprotegerin level and arterial stiffness in asymptomatic type 2 DM. Acta Diabetol 47(Suppl 1):145–152
5. Cheng S, Cohen KS, Shaw SY, Larson MG, Hwang SJ, McCabe EL et al (2010) Association of colony-forming units with coronary artery and abdominal aortic calcification. Circulation 122:1176–1182
6. Manenti G, Bolacchi F, Perretta T, Cossu E, Pistolese CA, Buonomo OC, Simonetti G et al (2009) Small breast cancers: in vivo percutaneous US-guided radiofrequency ablation with dedicated cool-tip radiofrequency system. Radiology 251:339–346
7. Fadini GP, Albiero M, Menegazzo L, Boscaro E, Agostini C, de Kreutzenberg SV et al (2012) Procalcific phenotypic drift of circulating progenitor cells in type 2 diabetes with coronary artery disease. Exp Diabetes Res 38:194–202
8. Tarallo V, Vesci L, Capasso O, Esposito MT, Riccioni T, Pastore L et al (2010) A placental growth factor variant unable to recognize vascular endothelial growth factor (VEGF) receptor-1 inhibits VEGF-dependent tumor angiogenesis via heterodimerization. Cancer Res 70:1804–1813
9. Cassinelli G, Zuco V, Petrangolini G, De Cesare M, Tortoreto M, Lanzi C et al (2010) The curative efficacy of namitecan (ST1968) in preclinical models of pediatric sarcoma is associated with antiangiogenic effects. Biochem Pharmacol 84:163–171
10. Orlandi A, Bochaton-Piallat ML, Gabbiani G, Spagnoli LG (2006) Aging, smooth muscle cells and vascular pathobiology: implications for atherosclerosis. Atherosclerosis 188:121–230
11. Cervelli V, Scioli MG, Gentile P, Doldo E, Bonanno E, Spagnoli LG et al (2012) Platelet-rich plasma greatly potentiates insulin-induced adipogenic differentiation of human adipose-derived stem cells through a serine/threonine kinase Akt-dependent mechanism and promotes clinical fat graft maintenance. Stem Cells Trans Med 1:206–220