Is PlGF a plaque growth factor?

Julie Sainz 1 and Masataka Sata 2*

1INSERM U833, Collège de France, Paris, France; and 2Department of Cardiovascular Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-18-15 Kuramoto-cho, Tokushima-city, Tokushima 770-8503, Japan

Online publish-ahead-of-print 1 February 2010

This editorial refers to ‘Short-term delivery of anti-PlGF antibody delays progression of atherosclerotic plaques to vulnerable lesions’ by C. Roncal et al., pp. 29–36, this issue.

The placentall growth factor (PlGF) is a cysteine-knot protein, highly homologous to the vascular endothelial growth factor (VEGF). Initially described in placenta, it was subsequently demonstrated to be expressed in other tissues, including the lung and heart. Circulating levels of PlGF are normally undetectable. However, increased PlGF levels have been described under several pathological conditions, including cancer, cutaneous wounds, bone fractures, sickle-cell disease, and atherosclerosis. In humans, the PlGF gene encodes four different isoforms (PlGF-1, -2, -3, and -4) that are generated by alternative splicing and differ in their binding affinities and secretion properties. In mice, PlGF-2 is the only isoform of PlGF.

Roncal et al. report the efficacy of short-term anti-PlGF treatment in preventing atherosclerosis development by using a neutralizing anti-PlGF monoclonal antibody (αPlGF mAb) at early stages of the disease. Administration of the αPlGF mAb for 5–10 weeks was sufficient to reduce lesion size and inflammation in the less severe murine atherosclerosis models. The antibody used in this study (clone PL5D11D4) specifically recognizes murine PlGF-2 and inhibits its binding to the VEGF receptor-1 (VEGFR-1/Flt-1) and to one of its semaphorin co-receptors, namely neuropilin-1 (NRP-1). The importance of PlGF-2 in the pathogenesis of atherosclerosis was formerly brought to light by Khurana et al., who reported that (i) perivascular transfer of PlGF-2 in hypercholesterolaemic rabbits resulted in enhanced neo-intima formation and macrophage accumulation, and (ii) early atherosclerotic lesions of ApoE−/−PlGF−/− mice were smaller and had less macrophage accumulation than ApoE−/−PlGF+/+ mice.

In the present work, the authors first show increased expression of PlGF and its receptor Flt-1 in ApoE−/− mice. PlGF was mainly located at the shoulders of atherosclerotic plaques. Then, several murine models of mild and aggressive atherosclerosis were used to assess the potential range of efficacy of short-term αPlGF mAb treatment. These models include: (i) ApoE−/− mice fed a normal chow (mild ApoE−/−), which induces mild atherosclerosis development; (ii) ApoE−/− mice that were put on a hypercholesterolaemic diet for 10 or 20 weeks (HC10 or HC20 ApoE−/−), which triggers enhanced atherogenesis; and (iii) CD4:TGFβRIIDN × ApoE−/− mice with defective TGF-β signalling in T-cells, which leads to the most severe form of atherosclerosis studied in this work (vulnerable ApoE−/−). Results showed that short-term αPlGF mAb treatment modestly but significantly inhibited early lesions, but was ineffective in affecting more advanced stages of plaque development. Moreover, αPlGF mAb reduced both macrophage and T-cell infiltration in early lesions, but not in more advanced stages of atherogenesis. Immunostaining against CD11c revealed that αPlGF mAb had no effect on accumulation of dendritic cells in the mild or more aggressive atherosclerosis models.

In order to gain insight into the underlying mechanisms of action of the αPlGF mAb, the authors investigated whether the therapy could affect the balance of smooth muscle cell (SMC) phenotypes found inside the plaque. It did not modify the content of either contractile or synthetic SMCs. However, it diminished the endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), a key molecule in the monocyte adhesion and rolling processes at the luminal side of the arteries. Consistent with these findings, previous work had featured the capacity of PlGF-2 to augment the expression of VCAM-1, either directly through activation of Flt-1 in endothelial cells or indirectly by inducing an increased secretion of TNFα and IL-1β by macrophages that express Flt-1, which in turn activate VCAM-1 expression at the surface of endothelial cells. The treatment also had an effect neither on global content nor on the quality of the intra-plaque collagen.

In addition to Flt-1 and NRP-1, PlGF-2 may also specifically bind polyanionic substances such as heparan sulfate proteoglycans (HSPGs), which can be found in significant amounts in arteries during atherosclerosis development. It was shown that heparan sulfate chains of perlecan promote atherosclerosis in mice, most likely through retention of lipoproteins. In this setting, it may be preferable that the αPlGF mAb should not prevent the binding of PlGF to vascular HSPGs, otherwise HSPGs could become more readily available to trap low-density lipoproteins, thus aggravating atherosclerosis progression. Besides, PlGF may also bind neuropilin-2 (NRP-2). Additional insights into the impact of interaction between PlGF and NRP-2 in vascular and other tissue contexts may be warranted in order to ensure the safety of αPlGF-blocking therapy. Last, PlGF has been reported to form heterodimers with VEGF in vivo. Such heterodimers may be secreted by tumour cells, for instance. In vitro data reported by Cao et al. suggest that PlGF could decrease the mitogenic function and increase the chemotactic properties of
VEGF on endothelial cells by forming heterodimers with VEGF. Hence, the conception of an antibody against PlGF that might be used in humans should also take into account its possible actions on these PlGF/VEGF heterodimers and consequences from the point of view of pharmacological efficacy. Finally, PlGF was also formerly reported to promote the mobilization, chemotaxis, and recruitment of bone marrow-derived endothelial progenitor cells to tissues. Depending on the pathophysiological circumstances, this mobilization may be beneficial or deleterious. Such a property of PlGF should hence be kept in mind when considering treating patients with αPlGF mAb.

In conclusion, in the present work, the investigators elegantly demonstrated the promising potential of an αPlGF mAb to prevent atherosclerosis development when the pathology is in its early stages. However, since the efficacy of such a treatment depends on its precocious administration, further studies are warranted to determine whether it may be efficient in patients where clinical symptoms have already arisen. Also, prior to using the αPlGF mAb as a therapeutic tool in humans, all potential targets and those of its ligands should be clearly identified and considered in order to anticipate and counterbalance any adverse effects and ensure treatment safety.

Conflict of interest: none declared.

Funding
This study was supported in part by the Program for Promotion of Basic and Applied Researches for Innovations in Bio-oriented Industry and by grants from the Ministry of Education, Culture, Sports, Science and Technology (Knowledge Cluster and New Research Area) and the Ministry of Health, Labor and Welfare of Japan.

References