

# Smooth muscle overexpression of PGC1 $\alpha$ attenuates atherosclerosis in rabbits

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In a new study published in *Circulation Research*, Chen-Yu Zhang and Xiaohong Jiang's group from Nanjing University and Dongjin Wang's group from Nanjing Drum Tower Hospital reported a critical role of

PGC1 $\alpha$  in maintaining the contractile phenotype of vascular smooth muscle cells (VSMCs) and highlighted the therapeutic potential of PGC1 $\alpha$  for atherosclerosis.

The traditional view holds that aberrant proliferation of VSMCs promotes plaque formation after vessel injury and inflammation, whereas the presence of VSMCs in the fibrous cap of the plaque is beneficial. Although it has long been assumed that these seemingly contradictory functions of VSMCs during atherosclerosis arise from their remarkable plasticity, direct evidence that VSMCs undergo phenotypic switching during atherogenesis in vivo has only been proven recently by rigorous lineage tracing studies. These studies showed that the contribution of VSMCs to atherosclerosis has been greatly underestimated. Despite the importance of VSMC phenotypic modulation in lesion pathogenesis and plaque composition, the underlying molecular mechanisms remain to be elucidated.

Among the different animal models that have been used to study atherosclerosis, rabbits not only have provided many insights into the pathogenesis of human AS but also have contributed greatly to translational research. Rodents, such as mice and rats, are quite resistant to atherosclerosis due to high levels of HDL in circulation. Like humans but unlike rodents, rabbits are considered LDL mammals, which are sensitive to dietary cholesterol and spontaneously develop AS. However, due largely to the relative ease of their genetic manipulation and breeding, compared with those of rabbits, mice—such as ApoE $^{-/-}$  and LDLR $^{-/-}$  mice—are still the most widely used laboratory models. However, owing to their unique features of lipoprotein metabolism, which are pathophysiologically more similar to those of primates than those of rodents, transgenic rabbits have still been used during the past decades to study human atherosclerosis in order to bridge the gaps between mice and humans; thus, rabbits are an indispensable model for studying human atherosclerosis.

Although aberrant expression of PGC1 $\alpha$ , a master regulator of mitochondrial biogenesis, has been shown to be associated with cardiovascular diseases, the role of PGC1 $\alpha$  overexpression in VSMCs in the formation of atherosclerotic lesions has not been elucidated. In the current study, Wei et al. generated Tg rabbits with SMC-specific PGC1 $\alpha$  overexpression and showed that overexpression of PGC1 $\alpha$  in VSMCs significantly ameliorated high cholesterol diet-induced atherosclerotic plaque formation. After feeding cholesterol rich diet, the VSMCs from Tg rabbits exhibited a more contractile phenotype than their non-Tg littermates, which resulted in decreased macrophage infiltration, vascular inflammation, ROS production, vascular senescence, and VSMC proliferation. In addition, similar vasoprotective effects were observed in cultured human aortic SMCs and clinical samples. Collectively, their findings demonstrate a beneficial role for PGC1 $\alpha$  in modulating VSMC phenotype and the pathogenesis of atherosclerosis.

This work is essential for the following reasons:

1. As the first and one of the best animal models for investigating AS, the rabbit model is a better overall approximation to humans. However, to date, only 22 lines of Tg rabbits have been established to study CVD due to the relative difficulty of genetically manipulating and breeding rabbits compared with mice. Most of these exogenous genes were either systemically or specifically expressed in rabbit liver cells and directly participated in lipoprotein metabolism, for example, apolipoproteins and their associated enzymes. Although many lipid metabolism related factors have been expressed in [rabbit](#) livers and macrophages, models with artery-specific overexpression of genes are lacking. By generating transgenic rabbits that expressed PGC1 $\alpha$  under the control of a minimal SM22 promoter, whose activity was constitutive in arterial SMCs. Zhang's group found that after HCD feeding, although Tg rabbits developed hypercholesterolemia similar to that in their non-Tg littermates, the mean aortic lesion size in Tg rabbits was markedly

reduced. This finding is consistent with previous observations in vitro studies in cultured VSMCs, indicating a direct atheroprotective role of PGC1 $\alpha$  in arterial VSMCs.

2. As a powerful orchestrator of energy metabolism, PGC1 $\alpha$  is highly expressed in energy demanding tissues, such as brown fat, liver, brain, and muscles. The function of PGC1 $\alpha$  is less studied in VSMCs, the ultimate effectors of vasomotion and a major cell type present at all stages of AS than in skeletal muscle and cardiac muscle cells. Although previous in vitro studies showed that PGC1 $\alpha$  can inhibit pathological factor-induced VSMC proliferation and senescence, increased local PGC1 $\alpha$  expression in AS has not been conclusively demonstrated in vivo. In the present study, based on RNA-seq analysis and a set of experimental assays of the aortic media from HCD-fed control and Tg rabbits, they found that the PGC1 $\alpha$  level was positively associated with the VSMC-restricted contractile gene expressions, but negatively correlated with the atherogenic synthetic phenotype-related features of VSMCs, such as increased expression of proinflammatory factors and MMPs, enhanced ROS production and senescence, and elevated VSMC proliferation. These in vivo observations were also confirmed in cultured VSMCs, hence revealing the novel role of PGC1 $\alpha$  in preserving the beneficial contractile phenotype of VSMCs and bolstering its antiatherogenic function.

3. Their data indicated a potential atheroprotective role of PGC1 $\alpha$  in clinical atherosclerotic samples, yet further studies with more accurate lineage identification techniques are needed to address this possibility, and regulating PGC1 $\alpha$  itself or increasing the level of PGC1 $\alpha$  in VSMCs might be feasible therapeutic strategies for atherosclerosis.

**More information:** Zhe Wei et al, Smooth Muscle Overexpression of PGC1 $\alpha$  Attenuates Atherosclerosis in Rabbits, *Circulation Research* (2021). [DOI: 10.1161/CIRCRESAHA.120.317705](https://doi.org/10.1161/CIRCRESAHA.120.317705)

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