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Atorvastatin exerts inhibitory effect on endothelial senescence in hyperlipidemic rats through a mechanism involving down-regulation of miR-21-5p/203a-3p

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ABSTRACT

Statins are reported to exert benefits on endothelial function through a mechanism involving in prevention of endothelial senescence. This study aims to explore whether atorvastatin exerts inhibitory effect on endothelial senescence in hyperlipidemic rats or ox-LDL-treated HUVECs through a mechanism involving suppress of miR-21-5p/203a-3p expression and their downstream pathway. The rats were fed with high-fat diet to establish a hyperlipidemic model, which showed an increase in plasma lipids and endothelial senescence, accompanied by the elevation in plasma levels of miR-21-5p/203a-3p, down-regulation of Drp1 and up-regulation of p53 in the aorta of hyperlipidemic rats; these phenomena were reversed by atorvastatin. Next, HUVECs were incubated with ox-LDL to establish a senescent model in vitro. Consistent with the finding in vivo, atorvastatin treatment decreased the level of miR-21-5p and miR-203a-3p in the ox-LDL-treated HUVECs, restored Drp1 expression and mitochondrial function, as well as suppressed p53 and p16 expression and endothelial senescence. Based on these observations, we conclude that atorvastatin exerts inhibitory effect on endothelial senescence in hyperlipidemic rats through a mechanism involving down-regulation of miR-21-5p/203a-3p, which leads to the restoration of Drp1 level and recovery of mitochondrial function. Our findings highlight a novel non-lipid effect for atorvastatin besides its function in modulation of lipids.

1. Introduction

It is well known that hyperlipidemia is an independent risk factor for many cardiovascular diseases. The excessive lipids, particularly the oxidized low density lipoprotein (ox-LDL), cause endothelial dysfunction and result in multiple cardiovascular diseases ultimately (Tian et al., 2016). Besides apoptosis and necrosis, ox-LDL induced endothelial senescence also contributes to endothelial dysfunction (Liu et al., 2015). Minamino et al. reported that there were vascular endothelial cells with senescence-associated phenotypes present in human atherosclerotic lesions (Minamino et al., 2002). Therefore, elucidating the mechanisms for endothelial dysfunction is of great significance for the prevention and treatment of cardiovascular diseases.

Statins are commonly used to reduce blood lipids level through inhibiting the activity of HMG-CoA reductase (Yang et al., 2016). In addition to inhibition of cholesterol synthesis, statins can exert cardiovascular benefits through other mechanisms, such as increase of low-density lipoprotein uptake, suppress of inflammation and improvement of endothelial function. There is evidence that statins exert benefits on endothelial function through a mechanism involving in prevention of endothelial senescence. In H_2O_2-induced senescent model of endothelial cells, atorvastatin could reduce the number of senescent cells (Haendeler et al., 2004; Ota et al., 2010); atorvastatin treatment could also prevent the senescence of cultured endothelial progenitor cells (EPCs) (Assmus et al., 2003); in vivo, long-term administration of atorvastatin improved endothelium-dependent relaxation and dose-dependently delayed the cardiovascular aging in old rats (Gong et al., 2014; Han et al., 2013). However, the mechanisms for the inhibitory effects of statins on endothelial senescence are not fully elucidated.

Recently, lots of studies have revealed that statins are able to

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Table 1
Body weight and plasma lipids.

	Control	Hyperlipidemia	+Atorvastatin(L)	+Atorvastatin(H)	+Vehicle
Body weight (g)	454.4 ± 5.1	510.0 ± 2.3**	501.0 ± 5.1	471.1 ± 9.4$^{\#\#}$	509.6 ± 1.9
TC (mmol/L)	1.54 ± 0.07	2.50 ± 0.21**	2.24 ± 0.19	2.01 ± 0.06$^{\#}$	2.64 ± 0.29
TG (mmol/L)	1.00 ± 0.09	1.53 ± 0.13**	1.27 ± 0.08	1.17 ± 0.06$^{\#}$	1.49 ± 0.12
LDL (mmol/L)	0.46 ± 0.02	0.83 ± 0.06**	0.73 ± 0.09	0.63 ± 0.04$^{\#}$	0.82 ± 0.09
Ox-LDL (μg/L)	40.80 ± 3.18	54.64 ± 2.92**	50.45 ± 2.79	45.32 ± 2.05$^{\#}$	54.18 ± 3.52
HDL (mmol/L)	0.62 ± 0.02	0.39 ± 0.01**	0.40 ± 0.03	0.49 ± 0.04$^{\#}$	0.39 ± 0.02

TC: total cholesterol; TG: total triglycerides; LDL: low-density lipoprotein.
HDL: high density lipoprotein; ox-LDL: oxidized low density lipoprotein.
n = 8, $^{**}P < 0.01$ vs control; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs hyperlipidemia.

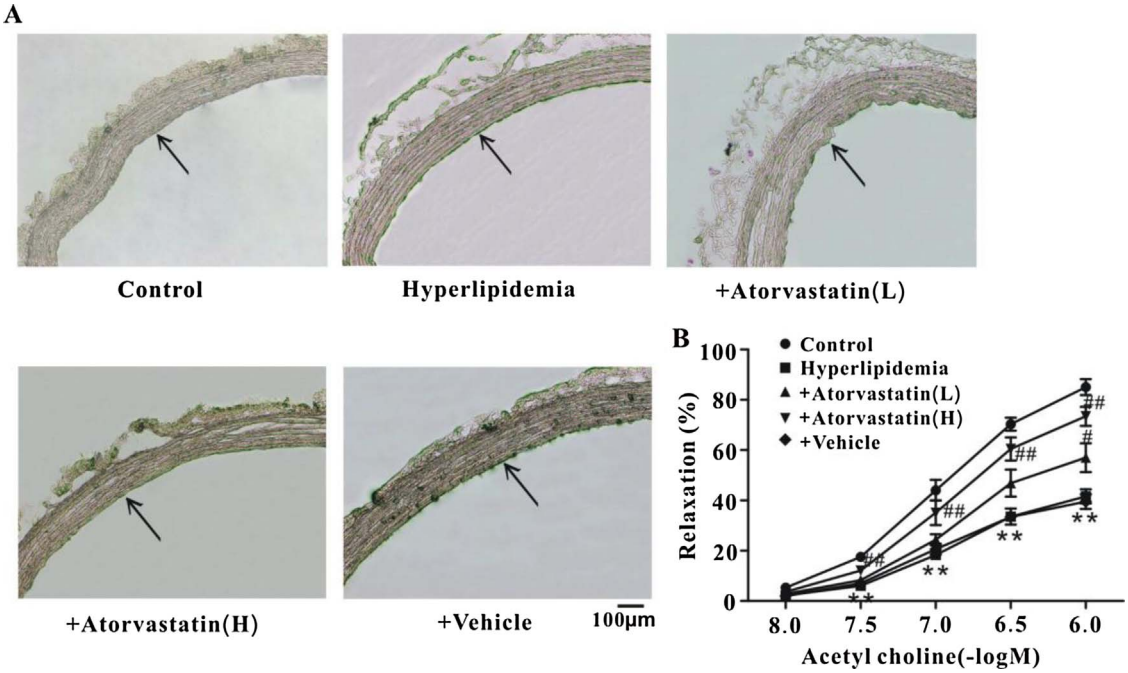

Fig. 1. Atorvastatin reduced the endothelial senescence and improved the endothelium relaxation in hyperlipidemic rats. A. Representative images of β-galactosidase staining for rat aortas. B. Vasodilator responses of the isolated rat aortas to acetylcholine (n = 6 per group). +Atorvastatin (L): hyperlipidemia + atorvastatin (3 mg/kg/d); +Atorvastatin (H): hyperlipidemia + atorvastatin (10 mg/kg/d); +Vehicle: hyperlipidemia +0.5% sodium carboxymethylcellulose. All values are expressed as mean ± SEM. $^{**}P < 0.01$ vs control; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs hyperlipidemia.

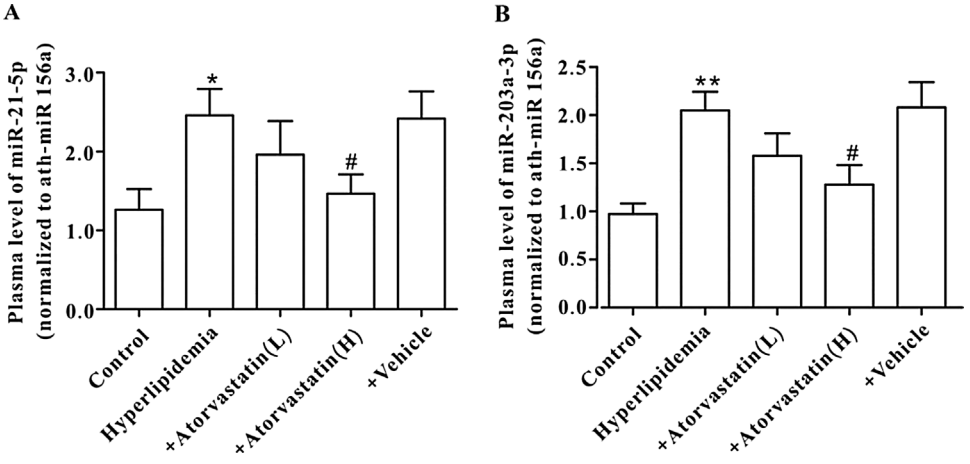

Fig. 2. Atorvastatin reduced the plasma levels of miR-21-5p/203a-3p in hyperlipidemic rats. A. Plasma level of miR-21-5p. B. Plasma level of miR-203a-3p. +Atorvastatin (L): hyperlipidemia + atorvastatin (3 mg/kg/d); +Atorvastatin (H): hyperlipidemia + atorvastatin (10 mg/kg/d); +Vehicle: hyperlipidemia + 0.5% sodium carboxymethylcellulose. All values are expressed as mean ± SEM, n = 8 per group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs control; $^{\#}P < 0.05$ vs hyperlipidemia.

modulate miRNA expression. For example, incubation of EPCs from patients with coronary artery disease with atorvastatin enhanced the expression of miR-221, miR-222 and miR-92a while decreased the expression of miR-34a (Tabuchi et al., 2012; Zhang et al., 2011); in apolipoprotein E-knockout (ApoE$^{-/-}$) mice, atorvastatin could up-regulate miR-126 expression and decrease the atherosclerotic plaque area in right carotid arteries when they were fed on a high-fat diet (Pan et al., 2017). These reports confirmed that statins, particularly atorvastatin, could exert protective effect of endothelial function through modulation of miRNA expression. Most recently, we have reported that