

Safflower Seed-derived Des-1,2-apoA1milano Reduces Atherosclerosis in Hypercholesterolemic Apolipoprotein E (-/-) Mice

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Abstract

Background: Recombinant apoA1milano-produced in bacterial vectors reduces murine and human atherosclerosis, but is costly to produce and difficult to purify. To circumvent these issues, recombinant apoA1milano has recently been expressed in Safflower seed from which it is extracted as Des-1,2-apoA1milano (Apo A1milano without first 2 amino acids, DA1milano). We tested an unoptimized formulation of DA1milano complexed with a phospholipid carrier (POPC) in apoE (-/-) mice fed a high cholesterol diet.

Method and results: Ten intravenous injections of DA1milano were given weekly from 25 to 35 weeks of age. Mice receiving saline or POPC alone served as control. DA1milano significantly reduced atherosclerosis compared to saline or POPC alone (Table) without changes in circulating cholesterol levels. To test if DA1milano mobilized tissue cholesterol, we measured free cholesterol levels before and 1 hour after injection of POPC or DA1milano in apoE (-/-) mice at a dose of 400mg/kg. Compared to POPC, DA1milano significantly increased circulating free cholesterol level in vivo ($-1 \pm 27\%$, $n=16$ vs. $69 \pm 29\%$, $n=18$, respectively; $p < 0.05$) suggesting efflux from tissue.

Conclusions: Our preliminary data show that intravenous Safflower seed-derived recombinant DA1milano mobilizes tissue cholesterol and reduces murine atherosclerosis. Further optimization of the formulation to enhance its potency is planned.

	Saline control	POPC 40 mg/kg	DA1m-POPC 4 mg/kg	DA1m-POPC 10 mg/kg	DA1m-POPC 40 mg/kg
Aortic lesions (%)	40 \pm 13 (n=18)	38 \pm 5 (n=19)	30 \pm 7*† (n=18)	32 \pm 7† (n=14)	29 \pm 7*† (n=18)

*p < 0.05 compared to POPC group; †p < 0.05 compared to saline group