The natural human apoA-I mutation V19L, that has been associated with increased HDL-cholesterol levels, alters apoA-I and HDL structure and functionality

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Aim

Apolipoprotein A-I (apoA-I), the major protein constituent of high-density lipoproteins (HDL), plays crucial roles in the biogenesis, plasma concentration and atheroprotective functions of HDL. Several hereditary point mutations in human apoA-I have been associated with low HDL-cholesterol (HDL-C) levels and/or increased coronary artery disease (CAD) risk. However, one apoA-I mutation, the V19L, has been associated with increased HDL-C levels and decreased CAD risk. Here we examined how this mutation in apoA-I affects the conformational integrity, as well as functional properties of apoA-I or HDL.

Results

Effect of mutation V19L on the secondary structure of lipid free apoA-I

✓ The V19L mutation significantly decreases the α-helical content of apoA-I, based on molecular ellipticity at 208 nm

Effect of mutation V19L on hydrophobic surface exposure of lipid-free apoA-I

✓ The V19L mutation increases the exposure of hydrophobic surfaces of apoA-I to the solvent

Effect of mutation V19L on the thermodynamic stability of lipid-free apoA-I

apoA-I	Thermal Denaturation	
	app T _m (°C)	app ΔH _v (kcal/mol)
WT	58.3 ± 0.7	32.3 ± 0.9
V19L	57.5 ± 0.6	24.9 ± 0.7***

apoA-I	Chemical Denaturation	
	D _{1/2} (M)	ΔG _D ^o (kcal/mol)
WT	1.01 ± 0.02	4.9 ± 0.6
V19L	0.89 ± 0.08*	2.3 ± 0.2***

✓ ApoA-I[V19L] is more thermodynamically destabilized compared to apoA-I WT

Lipid binding ability of apoA-I[V19L]

✓ ApoA-I[V19L] has increased capacity to remodel DMPC vesicles compared to apoA-I WT

Biophysical analysis of apoA-I[V19L] in reconstituted HDL (rHDL) particles

✓ There are no significant alterations on the α-helical content of apoA-I[V19L] in rHDL
✓ ApoA-I[V19L] in rHDL appears more thermodynamically stabilized than apoA-I WT

Effect of apoA-I[V19L] on the HDL biogenesis pathway

✓ ApoA-I[V19L], in lipid free form, displays normal capacity to promote ABCA1-mediated cholesterol efflux
✓ ApoA-I[V19L], in rHDL, displays normal capacity to activate the cholesterol esterifying enzyme LCAT

Effect of apoA-I[V19L] on the HDL remodeling pathway

✓ rHDL-apoA-I[V19L] has normal capacity to promote ABCG1-mediated cholesterol efflux
✓ SR-BI-mediated cholesterol efflux is increased in the presence of rHDL-apoA-I[V19L]

Conclusion

Overall, our findings show that the V19L mutation does not affect the formation of HDL. However, the increased capacity of apoA-I[V19L] to associate with phospholipids, in combination with the increased thermodynamic stability of HDL-containing apoA-I[V19L] particles and their increased capacity to accept additional cholesterol by SR-BI could account for the increased HDL-cholesterol levels observed in human carriers of the mutation.

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