CYP26B1 as regulator of Retinoic acid in vascular cells and atherosclerotic lesions

av

Ali Ateia Elmabsout

Akademisk avhandling

Avhandling för medicine doktorsexamen i Biomedicin, som enligt beslut av rektor kommer att försvaras offentligt
Torsdag den 07 Juni 2012 kl. 13.15,
Hörsal P1, Örebro universitet

Opponent: professor Helen Håkansson
Institutet för miljömedicin (IMM)
Karolinska Institutet

Örebro universitet
Institutionen för hälsovetenskap och medicin
701 82 ÖREBRO
Abstract


Cardiovascular disease (CVD), currently the most common cause of morbidity and mortality worldwide, is caused mainly by atherosclerosis. Atherosclerosis is a chronic multifocal, immunoinflammatory, fibroproliferative disease of medium and large arteries. Atherosclerotic lesions and vascular cells express different genes, among these are genes regulated by retinoic acid. Retinoids have pleiotropic effects and are able to modulate gene expression involved in growth, function and adaptation. During atherosclerosis development, there is endothelial perturbation, lipid accumulation, attraction of immune cells, smooth muscle cell migration and extracellular matrix remodeling and ultimately fibrous cap formation which results in plaques. Retinoids have been demonstrated to either inhibit or modulate the above processes, resulting in amelioration of atherosclerosis. So far, retinoids are known to have impact on cellular processes in SMC, vascular injury and atherosclerosis. However, little is known about catabolism of retinoids in vascular cells and lesions and the effects of alteration of retinoic catabolizing enzymes on retinoids’ status. Therefore, we investigated the expression of Cytochrome P450 26 (CYP26) which is thought to be dedicated to retinoid catabolism. In vascular SMCs and atherosclerotic lesions, we found that CYP26B1 was the only member of the CYP26 family expressed, and it was highly inducible by atRA. Our data revealed that blocking CYP26B1 by chemical inhibition, or by targeted siRNA knock-down, resulted in significantly increased cellular retinoid levels. This indicates that CYP26B1 is an important modulator of endogenous retinoic acid levels. Therefore, we studied the effect of the CYP26B1 nonsynonymous polymorphism rs224105 on retinoic acid availability and found that the minor allele was associated with an enhanced retinoic acid catabolism rate and also with a slightly larger area of atherosclerotic lesions. The expression of CYP26B1 in human atherosclerotic lesions was localized to macrophage rich areas, suggesting retinoic acid activity in macrophages. Furthermore, we demonstrated that a CYP26B1 splice variant, that lack exon two, is expressed in vascular cells and in vessels walls. It is functional, with a reduced catabolic activity to around 70%, inducible by atRA in vascular cells and expressed 4.5 times more in atherosclerotic lesions compared to normal arteries. Moreover, the statins simvastatin and rosuvastatin reduced CYP26B1 mediated atRA catabolism in a concentration-dependent manner, and in vascular cells increased the mRNA expression of the atRA-responsive genes CYP26B1 and RARβ. This could lead to statins indirectly augmenting retinoic acid action in vascular cells which mimic statins roles.

In conclusion, CYP26B1 is a major retinoic acid modulator in vascular cells and atherosclerotic lesions. Blocking of CYP26B1 could provide an advantageous therapeutic alternative to exogenous retinoid administration for treatment of vascular disorders.

Keywords: CYP26B1, alternative splice, vascular cells, atherosclerosis, all-trans-retinoic acid, gene polymorphism, inflammation, statins

Ali Ateia Elmabsout, School of Medical Sciences, Örebro University, SE-701 82 Örebro, Sweden, ali.elmabsout@oru.se
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