Epigenetic histone acetylation modifiers in vascular remodelling – new targets for therapy in cardiovascular disease

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In the past decade, research into cardiovascular diseases, such as atherosclerosis and restenosis, has been focused on the identification of genetic factors that determine disease risk besides clinical risk factors. Many genes in lipid metabolism, vascular homeostasis, haemostasis and inflammation have been found to be related to coronary artery disease¹ and the multifactorial nature of the disease suggests a role for many other, yet uninvestigated genes. Previous research from our department has demonstrated the importance of genetics in restenosis after a percutaneous coronary intervention (PCI). Polymorphisms in several inflammatory genes, such as TNF α , eotaxin, CD14, GM-CSF, IL-10, caspase-1, but also non-inflammatory genes, such as LPL, stromelysin-1 and the β adrenergic receptor have been found to be associated with the risk of restenosis.²⁻⁵ It has become clear, however, that part of the gene-environmental interactions relevant for complex diseases is regulated by epigenetic mechanisms such as histone acetylation and DNA methylation.

Epigenetics

Epigenetic processes modulate gene expression patterns without modifying the actual DNA sequence and have profound effects on the cellular repertoire of expressed genes.⁶ It is well known that epigenetic processes lead to meiotically and mitotically heritable changes in gene expression and play an important role in control of cell identity. These epigenetic

mechanisms act to change the accessibility of chromatin by methylation of DNA at CpG dinucleotides and by modification or rearrangement of nucleosomes, which include covalent post-translational modifications of histone tails.^{7,8} In this way gene function is affected without a change in the DNA sequence. Epigenetic modifications of histone tails include acetylation, methylation, ubiquitination and SUMOylation of lysine residues, phosphorylation of serine residues and methylation of arginines.

A major influence on gene expression is attributed to the counterbalancing action of histone acetyltransferases (HATs) and histone deacetylases (HDACs).⁹ HATs acetylate histones by transfer of an acetyl group to the ϵ -portion of lysine residues, which results in an open modification of chromatin structure and in accessibility of DNA to the basal transcription initiation machinery. Conversely, gene repression is mediated via HDACs, which remove acetyl groups and counteract the activity of HATs resulting in a closed chromatin structure. Since HATs and HDACs regulate the expression of multiple genes, they most likely play an important role in the multifactorial processes that lead to atherosclerosis and restenosis. Furthermore, as epigenetic processes are reversible by nature, they are amendable to pharmacological intervention. Several HAT and HDAC inhibitors have been identified and especially HDAC inhibitors have already been shown to exhibit clinical activity against several human neoplasms¹⁰ and are interesting candidates for future therapy of cardiovascular diseases.

A possible role for HATs and HDACs in cardiovascular disease

Currently, there is no evidence linking these fundamental processes directly to cardiovascular disease. However, HATs and HDACs have been shown to regulate several processes that play a key role in the development of atherosclerosis and restenosis, such as inflammation, proliferation of smooth muscle cells (SMCs) and matrix formation.

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Figure 1. The figure illustrates the dual role of p300, CBP and PCAF in the activation of NFκB-mediated transcription upon cell stimulation with NFκB inducers, such as reactive oxygen species (ROS), TNFα or IL-1β. These coactivators act as histone acetyltransferases (HATs) at the site of NFκB-regulated genes. Furthermore, they appear to acetylate the p65 subunit of NFκB, increasing its DNA binding and also causing transcriptional activation by this mechanism.

HATs, such as p300, CBP (CREB binding protein) and PCAF (p300/CBP associated factor), have been implicated in the modulation of NFκB activity. They are required to coactivate p65-dependent transcription and have been shown to directly activate the transcription of several NFκB-regulated inflammatory genes known to be involved in cardiovascular disease, such as eotaxin, GM-CSF and TNFα (figure 1).¹¹ HDACs have been shown to reverse this process and to repress NFκB-mediated gene expression,^{12,13} leading to a decrease in inflammation.

Because HDACs also modulate histone acetylation levels at the site of genes involved in cell cycle control, they have also been implicated in the proliferation of smooth muscle cells (SMCs).^{14,15} This is illustrated by the observation that the HDAC-inhibitor TSA was found to inhibit SMC proliferation via induction of p21WAF1.¹⁶ Activity of p21WAF1 is known to induce cell-cycle arrest in vascular SMCs,¹⁷⁻²⁰ and A20, a NFκB-dependent gene that has been shown to inhibit proliferation of vascular SMCs via increased expression of p21WAF1, has been shown to prevent neointima formation after balloon angioplasty in a rat model of carotid artery stenosis.²¹

Histone acetylation modifications have also been shown to play a role in the expression of matrix metalloproteinases (MMPs), critical mediators in vascular remodelling. Cell stimulation with IFN-γ leads to downregulation of MMP9, which is exerted by CIITA through sequestering of CBP from the MMP9 promoter, effectively reducing histone H3

acetylation. Also, the metastases associated gene MTA1 represses MMP9 expression, in part by the recruitment of HDAC2 to the distal MMP9 promoter region.²² Further support for a role of epigenetic mechanisms in the regulation of MMP expression comes from the observation that the transcription factors Ets-1 and Ets-2 recruit p300 and CBP to the human stromelysin-1 (MMP3) promoter to activate transcription,²³ whereas the TEL (translocation-ETS-leukaemia) protein, which specifically associates with HDAC3, represses transcription of the stromelysin-1 gene.

Together there are several lines of evidence which suggest an important role of altered histone acetylation levels in inflammation, proliferation and remodelling, processes associated with the development of atherosclerosis and restenosis.

Genes encoding HATs and HDACs

Thus far, the main focus has been to investigate the environmental influence on epigenetic processes. Research in this field has shown that epigenetic differences arise during the lifetime of monozygotic twins.⁶ Monozygous twins were found to be epigenetically indistinguishable during the early years of life, while older twins exhibited remarkable differences in their overall histone acetylation. Furthermore, research in airway diseases has demonstrated that oxidative stress and cigarette smoke influence the balance between HATs and HDACs in favour of HATs, leading to an increase in inflammation.²⁴

We introduce the hypothesis that epigenetic processes are also under genetic control and that, besides the environment, genetic variation in genes encoding HATs and HDACs could also be an important determinant of susceptibility to cardiovascular diseases.

At our department, several of these genes are currently being investigated in relation to several aspects of cardiovascular disease, such as restenosis after PCI and incidence of / mortality due to myocardial infarction. Important candidates include PCAF, p300, CBP, HDAC2 and HDAC3.

A further understanding on the role of epigenetic processes in cardiovascular disease processes such as atherosclerosis and restenosis might provide novel opportunities to understand disease pathology. This would provide the necessary knowledge platform for design of alternative treatment strategies, which are aimed at interfering in these epigenetic processes for the management of atherosclerosis and restenosis. ■

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