AMANDA FOKS Leiden Academic Centre for Drug Research

Tim-proteins control early atherosclerosis

In an early stage of atherosclerosis, dead cells are removed from plaque and inflammation is suppressed. Amanda Foks identified two proteins that are essential for this process, but apparently are unable to function in advanced stages of the disease. Her research, conducted at Harvard University, was published last summer in *Arteriosclerosis, Thrombosis, and Vascular Biology.*

By Willy van Strien

Biopharmaceutical scientist AMANDA FOKS carried out her PhD research at Leiden University and then moved to Harvard University for a postdoctoral project. She returned, and now holds a fellowship from the Dutch Heart Foundation.

'Until now, no cure has been found for atherosclerosis, the main cause of cardiovascular disease,' Amanda Foks says. 'Lifestyle adaptations and the use of statins at best stabilise atherosclerotic plaques and prevent that they occlude arteries or cause an infarct after rupture. But there is still no therapy that induces regression of plaques.'

Still, such a therapy is conceivable. Atherosclerotic plaques consist of accumulated lipids and immune cells. Lipid-loaded immune cells – foam cells – undergo programmed cell death (apoptosis). In an early stage, these dead cells are quickly and neatly cleared by other immune cells while inflammation is kept at bay. But for some reason, this clearance of apoptotic cells stops in a more advanced stage of atherosclerosis. The dead cells then become necrotic and lose their contents, which triggers further inflammation and growth of the plaques.

Foks: 'This means that, if we find a way to restore the removal of dead foam cells, we may be able to stop progression and possibly even induce regression of atherosclerosis.'

To help develop such a therapy, she first wanted to unravel the process of clearance. She elucidated the role of two proteins which are present on the surface of immune cells that are involved in clearance. These proteins, tim-1 and tim-4, recognise the 'eat me' signal that apoptotic cells emit, she showed. They then induce the clearing cells to ingest these apoptotic cells and to regulate inflammation. When Foks blocked either tim-1 or tim-4 with antibodies, atherosclerotic plaques progressed. Atherosclerosis aggravated even more when she blocked both proteins simultaneously. 'The reason is that tim-1 and tim-4 occur on partly different subsets of immune cells,' she explains.

Now that she has shown that tim-1 and tim-4 play an essential role in the clearance of apoptotic cells, she aims to understand why these proteins no longer respond to the 'eat me' signal of apoptotic cells in advanced plaques. The next step will be to investigate how this response can be restored.