Blocking blood vessel buildup

By Tim Fulmer, Senior Writer

A study by Japanese and Austrian researchers published in *The Journal of Clinical Investigation* has uncovered a connection between the angiotensin II type 1 receptor and the lipoprotein receptor sortilin-related receptor, L(DLR class) A repeats-containing (LR11; SORL1) in vascular smooth muscle cells, suggesting that LR11 could be a better target for slowing or preventing vessel wall thickening and remodeling.[1] According to researchers and companies polled by *SciBX*, although these findings may have some implications for atherosclerotic disease, more immediate benefits of targeting LR11 may lie in conditions caused by aberrant migration and proliferation of vascular smooth muscle cells, such as restenosis.

Vascular smooth muscle cells (VSMCs) line the walls of blood vessels and are responsible for changing local blood pressure by contracting or relaxing in response to neural and hormonal signals. During vascular injury, VSMCs migrate from the outer layers of a blood vessel (the media) to the innermost layer (the intima), which makes direct contact with flowing blood. There, VSMCs can contribute to remodeling and thickening of the vessel wall and, over time, can cause narrowing of the vessel lumen and restriction of local circulation.[2,3]

Although angiotensin II type 1 receptor (AT_1R) blockers have been shown to slow progression of atherosclerotic lesions in animals,[4,5] the mechanism by which this occurs was unknown. There are at least two main culprits involved in prompting VSMCs to migrate—LR11[6,7] and

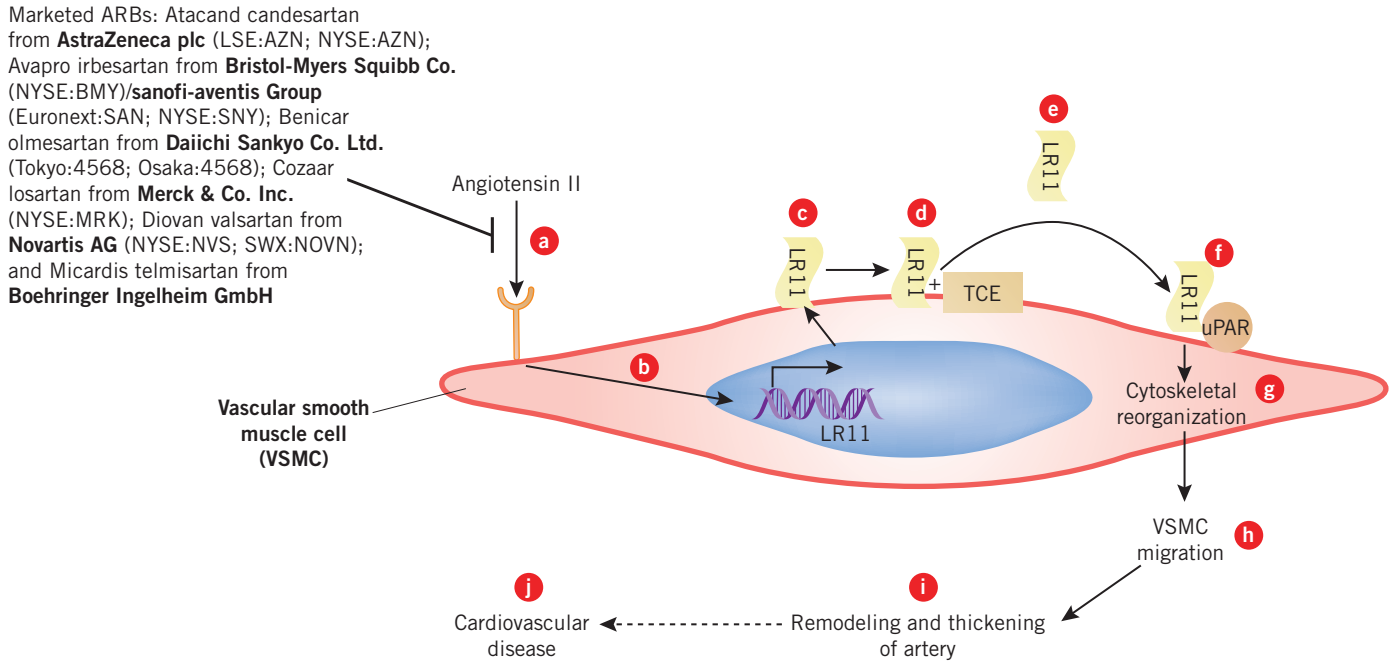

Figure 1. Blocking cell migration in cardiovascular disease. Japanese and German scientists have identified sortilin-related receptor, L(DLR class) A repeats-containing (LR11; SORL1), which might play a key role in mediating the effects of angiotensin II on vascular smooth muscle cells (VSMCs) in cardiovascular disease.

[**a**] Circulating angiotensin II binds and activates angiotensin II type 1 receptor, which activates downstream transcription of the *LR11* gene in VSMCs [**b**]. Following protein synthesis, LR11 is localized to the surface of VSMCs [**c**], where the protein is cleaved by tumor necrosis factor-α (TNF-α)-converting enzyme (TCE) [**d**] to become solubilized [**e**]. Soluble LR11 then binds to the urokinase-type plasminogen activator receptor (uPAR) on the surface of the same cell or on neighboring cells [**f**] to trigger cytoskeletal reorganization [**g**] and VSMC migration [**h**]. VSMC migration can lead to thickening of the arterial wall [**i**], which may contribute to cardiovascular disease [**j**].

Potential therapeutic interventions would include angiotensin receptor blockers (ARBs) as well compounds that antagonize LR11.

AT_1R—although any relation between the two targets had not been elucidated.

The *JCI* paper shows that angiotensin II–induced VSMC migration requires the presence of downstream LR11 (*see* **Figure 1, "Blocking cell migration in cardiovascular disease"**).[1] Cultured VSMCs isolated from the aortas of LR11 knockout mice showed lower rates of cell migration and attachment following angiotensin II treatment than VSMCs from mice expressing LR11.

"Stents that elute anti-LR11 antibodies or LR11 antisense compounds could have clinical value."
—Jorge Plutzky, Brigham and Women's Hospital

In mouse models of post-injury arterial thickening, the AT_1R blocker (ARB) Atacand candesartan significantly minimized intima thickness compared with that seen in untreated controls ($p<0.05$). However, overexpression of LR11 abolished sensitivity to Atacand, which is marketed by **AstraZeneca plc** to treat hypertension and heart failure.

LR11 knockout mice also had significantly lower femoral arterial intima thickness at four weeks than mice that expressed LR11 ($p<0.05$).

Finally, serum from 402 patients with dyslipidemia showed that circulating levels of LR11 were correlated with higher carotid intima-media thickness (IMT).

Hideaki Bujo, corresponding author on the *JCI* paper, written with colleagues at the **Medical University of Vienna**, and a researcher in the Department of Genome Research and Clinical Application in the Graduate School of Medicine at **Chiba University**, told *SciBX* that next steps include "analysis of circulating LR11 in subjects with various types of atherosclerotic disease."

Bujo said his group has recently established an ELISA system for the task. "We speculate that plasma concentrations of soluble LR11 could be a novel marker for conditions involving vascular smooth muscle cells and might also contribute to the diagnosis of atherosclerosis," he added.

To help establish the validity of LR11 as an atherosclerosis target, Mingyi Wang suggested reproducing the *JCI* findings in a variety of other preclinical models. These would include murine apolipoprotein E knockout models of atherosclerosis, nonhuman primates fed high-cholesterol diets and cultured human VSMCs, said Wang, who is a researcher in the Laboratory of Cardiovascular Science in the Gerontology Research Center at **NIH**'s **National Institute on Aging**.

Putting LR11 to rest(enosis)

Other researchers contacted by *SciBX* think establishing LR11 as a biomarker or target in atherosclerosis will be an uphill climb. The lower-hanging fruit, they said, would be in indications that specifically involve arterial thickening, such as restenosis.

Restenosis is reocclusion of a blood vessel that can occur following vascular surgery to remove a blockage.

"Acute coronary events and intima-media thickness are not necessarily correlated, and having linked LR11 to vascular cell migration, we cannot then simply conclude that LR11 is also associated with atherosclerosis," said Jorge Plutzky, director of the Vascular Disease Prevention Program at **Brigham and Women's Hospital**.

Andrew Plump, VP and integrator of the cardiovascular disease franchise at the Merck Research Laboratories unit of **Merck & Co. Inc.**, agreed. "Thickening of the arterial wall is best considered distinct from atherosclerosis," he said. "The former may be driven primarily by migration and hyperproliferation of VSMCs. However, the latter is typically a much more complex disease process that occurs over decades and involves plaque formation, plaque rupture, thromboembolism and, ultimately, cardiovascular events."

Plump said establishing LR11 as a biomarker in cardiovascular disease "will likely require correlating LR11 serum levels with the frequency of cardiovascular events such as myocardial infarction. This work could be done using patient cohorts with properly matched controls, and this would probably be a key next step toward establishing high serum LR11 as a risk marker for atherosclerosis."

Nevertheless, he added, "if additional work confirms that LR11 is at least associated with increased VSMC migration in the vessel wall, the protein could still serve as a biomarker for restenosis."

"In restenosis, targeting LR11 to slow or prevent VSMC migration would be a reasonable strategy," said Plutzky. "Thus, LR11 might be a more appealing target in restenosis than in atherosclerosis. In this regard, stents that elute anti-LR11 antibodies or LR11 antisense compounds could have clinical value."

Marketed coated stents include Taxus, a paclitaxel-eluting stent from **Boston Scientific Corp.**, and Cypher, a sirolimus-eluting stent from **Johnson & Johnson**. Taxus, and Boston Scientific's other coated stents, posted 2Q08 sales of $382 million. J&J's 2Q08 drug-eluting stent sales were $394 million.

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