Serum Heat Shock Protein 27 Levels Represent a Potential Therapeutic Target for Atherosclerosis

Observations From a Human Cohort and Treatment of Female Mice

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Objectives
The aim of this study was to evaluate the potential of serum heat shock protein 27 (HSP27) as a therapeutic target in coronary artery disease.

Background
Expression of HSP27 in human coronary arteries diminishes with the progression of atherosclerosis, whereas ubiquitous HSP27 overexpression in apolipoprotein E−/− (ApoE−/−) mice attenuates atherogenesis. However, it remains unclear whether increasing serum HSP27 levels alone is sufficient for atheroprotection.

Methods
Low- and intermediate-risk patients undergoing coronary or computed tomography angiography had serum HSP27 levels measured. Elevated serum HSP27 levels in female atheroprone ApoE−/− mice were achieved by transplantation with HSP27 overexpressing bone marrow or by administering recombinant HSP27.

Results
Patients with >50% stenosis in any major epicardial artery had lower HSP27 levels compared with those free of atherosclerosis (median [interquartile range]: 2.176 pg/ml [551–5,475] vs. 6,200 pg/ml [2,575–9,560]; p < 0.001). After a 5-year period of clinical follow-up, low serum HSP27 levels (<50th percentile) were predictive of subsequent major adverse cardiovascular events (hazard ratio: 2.93, 95% confidence interval: 1.06 to 8.12; p = 0.04). In experimental murine models of atherosclerosis, increasing serum HSP27 levels both reduced de novo atherosclerotic lesion formation and enhanced features of plaque stability.

Conclusions
In humans, low serum HSP27 levels are associated with the presence of coronary artery disease and prognostic of future adverse clinical events. In mouse models of atherosclerosis, increasing HSP27 levels reduced lesion progression and promoted features of plaque stability. Serum HSP27 levels may represent a potential therapeutic target for atherosclerosis. (J Am Coll Cardiol 2013;62:1446–54) © 2013 by the American College of Cardiology Foundation

Atherosclerosis is a complex inflammatory disease process that is the major underlying cause of coronary artery disease (CAD) (1). We initially identified heat shock protein 27 (HSP27), a member of the small HSP family, as a protein with an expression pattern in human coronary arteries that inversely correlates with plaque burden (2,3). Although HSPs were traditionally considered intracellular chaperone proteins, many, including HSP27, are now recognized to...
have functional roles in the extracellular space (4,5). HSP27 is known to be a cytoprotective, antiapoptotic (6), and anti-inflammatory protein (5,7,8).

Ubiquitous overexpression of HSP27 in atherosclerosis-prone apolipoprotein (A) E−/− mice reduced aortic plaque burden in female, but not male, mice (9). The extent of atheroprotection in these female mice was related to elevated serum HSP27 levels that required intact ovarian function or exogenous estrogenic hormone replacement therapy (9–11). In humans, reduced levels of HSP27 have been recovered from the secretome of atherosclerotic carotid endarterectomy samples compared with control specimens; furthermore, HSP27 release from complicated plaques is reduced compared with release from noncomplicated plaques (12). Finally, although it has been reported in a small cohort that serum HSP27 levels are reduced in patients with carotid atherosclerosis (12) and increased in those with acute coronary syndromes (13), it remains unclear whether these levels correlate with the angiographic presence of CAD or are indicative of future events. Moreover, it is unclear whether increasing serum HSP27 levels have therapeutic potential or whether HSP27, like C-reactive protein (14) and homocysteine (15), is simply a biomarker.

In the current study, we explored whether serum HSP27 levels are lower in patients with CAD compared with healthy controls and whether these levels hold prognostic significance. We assessed whether increasing serum HSP27 is a potential therapeutic target by treating female ApoE−/− mice with HSP27 overexpressing bone marrow or recombinant HSP27 (rHSP27) and subsequently evaluated de novo atherosclerotic lesion formation. Finally, we examined whether rHSP27 treatment can attenuate lesion progression and enhance lesion remodeling.

Methods

For full details of the methods, please see the Online Appendix.

Results

Serum HSP27 levels are lower in patients with CAD and are predictive of future adverse cardiovascular events. To establish whether serum HSP27 levels are lower in patients with CAD, we prospectively enrolled 129 individuals presenting for assessment for CAD from July 2006 to February 2008. Baseline patient characteristics are outlined in Table 1 and in Online Tables I and II. Low- and intermediate-risk patients underwent coronary evaluation by invasive angiography or computed tomography, and baseline serum HSP27 levels were quantified by enzyme-linked immunosorben assay. Patients with >50% stenosis in any major epicardial artery had lower HSP27 levels compared with those free of atherosclerosis (median [interquartile range (IQR]): 2,176 pg/ml [551 to 5,475] vs. 6,200 pg/ml [2,575 to 9,560]; p < 0.001) (Fig. 1A). Consistent with previous murine studies (9–11), females had higher HSP27 levels than males (median [IQR]: 6,175 pg/ml [747 to 9,800] vs. 2,779 pg/ml [1,130 to 5,793]; p = 0.049) (Fig. 1B), although in CAD patients, HSP27 levels were markedly lower in both sexes (p = 0.02 for females; p < 0.01 for males). To determine whether serum HSP27 levels are predictive of future cardiovascular events, patients were followed for subsequent myocardial infarction, stroke, or death (major adverse cardiovascular events [MACE]). Overall, the time to event ranged from 24 to 1,852 days of follow-up, with the median being 828 days (IQR: 356 to 1,092 days). Patients in the lower 50th percentile of serum HSP27 levels had a markedly higher risk of MACE (hazard ratio: 2.93; 95% confidence interval: 1.06 to 8.12; p = 0.04) (Fig. 1C). As well, within the cohort of patients with CAD at baseline, patients in the lower 50th percentile of serum HSP27 levels showed a strong trend toward a higher risk of MACE (hazard ratio: 3.08; 95% confidence interval: 0.99 to 9.52; p = 0.05) (Fig. 1D). Thus, in humans, lower serum HSP27 levels are not only associated with the presence of disease but also are prognostic of future adverse clinical events.

Blood-borne HSP27 is sufficient for atheroprotection. Previously we demonstrated that the ubiquitous overexpression of HSP27 in female ApoE−/− mice, which do not have the gene HSPB1, which encodes for HSP27, was protective against the development of atherosclerosis (9). The atheroprotective effects appeared to be related to elevated serum HSP27 levels.

Table 1  Baseline Characteristics of the Total Cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HSP27 &lt; 3,503 pg/ml (n = 65)</th>
<th>HSP27 &gt; 3,503 pg/ml (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62.0 ± 12.4</td>
<td>59.3 ± 11.6</td>
</tr>
<tr>
<td>Males</td>
<td>42 (64.6)</td>
<td>34 (53.1)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>33 (50.8)</td>
<td>23 (35.9)</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>20 (30.8)</td>
<td>16 (25.0)</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>36 (55.4)</td>
<td>27 (42.2)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (29.2)</td>
<td>14 (21.9)</td>
</tr>
<tr>
<td>Lipid profile, mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.0 ± 1.1</td>
<td>4.8 ± 1.3</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>2.3 ± 0.9</td>
<td>2.8 ± 1.0</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (8.7)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (18.5)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). *Patients had a clinical diagnosis by a treating physician. HDL = high-density lipoprotein; LDL = low-density lipoprotein.
that required intact ovarian function or exogenous estrogenic hormones (10,11). However, it remained unclear whether serum or vascular tissue HSP27 levels were responsible for atheroprotection. Because we previously demonstrated the secretion of HSP27 from macrophages (9,10), we sought to determine whether nonvascular sources of increased serum HSP27 would protect against atherosclerosis. Bone marrow from 10-week-old female ApoE<sup>C0</sup>/C0/C0/HSP27<sup{o/e}</sup> mice was transplanted into 10-week-old female ApoE<sup>C0</sup>/C0/C0/littermates, which do not have the gene HSPB1, which encodes for HSP27. The effect on atherogenesis was compared with that in a control group in which 10-week-old female ApoE<sup>C0</sup>/C0/C0 bone marrow was transplanted into 10-week-old female ApoE<sup>C0</sup>/C0/C0/littermates (Fig. 2A). Mice were allowed to recover from the transplantation for 6 weeks before being fed an atherogenic diet (high-fat diet [HFD]: 15.8% fat and 1.25% cholesterol) for 4 weeks. No significant differences were found in the mean body weights of the 2 transplant groups (data not shown). As expected, serum HSP27 levels were undetectable in the control group (ApoE<sup>C0</sup>/C0/C0 bone marrow recipients, n = 10) (Fig. 2B). In contrast, transplantation of bone marrow from ApoE<sup>C0</sup>/C0/C0/HSP27<sup{o/e}</sup> mice (n = 8) resulted in serum HSP27 levels of 588 ± 203 pg/ml (Fig. 2B). Despite no obvious differences in total serum cholesterol levels between the 2 groups (p = 0.219) (Fig. 2C), mice receiving ApoE<sup>C0</sup>/C0/HSP27<sup{o/e}</sup> bone marrow showed reductions in aortic lesion burden in both en face (50%; p = 0.002) (Fig. 2D) and aortic sinus lesions (28%; p = 0.002) (Figs. 2E and 2F). In addition to decreased aortic lesion burden in the ApoE<sup>C0</sup>/C0/HSP27<sup{o/e}</sup> transplant recipients, the area occupied by cholesterol clefts and the necrotic core area were decreased, without differences in lesion macrophage area (p = 0.457) (Figs. 2E and 2F). Finally, there was a 59% decrease in the terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling assay–positive intimal cell area in mice that received ApoE<sup>C0</sup>/C0/HSP27<sup{o/e}</sup> bone marrow compared with the ApoE<sup>C0</sup>/C0 controls (p = 0.007) (Figs. 2G and 2H). Thus, increasing serum HSP27 through overexpression from nonvascular tissues is sufficient to attenuate de novo atherosclerotic lesion formation in atheroprone mice, suggesting a potential therapeutic benefit.

Therapeutic administration of rHSP27 attenuates the progression of atherogenesis. Recent studies have highlighted the importance of differentiating genuine therapeutic targets from biomarkers of disease (14,15). Given the observation in humans that CAD is associated with low serum HSP27 levels and the atheroprotection afforded by increasing serum HSP27 levels in overexpressing models (9), we synthesized rHSP27 to explore its potential therapeutic effects in de novo lesion formation. Seven-week-old female ApoE<sup>C0</sup>/C0 mice were randomized to receive subcutaneous injections of either rHSP27 (100 μg) or vehicle (phosphate-buffered saline [PBS]) twice daily while being maintained on an atherogenic diet (HFD: 15.8% fat and 1.25% cholesterol), for 3 weeks (Fig. 3A). Serum HSP27 levels were detectable by enzyme–linked immunosorbent assay after the subcutaneous injection, with a peak serum
Figure 2  Blood-borne HSP27 Is Sufficient for Atheroprotection

(A) Experimental overview: 10-week-old female apolipoprotein (Apo) E−/− mice were lethally irradiated and transplanted with bone marrow cells from ApoE−/−/HSP27o/e or ApoE−/− littermates and allowed to recover for 6 weeks. Mice were then placed on an atherogenic diet (high-fat diet, 15.8% fat and 1.25% cholesterol) for 4 weeks to accelerate atherosclerosis.

(B) End-of-study serum heat shock protein 27 (HSP27) levels. HSP27 is present in the serum of mice receiving ApoE−/−/HSP27o/e bone marrow but not ApoE−/− bone marrow.

(C) No difference in total serum cholesterol was observed between the groups at the end of the study (p = 0.2).

(D) Expression of HSP27 by bone marrow–derived hematopoietic cells reduces en face atherosclerotic lesion size in ApoE−/− mice. Quantification of lesion area/total aortic arch area revealed a 50% reduction in lesion burden in ApoE−/− mice receiving ApoE−/−/HSP27o/e bone marrow (p = 0.002).

(E, F) Expression of HSP27 by bone marrow–derived cells reduces lesion size in the aortic sinus of ApoE−/− mice. Quantification of aortic sinus lesion area revealed a 28% reduction in lesion burden in ApoE−/− mice receiving ApoE−/−/HSP27o/e bone marrow (p = 0.002). Transplantation of ApoE−/−/HSP27o/e bone marrow reduced the cholesterol cleft area of aortic sinus lesions by 23% relative to mice receiving the ApoE−/− bone marrow (p = 0.002).

(G, H) Expression of HSP27 by bone marrow–derived cells reduces the terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) assay–positive area within aortic sinus lesions of ApoE−/− mice. Quantification of aortic sinus TUNEL-positive cell area revealed a 59% reduction in apoptosis in ApoE−/− mice receiving ApoE−/−/HSP27o/e bone marrow (p = 0.007).
concentration of 219 ng/ml (± 62 SEM) after 80 min (Online Fig. 1). As expected, serum HSP27 levels in the vehicle control group (PBS injection) were not detectable (data not shown), as ApoE−/− mice do not endogenously express HSP27. Body weight remained stable and similar between groups (data not shown). Treatment with rHSP27 reduced total aortic lesion area by 31% and 40% for the en face and the sinus tissue preparations, respectively (p = 0.003 and p = 0.002) (Figs. 3B and 3C). Interestingly, total serum cholesterol levels were 42% lower with rHSP27 treatment (p < 0.001) due to reductions in very-low-density lipoprotein and intermediate-IDL/low-density subfractions (Figs. 3D and 3E).

Therapeutic administration of rHSP27 promotes morphological features of plaque stability in the setting of established atherosclerosis. Clinical therapies are routinely initiated in patients with established disease after events such as myocardial infarction and stroke. Thus, we tested the ability of rHSP27 to modulate the progression and morphology of established atherosclerotic lesions. ApoE−/− mice maintained on an atherogenic diet (HFD: 15.8% fat and 1.25% cholesterol) to accelerate atherosclerosis for 4 weeks (designated as the baseline atherosclerotic state) were switched to a normal chow diet to simulate lipid management strategies such as lifestyle modifications and/or clinical interventions such as statin therapy. They then began subcutaneous injections of either rHSP27 (100 μg) or PBS twice daily for 3 weeks (Fig. 4A). Total serum cholesterol levels were similar in both groups at baseline (PBS: 1,675 ± 122 mg/dl vs. rHSP27: 1,706 ± 103 mg/dl). Levels decreased 5- and 7-fold after a switch to chow diet in the vehicle and therapy arms, respectively, yet were 27% lower with rHSP27 treatment at the time of euthanasia (PBS: 335 ± 18 mg/dl vs. rHSP27: 243 ± 17 mg/dl; p = 0.004) (Fig. 4B).

Aortic lesion area was reduced by 20% and 24% on en face and sinus cross-sectional analyses in rHSP27- vs. PBS-treated mice (p = 0.008 and p = 0.001; respectively) (Figs. 4C and 4D) and comparable to baseline (p = 0.21). Moreover, compared with PBS-treated mice, the intimal plaque areas of mice receiving rHSP27 treatment had fewer macrophages (reflected by anti-Mac-2 immunolabeling), less free cholesterol accumulation (reflected by filipin staining), and less area occupied by cholesterol clefts (Fig. 4E). Of note, the role of cholesterol crystals in plaque inflammation was...
levels of HSP27 were increased either by expression from indicating that HSP27 may act as both a biomarker and correlate with disease severity or ongoing atherogenesis, thus the study design between the WHS and the current study. Important differences in both the populations examined and that patients with lower serum HSP27 had a markedly correlate with more advanced disease. Moreover, we found demonstrating that, similar to mouse studies, lower levels expression of HSP27 in female mice reduces aortic plaque development of de novo atherosclerotic lesions and ubiquitous over- HSP27 expression is diminished in advanced human coronary artery atherosclerotic lesions, and ubiquitous over- expression of HSP27 in female mice reduces aortic plaque burden to a degree that is proportional to the increase in serum HSP27 levels (3,9–11). However, it remained unclear whether human serum HSP27 levels correlated with disease presence. In the current study, we identified a strong relationship between serum HSP27 levels and CAD in humans, demonstrating that, similar to mouse studies, lower levels correlate with more advanced disease. Moreover, we found that patients with lower serum HSP27 had a markedly higher risk of MACE—suggesting that low HSP27 levels correlate with disease severity or ongoing atherogenesis, thus indicating that HSP27 may act as both a biomarker and potential therapeutic target. To test this hypothesis we used 2 distinct mouse atherosclerosis models in which serum levels of HSP27 were increased either by expression from bone marrow–derived cells or exogenous administration. In both models, increasing serum HSP27 levels attenuated the development of de novo atherosclerotic lesions and shifted plaques to a more stable morphology.

Few studies have delineated the relationship between HSP27 and atherosclerosis in humans. Martin-Ventura et al. (12,18) demonstrated in a small atherosclerotic group (n = 28) that the secretion of HSP27 from the vascular wall diminishes as plaque complexity increases, and serum HSP27 levels are lower than those found in healthy controls (n = 12). Yet, the same group noted no relationship between serum HSP27 levels and the development of ischemic myocardial or cerebrovascular complications in a prospective case–control study of apparently healthy middle-age women from the WHS (Women’s Health Study) (19). However, there are important differences in both the populations examined and the study design between the WHS and the current study. First, the WHS identified participants based on the occurrence of cardiovascular events (approximately half of which were strokes) and controls as individuals free of these events. In contrast, the current study used an angiographic definition for the absence of coronary disease, removing the potential for undiagnosed controls contaminating results.

Moreover, the prognostic significance of lower serum HSP27 levels within the cohort further validates our findings, suggesting that a dose response to serum HSP27 levels can be identified in the natural history of CAD. Second, we did not limit our study to women. Given the role that estrogen and ovarian function plays in the extracellular release of HSP27 (9,10), sex differences in these studies may be important. This is an issue that we aim to address in future studies with larger patient cohorts.

Although the potential prognostic value of serum HSP27 levels in humans may be clinically relevant, it does not address whether increasing HSP27 levels is sufficient to prevent or stabilize atherosclerosis. Earlier studies (9) and the current human data suggest a potential vascular benefit to increasing serum HSP27 levels; thus, we used 2 distinct experimental mouse models in which serum HSP27 levels were increased by endogenous nonvascular expression or by exogenous administration of rHSP27 to determine the effect of increasing serum HSP27 on atherogenesis.

Transplantation of HSP27-overexpressing bone marrow (ApoE<sup>−/−</sup>HSP27<sup>o/e</sup>) to ApoE<sup>−/−</sup> mice increased serum HSP27 levels as well as reduced the burden of atherosclerosis when mice were fed an atherogenic diet for 4 weeks. The aortic lesions in mice that were recipients of ApoE<sup>−/−</sup>HSP27<sup>o/e</sup> bone marrow had fewer apoptotic intimal cells, less area occupied by cholesterol clefts, and smaller necrotic cores, despite no changes in total serum cholesterol. Given that atheroprotective effects independent of changes in lipid levels have been documented in the experimental atherosclerosis literature (20,21), it may be the case that in this model, HSP27 has atheroprotective effects that are independent of changes in total serum cholesterol.

In our second model, we synthesized rHSP27 to determine whether achieving higher serum levels by exogenous administration would be sufficient for atheroprotection. In these studies, we observed that injection of rHSP27 twice daily increased serum HSP27 levels while similarly reducing the progression of atherosclerosis when mice were fed an atherogenic diet for 3 weeks, thus confirming that increasing serum HSP27 levels alone could exert therapeutic effects.

Finally, as clinical therapies to prevent atherogenesis are typically reserved for adult patients in whom atherosclerotic disease is already present, we tested the ability of rHSP27 to modulate the progression of established atherosclerotic lesions (achieved by feeding mice an atherogenic diet for 4 weeks). Our results indicate that not only could rHSP27 administrations attenuate the further progression of lesions in female ApoE<sup>−/−</sup> mice, but also that it decreased the area occupied by cholesterol clefts, free cholesterol, and macrophages. These observations are important because cholesterol crystals have been implicated in plaque inflammation through activation of the inflammasome and subsequent IL-1β production (16). Similarly, we previously demonstrated that extracellular HSP27 reduced the acetylated low-density lipoprotein–induced increase in IL-1β secretion from macrophages (9), suggesting that HSP27 therapy may have the capacity to dampen vascular inflammation.

**Study limitations.** It is important to note that our study is not without limitations. First, although human studies provide
compelling evidence that links HSP27 levels to CAD and prognosis, the current cohort is too small to fully adjust for known confounding variables and thus precludes a robust assessment of serum HSP27 as a biomarker. Nonetheless, this represents the largest and most thorough evaluation of serum HSP27 to date providing long-term follow-up on patients with angiographically confirmed disease. Larger ongoing studies will address the performance of serum HSP27 as a biomarker.

Second, there is evidence that in certain types of cancer, the inhibition of HSP27 may be a desirable therapeutic target (22). However, this dichotomous nature of HSP27’s role in cancer versus cardiovascular disease is analogous to one in which the goal in a cancer setting is to reduce tumor neovessels that contribute to metastatic spread of a cancer using antivascular endothelial growth factor strategies (23), whereas pro–vascular endothelial growth factor strategies have been used to enhance neovessels in the setting of atherosclerotic cardiovascular disease (24). Likewise, although the high expression of HSP27 in cancer is thought to be deleterious and therapies aim to inhibit HSP27 expression (25), the high expression of HSP27 is thought to be beneficial in neurodegenerative disease (26) and cardiac ischemia (27).
Third, there are important potential limitations for translational development (i.e., long-term rHSP27 could induce an immune response leading to adverse reactions to the therapy or attenuated activity). However, in our extensive animal studies to date, we have not observed any such consequences.

Fourth, although the current data provide proof-of-concept validation of serum HSP27 levels as a therapeutic target, we are still working out the details as to how HSP27 reduces atherosclerotic burden. Finally, accelerated models of atherogenesis such as those used in the current studies may not fully represent the human condition.

However, we do note that overexpression of HSP27 in ApoE−/− mice fed normal chow for 32 weeks also lowers serum cholesterol levels and atherosclerotic burden (Online Fig. 2). To our knowledge, we are the first to describe the phenomenon that HSP27 lowers serum cholesterol levels and are pursuing several hypotheses that could help to elucidate the putative mechanism(s) underlying these observations. We know that rHSP27 is able to stimulate signal transduction pathways in macrophages (8); hence, there is the possibility that HSP27 could affect key enzymes involved in lipid metabolism. For example, rHSP27 can induce the expression and secretion of granulocyte-macrophage colony-stimulating factor from macrophages (8) and granulocyte-macrophage cerebrospinal fluid can lower serum cholesterol levels in humans and rabbits (28–33). Alternatively, HSP27 may alter cholesterol levels by binding to lipid moieties and, via its chaperone
characteristics, alter the trafficking of cholesterol, resulting in increased clearance.

Conclusions

Our study is the first prospective human cohort study to establish a link between advanced atherosclerotic disease, serum HSP27 levels, and prognosis of adverse vascular events. We successfully demonstrated that elevation of serum HSP27 by either endogenous expression from nonvascular tissue or therapeutic administration is sufficient to prevent de novo lesion formation and stabilize developed atherosclerotic lesions. The current study serves as a proof-of-concept that serum HSP27 may be a bona fide therapeutic target for CAD.

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REFERENCES


Key Words: atherosclerosis · coronary disease · heat shock protein.

APPENDIX

For a supplemental Methods section, tables, and figures, please see the online version of the article.