Role of a p53 polymorphism in luminal narrowing after balloon coronary angioplasty

Dear Editors,

p53 is a tumour suppressor protein involved in the control of cell proliferation. Apart from mutant alleles of p53 frequently found in tumour cells, a common polymorphism of p53, either arginine (Arg) or proline (Pro) at amino acid residue 72, has been reported to be associated with the development of human papillomavirus-associated cancer [1]. Storey et al. reported that women who were homozygous for Arg72 were about seven times more susceptible to development of cervical cancer than those who were heterozygous. The effects of this polymorphism on p53 function seem to be related to susceptibility to E6 oncoprotein-mediated degradation of p53, and the arginine form of p53 was reported to be more susceptible to degradation than the proline form [1].

p53 also plays an important role in regulating the growth of vascular smooth muscle cells (VSMC). Loss of p53 activity results in growth of VSMC, while increased levels of p53 result in apoptosis of VSMC [2]. Human cytomegalovirus (HCMV) infection has been reported to predispose to coronary restenosis and atherosclerosis, possibly because HCMV IE84 protein binds to p53 and abolishes its activity [3]. Based on the hypothesis that Arg72Pro polymorphism of p53 may affect its activity in restenotic lesions where various infectious agents, such as HCMV, have been reported to be detected, we investigated whether this polymorphism affects the incidence of luminal narrowing after balloon coronary angioplasty.

The study population consisted of 66 consecutive subjects who underwent successful primary balloon angioplasty on 102 coronary segments. Using an automated edge-detection algorithm and the outer diameter of contrast-filled catheters for calibration, the reference lumen diameter and the minimal lumen diameter (MLD) were measured on the same view before, immediately after and 3 months after balloon coronary angioplasty. The results showed that the Arg72Arg genotype of p53 was associated with MLD 3 months after angioplasty (Table 1). There were no significant differences observed among three genotype groups in terms of other clinical factors. Stepwise multiple regression analyses, which included the p53 genotype, the reference lumen diameter, MLD before angioplasty, MLD immediately after angioplasty, age, gender, smoking history, diabetes mellitus, hypertension, body mass index, total cholesterol, high-density lipoprotein cholesterol and triglycerides as independent variables, indicated that MLD 3 months after angioplasty was determined ($P = 0.0001$, $R^2 = 0.365$) by the genotype of p53 (Arg/Arg = 0, Arg/Pro + Pro/Pro = 1) ($P = 0.0027$), MLD immediately after angioplasty ($P = 0.0025$), the reference lumen diameter ($P = 0.0066$), and body mass index ($P = 0.0025$).

The precise mechanism of the effects of this polymorphism on coronary artery narrowing is currently unknown. The Arg72Pro polymorphism of p53 might affect binding activity of IE2-84 of HCMV, which is frequently detected at restenotic lesions. However, the C terminal region of p53 (amino acid residue 339–363) has been reported to be involved in the IE2–p53 interaction [4]. A growing number of investigations have demonstrated that multiple infectious pathogens have

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Arg/Arga</th>
<th>Arg/Prob</th>
<th>Pro/Proc</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference lumen</td>
<td>2.48 ± 0.62</td>
<td>2.43 ± 0.67</td>
<td>2.35 ± 0.66</td>
<td>NSd</td>
</tr>
<tr>
<td>diameter (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal lumen</td>
<td>0.44 ± 0.38</td>
<td>0.39 ± 0.29</td>
<td>0.44 ± 0.31</td>
<td>NS</td>
</tr>
<tr>
<td>diameter (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before angioplasty</td>
<td>1.77 ± 0.46</td>
<td>1.94 ± 0.48</td>
<td>1.69 ± 0.51</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up (3 months)</td>
<td>0.95 ± 0.63</td>
<td>1.43 ± 0.70</td>
<td>1.24 ± 0.81</td>
<td>0.006</td>
</tr>
</tbody>
</table>

a Forty-two coronary segments in 27 subjects.
b Forty-five coronary segments in 32 subjects.
c Fifteen coronary segments in 7 subjects.
d NS, Not significant.

0021-9150/00/$ - see front matter © 2000 Elsevier Science Ireland Ltd. All rights reserved.
PII: S0021-9150(00)00452-4
been associated with atherosclerosis, suggesting that many atherogenic pathogens exist [5]. Therefore, it is possible that the Arg72Pro polymorphism of p53 may be associated with its activity at the lesion sites through interaction with unidentified infectious pathogens.

Although our present observation needs to be reconfirmed in larger study populations, it provides not only diagnostic value, but also a future target for therapy to prevent restenosis after coronary intervention.

References


Sunao Kojima,
Yoichi Goto,
Hiroshi Nonogi
Department of Medicine,
National Cardiovascular Center,
Osaka,
Japan

Hajime Horie,
Masahiko Kinoshita
Shiga University of Medical Science,
Otsu,
Japan

Naoharu Iwai
Research Institute, National Cardiovascular Center,
Osaka,
Japan

E-mail: niwai@res.ncvc.go.jp