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P27 and P53 Gene Polymorphisms and Restenosis following Coronary Implantation of Drug-Eluting Stents

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Key Words
P27 · P53 · Polymorphism · Drug-eluting stent · Restenosis

Abstract
Objective: Drug-eluting stents (DES) have reduced restenosis rates compared with bare-metal stents. P27 and P53 play important roles in the signal transduction leading to neointimal growth inhibition and induction of apoptosis of smooth muscle cells due to rapamycin and paclitaxel. We hypothesized that genetic variants of P27 and P53 influence the development of restenosis and the clinical outcome of patients receiving DES. ***Methods:*** Polymorphisms in the genes encoding for P27 and P53 were tested for their association with restenosis and major adverse cardiac events. P27 C-79T and P53 G72C polymorphism genotypes were determined in a series of 433 consecutive patients receiving DES. Follow-up angiography after 6 months was performed in 87% of the patients. Genotyping was performed with PCR-based methods. ***Results:*** For patients with the respective P27 C-79T and P53 G72C genotypes, the angiographic restenosis rates were between 5.0 and 22.0%, and the clinical restenosis rates were between 0.0 and 16.3%, without significant differences for the studied genotypes ($p > 0.19$). There was no association of the studied genotypes with the 1-year incidences of death and myocardial infarction. ***Conclusion:*** This study could not demonstrate a clinically relevant role of P27 and P53 polymorphisms in the processes leading to in-stent restenosis.

Introduction

Drug-eluting stents (DES) have revolutionized the treatment of coronary artery disease (CAD), reducing restenosis rates and the necessity of repeat target lesion revascularization compared with bare-metal stents [1–3]. Higher restenosis rates were observed even with DES for certain subsets of patients, including patients with restenotic and complex lesions, with long lesions and small vessels, and for diabetic patients [4–6]. In contrast, in certain populations, especially in Asian patients, restenosis rates were lower even for complex lesions [7, 8]. Studies from our institute showed a bimodal distribution for restenosis and a higher incidence in subsequent vessels for patients with previous restenosis, suggesting that genetic factors predispose certain patients for the development of restenosis [9, 10].

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Sirolimus and paclitaxel share signaling pathways, resulting in an inhibitory effect on the cell cycle with subsequent reduced neointimal formation [11–15]. Genetic variants found in genes of proteins in these signaling pathways may influence the disposition of certain patients for restenosis after DES implantation.

Sirolimus, or rapamycin, is a macrolide lactone with profound antiproliferative and anti-inflammatory effects. It binds to the mammalian target of rapamycin receptor and inhibits the cell cycle progression by influencing P27 and P53, leading to cell cycle arrest and apoptosis [11, 12]. Paclitaxel interferes with the microtubule disassembly in the G2/M mitotic interphase, but also influences the cell cycle progression through common pathways with rapamycin, including upregulation of P27 and P53 [13–15].

P27 (CDKN1B) belongs to the Cip/Kip family and functions as an important cell cycle gatekeeper and tumor suppressor gene [16]. P27 is located in the chromosomal region 12p12.3 [17]. P27 knockout mice exhibit gigantism, due to increased cell proliferation, and increased incidence of tumors, demonstrating the critical role of P27 in the suppression of cell proliferation and induction of apoptosis [18–20]. Sequencing data from 96 hereditary prostate cancer patients and association studies from 188 hereditary prostate cancer families revealed a highly significant association between the single-nucleotide polymorphism C-79T and prostate cancer ($p = 0.0005$) [21]. The C-79T single-nucleotide polymorphism is located in the 5′-regulatory CpG island, eliminating 1 CpG site. CpG sites are important for the promoter regulation, influencing the transcriptional activity [17, 21].

P53 is located in the chromosomal region 17p13.1 and plays an important role in the cell cycle regulation inhibiting cell proliferation and carcinogenesis. P53 mutations were associated with the development of multiple cancer types [22, 23]. The G72C single nucleotide polymorphism is located in the apoptosis-inducing region of the protein, and substitution of the G with a C nucleotide leads to an amino acid exchange from arginine to proline. The arginine variant of P53 induces apoptosis more efficiently through better binding of P53 to the mitochondria and subsequent release of cytochrome c from the mitochondria into the cytosol [24].

Our study is based on functional data from genetic analyses of populations with restenosis from our institute, data from cell culture experiments and animal models, and data from previous clinical association studies [10, 16, 18, 19, 21–25]. We hypothesized a positive association of the TT genotype of the P27 C-79T polymorphism and of the 72Pro variant (CC genotype) of the P53 polymorphism with a higher incidence of angiographic restenosis and major adverse cardiac events like death, myocardial infarction (MI) and target vessel revascularization in patients treated with Cypher or Taxus DES [4, 5].

Methods

Patients

The significance of the studied polymorphisms was evaluated in a cohort study that comprised 433 Caucasian patients with symptomatic CAD who underwent coronary angiography and Cypher or Taxus DES implantation at Deutsches Herzzentrum München and at 1. Medizinische Klinik rechts der Isar, Technische Universität München. Coronary stent implantation was performed as previously described [4, 5, 25]. Of the 200 patients treated for bare-metal stent restenosis in the ISAR DESIRE study, and of 250 patients with diabetes mellitus treated for de novo lesions in the ISAR DIABETES study, 225 patients were randomized to the treatment with Cypher stents and 225 patients to the treatment with Taxus stents [4, 5]. Blood was available for 433 of the 450 patients. All patients received a loading dose of 600 mg clopidogrel at least 2 h before the procedure. Postprocedural therapy consisted of aspirin (100 mg twice daily, indefinitely) and clopidogrel (75 mg once daily for at least 6 months). Follow-up angiography was routinely scheduled at 6 months after stenting or whenever the patient complained of anginal symptoms and was available for 378 (87.3%) patients. Creatine kinase levels and electrocardiographic changes were assessed systematically over 48 h after the procedure. Clinical events were monitored throughout a 1-year period following the intervention. The data regarding cardiovascular risk factors were obtained during the actual hospitalization or from the patient's chart. Exclusion criteria included acute ST segment elevation myocardial infarction, a target lesion in the left main trunk, any contraindication to the use of aspirin, heparin or clopidogrel, and lack of consent to participate in the study. The local ethics committee approved the study, and written informed consent was obtained from all patients for the procedure, the randomization to the Cypher and Taxus treatment options, and for the genetic analysis.

Definitions

The diagnosis of MI was based on the presence of new pathological Q waves or a value of creatine kinase or its MB isoenzyme at least 3 times the upper limit. Diabetes mellitus was defined in the presence of active treatment with insulin or an oral anti-diabetic agent; for patients on dietary treatment, documentation of an abnormal fasting blood glucose or glucose tolerance test based on the criteria of the World Health Organization Study Group for Diabetes Mellitus was required for establishing this diagnosis. Angiographic restenosis was defined as 'in-segment' restenosis, and the analysis included the proximal and distal 5-mm edges.

Genotyping

Genomic DNA was extracted from 200 μl of peripheral blood using commercially available kits (Qiagen, Hilden and Roche Molecular Biochemicals, Mannheim, Germany). Genotype analyses

Table 1. Baseline patient characteristics according to the genotypes of the P27 and P53 polymorphisms (n = 433)

	P27 C-79T				P53 G72C			
	CC (n = 269)	CT (n = 146)	TT (n = 18)	p value	GG (n = 212)	GC (n = 172)	CC (n = 49)	p value
Age, years	66.3 ± 10.0	65.6 ± 11.0	69.9 ± 9.5	0.226	66.6 ± 9.7	65.9 ± 10.4	65.9 ± 10.5	0.791
Women	65 (24.2)	37 (25.3)	3 (16.7)	0.719	53 (25.0)	38 (22.1)	14 (28.6)	0.607
Arterial hypertension	158 (58.7)	146 (59.6)	8 (44.4)	0.463	124 (58.5)	100 (58.1)	29 (59.2)	0.991
Current smoker	37 (13.8)	16 (11.0)	1 (5.6)	0.472	24 (11.3)	24 (14.0)	6 (12.2)	0.739
Hypercholesterolemia	156 (58.0)	91 (62.3)	6 (33.3)	0.061	127 (59.9)	96 (55.8)	30 (61.2)	0.660
Unstable angina	78 (29.0)	52 (35.6)	5 (27.8)	0.361	66 (31.1)	52 (30.2)	17 (34.7)	0.838
Previous MI	105 (39.0)	70 (47.9)	7 (38.9)	0.206	87 (41.0)	70 (40.7)	25 (51.0)	0.399
Previous CABG	33 (12.3)	16 (11.0)	2 (11.1)	0.921	22 (10.4)	22 (12.8)	7 (14.3)	0.648

Data are number of patients, with percentages in parentheses, or mean ± standard deviation. CABG = Coronary artery bypass grafting.

of the P27 C-79T and P53 G72C polymorphisms were based on PCR and the TaqMan assay and involved fluorogenic oligonucleotide probes. TaqMan assays were performed with the ABI Prism Sequence Detection System 7700 (Applied Biosystems, Darmstadt, Germany) [26]. Primers and probes were selected based on previously reported sequences (GenBank accession No. NM004064 for P27 and NM000546 for P53) in the proximity of the polymorphic sites using the 'Primer Express' software (Applied Biosystems). Sequences are available upon request. Of each probe pair, 1 probe was labeled with the fluorescent dye 6-carboxy-fluorescein and the other with VIC (Applied Biosystems, patent pending). Two primers (forward and reverse) and 2 probes (labeled with 6-carboxy-fluorescein or VIC) were used for typing of each polymorphism. DNA was amplified during 40 cycles of denaturation at 95°C for 15 s and primer annealing as well as extension at 60°C for 1 min (35 cycles of denaturation at 92°C for P27). The DNA from 2 healthy volunteers served as standards for the TaqMan analysis for each polymorphism. These initial genotypes were determined by screening 50 healthy volunteers with the use of Bsh12361I, an allele-discriminating restriction enzyme for the P53 G72C polymorphism, and sequencing for the P27 C-79T polymorphism with the ABI PRISM 3100 Genetic Analyser (Applied Biosystems) capillary sequencing system using the BigDye® Terminator version 1.1 Cycle Sequencing Kit (Applied Biosystems, patent No. 4336776) and the same primers as for the subsequent TaqMan assay.

To control for correct sample handling, genotyping was repeated with DNA from 20% of the patients. All control experiments revealed identical results compared with the first genotyping. Two independent operators blinded regarding the patients' clinical data assessed all TaqMan results.

Angiographic Assessment

Quantitative angiographic analysis was performed off-line using the automated edge detection system CMS (Medis Medical Imaging Systems, Nuenen, The Netherlands) assessing matched views of the target lesions. The operators were blinded to the patients' respective genotypes or the assigned DES treatment. The lesion morphology was assessed according to the modified American Heart Association/American College of Cardiology and classified as type A, B1, B2 or C. Lesions of types B2 and C were considered complex [27]. Lesion length, reference diameter, minimal lumen diameter and diameter stenosis were measured and assessed for each patient. Angiographic parameters were recorded before and immediately following the intervention, as well as at follow-up angiography.

Study Endpoints

The primary endpoint of the study was restenosis that was evaluated angiographically and clinically. Angiographic restenosis was defined as a diameter stenosis of ≥50% at 6-month follow-up angiography. Clinical restenosis was defined as the necessity for target lesion revascularization (TLR) with percutaneous transluminal coronary angioplasty or aortocoronary bypass grafting due to symptoms or signs of ischemia in the presence of angiographic restenosis during the first year following stenting. Secondary endpoints were the incidence of death from any cause and the incidence of nonfatal MI during a 1-year follow-up period.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and were compared by means of the unpaired, 2-sided t test or analysis of variance for more than 2 groups. Discrete variables were expressed as counts or percentages and compared with the χ^2 or Fisher's exact test, as appropriate. Pearson's goodness-of-fit χ^2 method was used to test for deviation from the Hardy-Weinberg equilibrium. Statistical analyses were performed using S-Plus software (Insightful Corp., Seattle, Wash., USA). A 2-sided p value <0.05 was considered statistically significant.

Results

The genotype distribution for the P27 C-79T polymorphism was 62.1% CC, 33.7% CT and 4.2% TT, and for the P53 G72C polymorphism 49.0% GG, 39.7% GC and

Table 2. Baseline lesion and procedural characteristics at the time of intervention according to the genotypes of the P27 and P53 polymorphisms (n = 433)

	P27 C-79T				P53 G72C			
	CC (n = 269)	CT (n = 146)	TT (n = 18)	p value	GG (n = 212)	GC (n = 172)	CC (n = 49)	p value
Stented vessel				0.308				0.557
LAD	115 (42.8)	77 (52.7)	8 (44.4)		95 (44.8)	86 (50.0)	19 (38.8)	
LCx	79 (29.4)	40 (27.4)	6 (33.3)		63 (29.7)	44 (25.6)	18 (36.7)	
RCA	75 (27.9)	29 (19.9)	4 (22.2)		54 (25.5)	42 (24.4)	12 (24.5)	
EF, %	53.0 ± 11.7	52.3 ± 13.1	51.1 ± 16.1	0.741	52.8 ± 13.6	52.5 ± 12.7	53.0 ± 11.8	0.959
Lesion length, mm	13.3 ± 7.9	14.2 ± 8.3	11.8 ± 5.7	0.358	13.7 ± 7.7	13.3 ± 7.4	14.2 ± 8.4	0.745
Baseline RVD, mm	2.70 ± 0.51	2.65 ± 0.51	2.63 ± 0.48	0.612	2.70 ± 0.47	2.66 ± 0.57	2.68 ± 0.47	0.683
Baseline MLD, mm	1.04 ± 0.41	1.05 ± 0.39	1.06 ± 0.48	0.952	1.06 ± 0.35	1.00 ± 0.40	1.12 ± 0.42	0.128
Baseline stenosis, %	61.2 ± 14.0	60.5 ± 12.7	60.0 ± 13.1	0.839	60.7 ± 12.9	62.3 ± 12.7	57.5 ± 14.2	0.084
Stent length, mm	22.4 ± 9.2	23.7 ± 9.4	22.6 ± 10.5	0.422	22.4 ± 9.3	23.8 ± 10.0	21.7 ± 8.7	0.224
Stents, n	1.09 ± 0.33	1.10 ± 0.37	1.17 ± 0.51	0.681	1.10 ± 0.29	1.13 ± 0.38	1.04 ± 0.33	0.261
Final MLD, mm	2.61 ± 0.45	2.56 ± 0.52	2.63 ± 0.44	0.660	2.62 ± 0.45	2.58 ± 0.50	2.5 ± 0.46	0.549
Final stenosis, %	8.8 ± 6.5	9.2 ± 11.2	7.1 ± 9.1	0.588	8.5 ± 7.4	9.04 ± 7.9	10.0 ± 9.2	0.547

Data are number of patients, with percentages in parentheses, or mean ± standard deviation. LAD = Left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; EF = ejection fraction; RVD = reference vessel diameter; MLD = minimal lumen diameter.

Table 3. Major adverse clinical events (TLR, MI and death) for the entire population (n = 433) and angiographic restenosis in the cohort with follow-up angiography (n = 378)

	P27 C-79T				P53 G72C			
	CC	CT	TT	p value	GG	GC	CC	p value
Entire population	269	146	18		212	172	49	
TLR	33 (12.3)	15 (10.3)	1 (5.6)	0.608	28 (13.2)	19 (11.1)	2 (4.1)	0.190
MI	6 (2.2)	4 (2.7)	1 (5.6)	0.674	7 (3.3)	3 (1.7)	1 (2.0)	0.611
Death	8 (3.0)	3 (2.1)	0 (0.0)	0.666	7 (3.3)	1 (0.6)	3 (6.1)	0.058
Cohort with follow-up angiography	235	127	16		187	151	40	
Angiographic restenosis	37 (15.7)	18 (14.2)	2 (12.5)	0.884	29 (15.5)	25 (16.6)	3 (7.5)	0.354

Data are number of patients, with percentages in parentheses.

11.3% CC, respectively, corresponding to the Hardy-Weinberg equilibrium (p = 0.74 for the P27 genotypes and p = 0.12 for the P53 genotypes). The baseline characteristics of the patients were evenly distributed between the studied genotype groups (table 1). The mean age was 66.2 years, the majority of patients were male, and there was a high prevalence of coronary risk factors. Similar distributions for lesion and procedural characteristics at the time of the intervention were observed for the genotype groups (table 2). The most common lesion location was in the left anterior descending coronary artery, the average stent length ranged between 21.7 and 23.8 mm, and the average final percent diameter stenosis was <10% in the studied groups. No significant differences were observed for the procedural characteristics comparing the populations treated with Cypher or Taxus stents. For the 378 patients (87.3%) with angiographic follow-up, the genotype distribution for the P27 C-79T polymorphism

was 62.2% CC, 33.6% CT and 4.2% TT, and for the P53 G72C polymorphism 49.5% GG, 40.0% GC and 10.6% CC, respectively, being in accordance with the Hardy-Weinberg equilibrium ($p = 0.82$ for the P27 polymorphism and $p = 0.25$ for the P53 polymorphism). The incidence of angiographic restenosis was not significantly different between the genotype groups of the studied polymorphisms, ranging from 12.5 to 15.7% for the P27 genotypes ($p = 0.88$) and from 7.5 to 16.6% for the P53 genotypes ($p = 0.35$; table 3). The TLR rate showed no statistically significant differences between the studied genotype groups for the overall population ($p \geq 0.190$; table 3). Finally, the incidence of MI and death during the first 12 months following intervention was similarly distributed between the studied genotype groups for the overall population (table 3). The lack of association between the studied genotypes on the one side and angiographic restenosis, TLR, death and MI on the other side was observed for both Cypher versus Taxus stents ($p \geq 0.218$), for diabetic versus nondiabetic patients ($p \geq 0.092$) and for de novo versus restenotic lesions ($p \geq 0.079$). The only exceptions observed were the association of P53 GC genotype with death for diabetic patients ($p = 0.012$) and patients with de novo lesions only ($p = 0.025$), due to no deaths in the heterozygote GC genotype group and low event numbers ($n \leq 7$) for the homozygote GG and CC genotypes.

Discussion

The incidence of restenosis as well as the restenosis pattern has changed since the introduction of DES. This is the first study to evaluate the significance of polymorphisms for the outcome of patients in the DES era. For our study, we have chosen a high-risk cohort for the development of subsequent restenosis, including diabetic patients and patients with previous bare-metal stent restenosis, for which investigations on additional genetic influences might be more relevant.

The hypothesis of our study, a positive association of the P27 C-79T TT genotype and the P53 G72C CC genotype with a higher incidence of restenosis and major adverse cardiac events, was based on previous results from cell culture experiments, animal models and association studies [18–24]. These studies showed an important role of P27 and P53 in the signal transduction leading to apoptosis and cell growth suppression and an association of the studied polymorphism with P27 and P53 protein production and function. In contrast, our study could not demonstrate a significant association of the P27 C-79T and P53 G72C polymorphisms with restenosis or adverse clinical events after coronary DES implantation. The lack of association between the studied genotypes on the one side and angiographic restenosis, TLR, MI and death on the other side persisted in the subgroup analyses, including Cypher versus Taxus stents, diabetic versus nondiabetic patients and de novo versus restenotic lesions. The positive association of the heterozygote P53 GC genotype with death for diabetic patients and patients with de novo lesions are presumably random findings after subgroup analysis, due to no deaths in the heterozygote GC genotype group and low event numbers for the homozygote GG and CC genotypes.

Strengths of our study were the series of 443 consecutive patients, a follow-up angiography rate exceeding 87%, the computer-based angiographic assessment and the use of different measurements to assure correct genotyping. The angiographic and clinical restenosis rate in this study was comparable with recently reported studies [1–3]. The reported genotype distributions were in accordance with the Hardy-Weinberg equilibrium and were similar to previously described genotype distributions for the P27 and P53 polymorphisms [21, 28].

To date, the data in the literature regarding the influence of genetic polymorphisms on the development of restenosis following bare-metal stent implantation are equivocal. Some studies were able to show a significant association of polymorphisms with restenosis after bare-metal stent implantation [27, 32], other studies failed to demonstrate a significant association despite previous functional data [33, 34]. Several studies have shown positive associations of the P27 C-59T and P53 G72C variants with cancer, suggesting an increased proliferation stimulus associated with these variants [21, 24]. Given the lack of data on the influence of genetic polymorphisms on the outcome after DES implantation, this work represents an important first step for the assessment of the impact of genetic variants for patients with CAD treated with DES.

One limitation of this study might be related to the power of the study. The sample size included had an 80% power to detect a significant 35% increase in target vessel revascularization among the P27 TT genotype and the P53 CC genotype groups, respectively, equivalent to absolute differences of 4–6%. We cannot exclude smaller differences influenced by the studied polymorphisms, but such small differences might not be clinically significant. The low event rate secondary to the reduced incidence of restenosis with DES should also be acknowl-

edged in the evaluation of this study, making possible effects of the studied genotypes harder to detect. Patients with restenotic lesions and diabetic patients were studied as one population, but there might be different mechanisms leading to the formation of neointima in these patients.

The trend towards a higher restenosis rate for patients with the P53 GC genotype can be interpreted as a signal and should be verified in a larger sample. Other proteins in the complex signaling pathways of these cytokines might induce or suppress neointimal growth, thereby counteracting the effect of the polymorphic variants analyzed in our study. Further, we cannot exclude that other polymorphisms or haplotypes of the studied genes might be relevant for the development of restenosis.

In conclusion, the results of the study argue against an association of the P27 C-79T polymorphism and the P53 G72C polymorphism with restenosis, MI or death in patients treated with Cypher and Taxus stents.

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