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Cyclosporin-induced gingival overgrowth is associated with elevated gene expression for MMP-1, MMP-10 and TIMP-1

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Authors:
Dr. med. dent. Bettina Dannewitz, Sektion Parodontologie, Universitätsklinikum Heidelberg
Christina Edrich, Poliklinik für Zahnerhaltungskunde, Universitätsklinikum Heidelberg
Prof. Dr. rer. nat. Pascal Tomakidi, Poliklinik für Kieferorthopädie, Universitätsklinikum Heidelberg
Annette Kohl, Poliklinik für Kieferorthopädie, Universitätsklinikum Heidelberg
Prof. Dr. med. dent. Peter Eickholz, Poliklinik für Parodontologie, Klinikum der Johann Wolfgang Goethe-Universität Frankfurt
Prof. Dr. med. dent. Gerda Komposch, Poliklinik für Kieferorthopädie, Universitätsklinikum Heidelberg
Dr. rer. nat. Thorsten Steinberg, Poliklinik für Kieferorthopädie, Universitätsklinikum Heidelberg

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Introduction

In humans, pathogenesis of cyclosporin A (CsA)-induced gingival overgrowth (GO) includes the accumulation of extracellular matrix (ECM) constituents, such as collagen type-I, type–III and proteoglycans in the subgingival connective gingival tissue. However, it remains unclear whether this increase is associated with alterations of molecules pivotal for the turnover of collagens and proteoglycans. Therefore, the present study explores the status of molecules which are involved in ECM-turnover. In detail, we have analysed the status of matrix metalloproteinase (MMP)-1, MMP-10, and their tissue inhibitor TIMP-1.

Material and Methods

The above-mentioned molecules were studied on the mRNA expression level by in situ hybridisation (ISH) and quantitative real-time PCR (RT-PCR) as well as on the protein level by indirect immunofluorescence (IIF). Tissue specimens derived from 5 patients with CsA-induced GO after renal transplantation and 5 patients with clinically heathy gingiva and were analysed on frozen sections.

Results

Molecule		Tissue area in normal gingiva			Tissue area in gingival overgrowth		
		Epithelial compartment	Papillary connective tissue	Deep connective tissue	Epithelial compartment	Papillary connective tissue	Deep connective tissue
IIF	MMP-1	-	-	-	-	+	-
	MMP-10	-	-	-	++	++	++
	TIMP-1	-	-	-	-	++	+++
ISH	MMP-1	+	+	+	+	++	++
	MMP-10	++	+	+	++	+	+++
	TIMP-1	+	+	+	++	+++	+++

Tab. 1: Relative expression of MMP-1, MMP-10, and TIMP-1 is given on an arbitrary scale (+++ strong, ++ intermediate variable, + low, - no expression).

ISH revealed elevated levels of MMP-1 mRNA expression in the epithelial compartment of GO compared to normal tissue (Fig. 1A and B, Tab. 1). This elevation also applied to MMP-10 (Fig. 1C and D, Tab. 1), while MMP-10 gene transcription appeared generally stronger, rather than that observed for MMP-1. For TIMP-1, transcription levels were week in normal and strong in GO tissue (Fig. 1E and F, Tab 1). These differences detected in ISH were corroborated by RT-PCR (Fig. 3). RT-PCR revealed for all three molecules an increase of the relative mRNA expression level in GO compared to normal gingiva, with TIMP-1 showing the most significant change (4.8-fold; Fig. 3 orange collum). Detection of the protein by IIF showed that normal gingival tissue was devoid of all three molecules, while they were detectable in GO tissue, with emphasis on TIMP-1 (Fig. 2, Tab. 1).

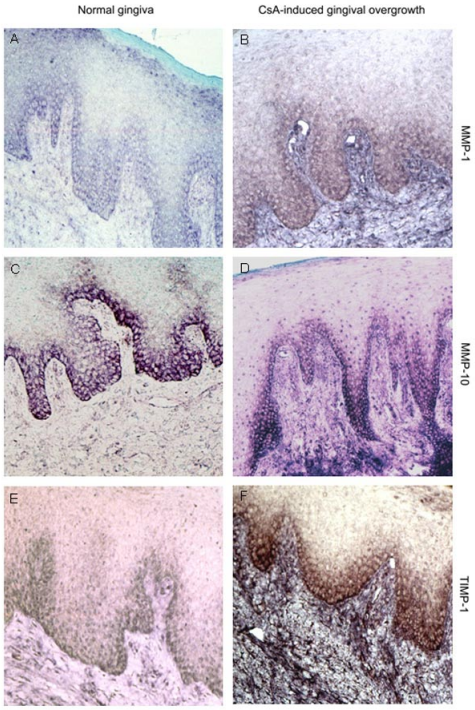

Fig. 1: ISH for MMP-1, MMP-10, and TIMP-1 in normal and overgrown gingiva.

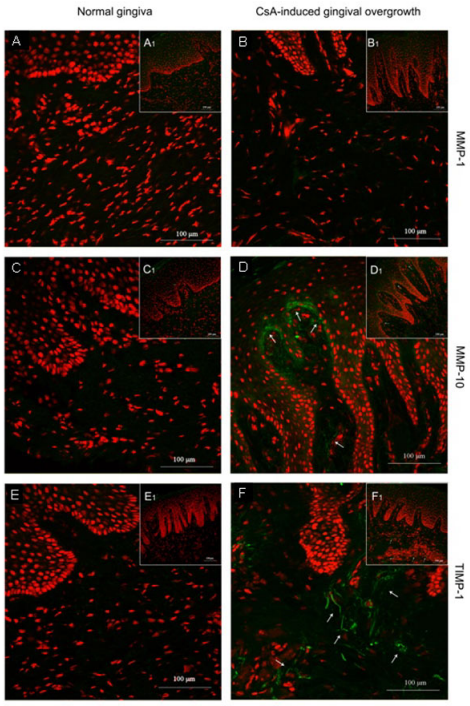

Fig. 2: ISH for MMP-1, MMP-10, and TIMP-1 in normal and overgrown gingiva.

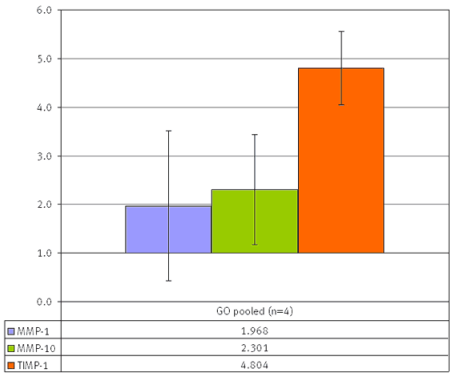

Fig. 3: Relative mRNA-expression for MMP-1, MMP-10, and TIMP-1 in CsA-induced gingival overgrowth compared to normal gingiva.

Conclusions

Analysis of our data indicates elevated levels of MMP-1, MMP-10 and particularly TIMP-1. With respect to TIMP-1, this elevation may in turn lead to alterations in ECM-degradadtion by abrogating MMP-1 and MMP-10, thereby contributing to ECM accumulation associated with GO.

This Poster was submitted by Dr. med. dent. Bettina Dannewitz.

Correspondence address:
Dr. med. dent. Bettina Dannewitz
Sektion Parodontologie
Poliklinik für Zahnerhaltungskunde MZK-Klinik
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 400
69120 Heidelberg

Poster Faksimile:

UniversityHospital Heidelberg

N°310 Aetiology and Pathogenesis

Cyclosporin-induced gingival overgrowth is associated with elevated gene expression for MMP-1, MMP-10 and TIMP-1

Dannewitz B[1,3], Edrich C[1,2], Tomakidi P[2], Kohl A[2], Eickholz P[3], Komposch G[2], Steinberg T[2]

[1]Department of Conservative Dentistry and Periodontology, Clinic for Oral, Dental and Maxillofacial Diseases, University Hospital of Heidelberg
[2]Department of Orthodontics and Dentofacial Orthopedics, Clinic for Oral, Dental and Maxillofacial Diseases, University Hospital of Heidelberg
[3]Department of Periodontology, Center for Dental, Oral and Maxillofacial Medicine, University Hospital Frankfurt

Aim

In humans, pathogenesis of cyclosporin A (CsA)-induced gingival overgrowth (GO) includes the accumulation of extracellular matrix (ECM) constituents, such as collagen type-I, type–III and proteoglycans in the subgingival connective gingival tissue. However, it remains unclear whether this increase is associated with alterations of molecules pivotal for the turnover of collagens and proteoglycans. Therefore, the present study explores the status of molecules which are involved in ECM-turnover. In detail, we have analysed the status of matrix metalloproteinase (MMP)-1, MMP-10, and their tissue inhibitor TIMP-1.

Material and Methods

The above-mentioned molecules were studied on the mRNA expression level by in situ hybridisation (ISH) and quantitative real-time PCR (RT-PCR) as well as on the protein level by indirect immunofluorescence (IIF). Tissue specimens derived from 5 patients with CsA-induced GO after renal transplantation and 5 patients with clinically heathy gingiva and were analysed on frozen sections.

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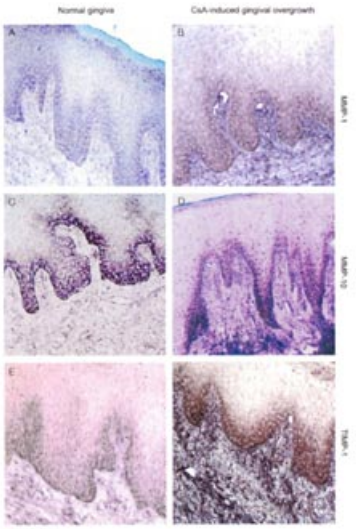

Figure 1

Table 1

	Molecule	Tissue area in normal gingiva: Epithelial compartment	Papillary connective tissue	Deep connective tissue	Tissue area in gingival overgrowth: Epithelial compartment	Papillary connective tissue	Deep connective tissue
IIF	MMP-1	-	-	-	-	+	-
	MMP-10	-	-	-	++	++	++
	TIMP-1	-	-	-	-	++	+++
ISH	MMP-1	+	+	+	+	++	++
	MMP-10	++	+	+	++	+	+++
	TIMP-1	+	+	+	++	+++	+++

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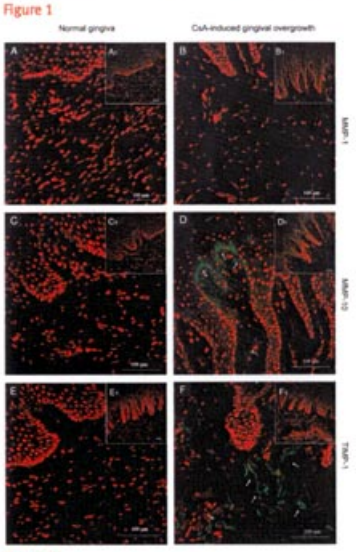

Figure 2

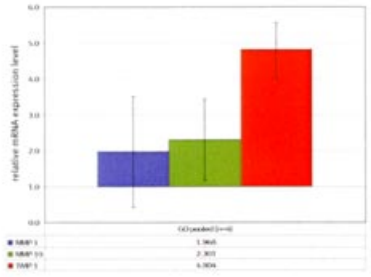

Figure 3

Correspondence to
Dr. Bettina Dannewitz, Department of Conservative Dentistry and Periodontology, Clinic for Oral, Dental and Maxillofacial Diseases, University Hospital Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Tel.: +49-6221-56 6020, Fax: +49-6221-56 50 74, Email: bettina_dannewitz@med.uni-heidelberg.de