

# Endoplasmic Reticulum Stress-Associated Chaperones, Bip/GRP78 and Calnexin are Overexpressed in Keratocystic Odontogenic Tumours

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## ABSTRACT

**Objectives:** Odontogenic keratocysts (OKCs) are developmental cysts that have been reclassified according World Health Organization (WHO), to keratocystic odontogenic tumours (KCOTs), a term that better reflects their neoplastic nature. The aim of present study is to evaluate the induction of stress of the endoplasmic reticulum and execution of the resulting unfolded protein response in keratinocystic odontogenic tumours.

**Material and Methods:** We analyzed by immunohistochemistry the expression of the chaperones BiP/GRP78 and calnexin in 24 cases of KCOTs. As controls, we have used 9 cases of periapical or radicular cysts (PACs) and 5 cases of Fibromas (FBs). The PACs and the FBs were included in the analysis, as PACs are the most common type of inflammatory odontogenic cysts of and FBs, as lesions of the connective tissue with unaffected epithelium.

**Results:** Analysis revealed a strong association between both BiP/GRP78 and calnexin expression and KCOTs: 18 out of 24 (75%) KCOTs expressed BiP/GRP78 as opposed to 1 out of 9 (13%) PACs, and none of 5 FBs evaluated ( $P < 0.001$ ,  $\chi^2$ -test). Calnexin was expressed in 11 out of 24 KCOTs (46%) but only one out of 9 (13%) PACs, and none of the 5 FBs analyzed ( $P < 0.001$ ,  $\chi^2$ -test).

**Conclusions:** Study results imply that induction of endoplasmic reticulum stress maybe of diagnostic value in keratocystic odontogenic tumours characterization. In addition to recent findings suggesting that endoplasmic reticulum stress plays a causative role in keratinization of epithelia, pharmacological interference with the execution of the unfolded protein response should be considered for the management of keratocystic odontogenic tumours.

**Keywords:** dental tissue neoplasms; endoplasmic reticulum stress; GRP78 protein; molecular chaperone; phosphoprotein pp90.

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## INTRODUCTION

The formation of cysts in the jaws possesses unique features regarding their pathology and implicates the odontogenic tooth-forming apparatus [1]. In most classification schemes odontogenic cysts are divided in two major categories, namely the developmental cysts and the cysts that are initiated in areas of acute or chronic inflammation, with odontogenic keratocysts (OKC) and periapical or radicular cysts (PACs) as the most common types, respectively [1,2]. The World Health Organization (WHO) reclassified OKC in its 2005 edition of histological classification of odontogenic tumours and according to this reclassification, the OKC is now considered as a KCOT. It is defined as “a benign uni- or multicystic, intraosseous tumour of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium that bears the potential for aggressive, infiltrative behaviour”, a term that better reflects its neoplastic nature [3]. Several factors form the basis of this decision: a. the clinical behaviour of the lesion, since KCOT is locally destructive and highly recurrent, b. the histopathologic characteristics, considering that the basal layer of the KCOT budding into connective tissue, in addition to the mitotic figures that are frequently found in the suprabasal layers [1,3-5], and finally c. genetic alterations, are the most important parameters [6]. KCOTs comprise approximately 11% of all cysts of the jaws [7]. They occur most commonly in the mandible, especially in the posterior body and ramus regions [1,2,7]. It may be solitary or multiple and the latter is usually characterizing the inherited nevoid basal cell carcinoma syndrome “NBCCS”. KCOTs have a high recurrence rate, ranging between 25% and 60% while when associated with nevoid basal cell carcinoma syndrome “NBCCS” or Gorlin-Goltz syndrome, the recurrence rate is about 82% [8,9]. So far, there is only limited evidence regarding the pathogenesis of the developmental cystic neoplasms of the jaws and for this reason they are considering of unknown aetiology. The endoplasmic reticulum (ER) is an organelle with a major role in the synthesis of lipid and proteins and leads many cellular processes such as organogenesis, transcriptional activity, stress responses, and apoptosis [10-14]. ER is responsible for the proper folding of the newly synthesized proteins that is facilitated with the assistance of various ER chaperones [10,11]. Unfolded or malfolded proteins are disposed by mechanisms implicating ER-associated protein degradation (ERAD). When the amount of unfolded protein

exceeds the folding capacity of the ER, human cells activate a homeostatic defence mechanism designated as the UPR that follows ER stress [11-16].

Among the various consequences of UPR is also the upregulation of BiP/GRP78 and of other chaperones that is considered diagnostic for the induction of ER stress in a given tissue [16-18]. BiP/GRP78 binds to the hydrophobic region of unfolded proteins via a substrate-binding domain and facilitates folding through conformational change evoked by the hydrolysis of ATP by the ATPase domain [19,20]. Calnexin and calreticulin are ER chaperones specifically involved in the folding of glycoproteins. High mannose type oligosaccharide is attached *en bloc* to most proteins synthesized in the ER, and then trimmed sequentially [21-23]. When two glucose residues are trimmed by glucosidase I or II and the protein contains only one glucose residue, calnexin and calreticulin bind and fold the client protein [21,22]. When the last glucose residue is trimmed by glucosidase II, the client is released from calnexin and calreticulin, and binds to UDP-glucose-glycoprotein glucosyltransferase [10,21]. If the protein is folded properly, it is released from the enzyme and transported to the Golgi apparatus. If it is not folded appropriately, UDP-glucose-glycoprotein glucosyltransferase attaches one glucose residue and returns it to calnexin and calreticulin. This folding process is called the calnexin cycle. Calnexin and calreticulin share a similar molecular structure and function, although they are transmembrane and luminal proteins, respectively [10,11,21,22]. Considering the neoplastic nature of KCOTs, in combination with their poorly defined aetiology we explored if ER stress is involved in disease development. Specifically, we evaluated the expression of the chaperones, BiP/GRP78 and calnexin in a panel of KCOTs as compared to PACs and FBs. Both of these markers is considered to accurately reflect the induction of ER stress which has been associated with neoplastic development [10,11].

## MATERIAL AND METHODS

### Patients and samples

Paraffin-embedded tissue specimens of KCOTs (24 cases), PACs (9 cases) and Fibromas (5 cases) were randomly selected from the archives of the Department of Oral Pathology, of the National and Kapodistrian University of Athens, Dental School spanning the years 2006 - 2011 and were analyzed by immunohistochemistry. We have analyzed the expression of chaperones BiP/GRP78 and calnexin

in a panel of 24 KCOTs and 9 PACs. The latter represent the most common type of inflammatory odontogenic cysts. In addition we have also included in our analysis 5 FBs as controls since they represent lesions of the connective tissue devoid of pathological findings in the epithelium.

### Details of ethics approval

No ethical issues are related to this study since only paraffin-embedded archival material has been used and no data related to the patients' clinical records have been disclosed. Therefore the study did not require review by the Institutional Review Board of the University of Athens.

### Immunohistochemistry

Immunohistochemistry was carried out in formalin fixed, paraffin embedded tissue specimens. The antibodies used were monoclonal rabbit anti-BiP (C50B12), by Cell Signaling Technology; 1:100 and monoclonal mouse anti-calnexin (sc-46669), by Santa Cruz Biotechnology, Santa Cruz, CA, USA; 1:75. Immunostaining was performed by using the Superpicture Polymer (Dab) Kit (Novocastra), following the manufacturer's instructions. Before evaluation, a weak counterstaining with hematoxylin was performed in all immunostained specimens. Specimens were evaluated blindly from two authors of the study (I.C., Pathologist and S.M., MSc in Oral Medicine and Pathology). The positive immunohistochemical staining, was graded semiquantitatively by using a 5-tier scoring system and classified according to the intensity of the labelling as: negative (-), marginal (+/-), mild (+), moderate (++) and intense (+++).

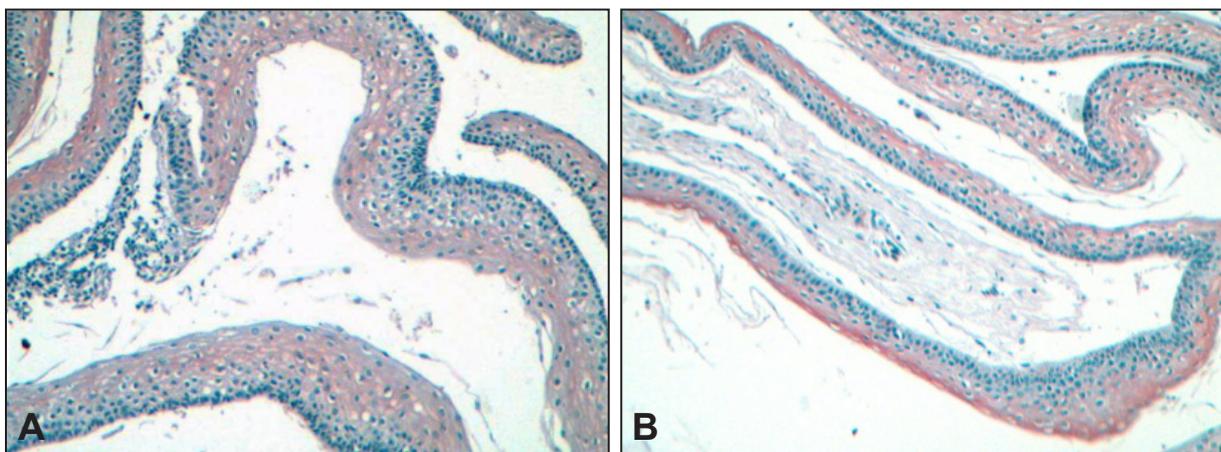
### Statistical analysis

Chi-square test was used to statistical evaluate the results.

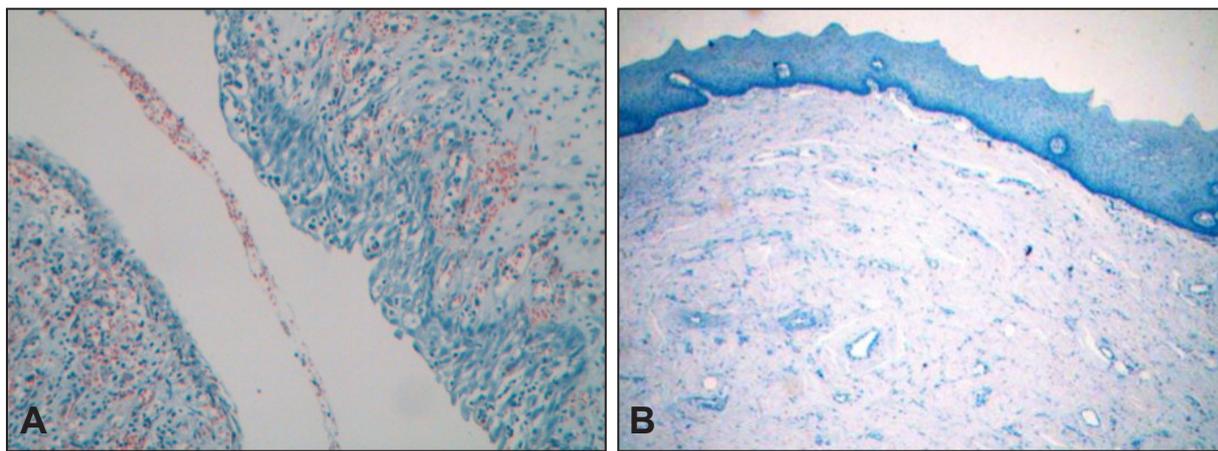
### RESULTS

In all specimens analyzed and for both antigens, immunopositivity was relatively homogenous among cells and varied only in terms of intensity. As shown in Table 1, BiP/GRP78 immunopositivity was detected in 18 out of 24 (75%) KCOTs. Positivity was marginal (+/-) in one sample, mild (+) in 10, moderate (++) in 6 and very intense (+++) in one specimen. With the exception of 3 specimens exhibiting moderate or very intense immunopositivity and at which BiP/GRP78 expression was primarily localized in the upper layers of the epithelium (Figure 1A), in all other cases BiP/GRP78 immunopositivity spanned full thickness of the epithelium (Figure 1B). As opposed to KCOTs, PACs exhibited BiP/GRP78 immunopositivity in only 1 out of 9 (13%) cases (Figure 2A) while all five FBs were negative for BiP/GRP78 expression (Figure 2B) suggesting that the overexpression of BiP/GRP78 in KCOTs was statistically significant ( $P < 0.001$ ,  $\chi^2$ -test).

The same panel of specimens was also analyzed for the expression of calnexin. Our results that are summarized in Table 1 show that calnexin expression is significantly higher ( $P < 0.001$ ,  $\chi^2$ -test) in KCOTs since it was expressed in 11 out of 24 KCOTs (46%) but only one out of 9 (13%) PACs and none of the 5 FBs analyzed. Immunopositivity in KCOTs ranged from marginal (+/-) in 5, mild (+) in 5 and moderate (++) in one specimen while the single PAC that was positive for calnexin expression exhibited marginal immunopositivity.



**Figure 1.** Immunohistochemical expression of BiP/GRP78 in keratocystic odontogenic tumours (x10). (A) Brown colour (DAB) indicates staining in the upper layers of the epithelium or (B) in the full thickness with stronger intensity in the upper layers. Weak counterstaining with haematoxylin was performed in all samples following immunostaining (original magnification x20).

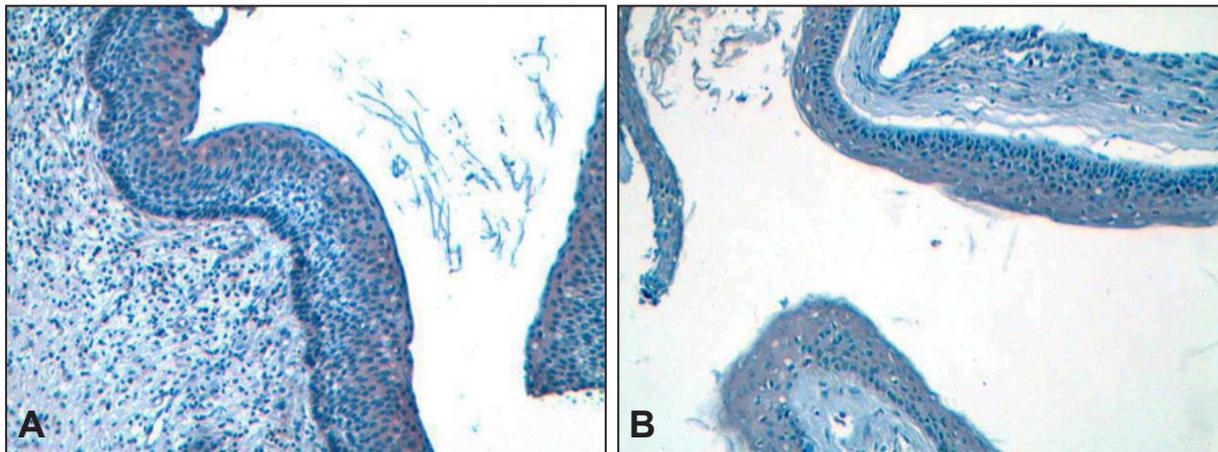


**Figure 2.** The microphotograph shows negative staining for BiP/GRP78 in the epithelium of periapical cyst (A) and negative staining for calnexin in the epithelium of a fibroma (B). Weak counterstaining with haematoxylin was performed in all samples following immunostaining (original magnification x20).

**Table 1.** Expression levels and localization of BiP/GRP78 and calnexin in KCOTs, PACs and FBs

Specimen No.	Age	BiP/GRP78 expression intensity	BiP/GRP78 expression localization	Calnexin expression intensity	Calnexin expression localization
<b>KCOTs</b>					
1	47	-		+	FT
2	74	+	FT	±	FT
3	58	+	FT	±	FT
4	40	-		-	
5	65	++	UL	-	
6	62	-		-	
7	60	-		-	
8	43	++	FT/UL	+	UL
9	24	+++	UL	+	UL
10	33	++	FT/UL	+	UL
11	51	++	FT/UL	++	FT/UL
12	70	-		-	
13	66	-		-	
14	44	+	FT	-	
15	40	±	FT	±	FT
16	46	+	FT	-	
17	47	+	FT	+	FT
18	8	++	FT/UL	+	FT
19	28	++	FT	++	FT
20	57	+	FT	±	FT
21	48	+	FT	-	
22	45	+	UL	-	
23	75	+	FT/UL	-	
24	32	+	FT	-	
<b>PACs</b>					
1	57	+	FT	±	FT
2	45	-		-	
3	32	-		-	
4	30	-		-	
5	53	-		-	
6	40	-		-	
7	52	-		-	
8	40	-		-	
9	45	-		-	
<b>FBs</b>					
1	10	-		-	
2	56	-		-	
3	67	-		-	
4	50	-		-	
5	34	-		-	

KCOTs = keratocystic odontogenic tumors; PACs = periapical or radicular cysts; FBs = fibromas; FT = full thickness of the epithelium; UL = upper layers; FT/UL = full thickness with stronger intensity in the upper layers.



**Figure 3.** Immunohistochemical expression of calnexin in keratocystic odontogenic tumours (x10). (A) Brown colour (DAB) indicates staining in the upper layers of the epithelium or (B) in the full thickness. Weak counterstaining with haematoxylin was performed in all samples following immunostaining (original magnification x20).

In all but 3 cases that exhibited mild immunopositivity and was localized in the upper layers of the epithelium (Figure 3A), calnexin expression was spanned the full thickness of the epithelium (Figure 3B).

Considering that calnexin and BiP/GRP78 are both indicators of ER stress we asked if their expression is correlated in the same specimens. Indeed, out of the 38 specimens subjected to our analyses, 29 were either positive or negative for both antigens while only 9 exhibited expression for either BiP/GRP78 or calnexin. This observation confirms that BiP/GRP78 and calnexin are co-expressed ( $P < 0.001$ ,  $\chi^2$ -test).

## DISCUSSION

In order to better understand the pathogenic mechanisms that underline the development of KCOTs we have hypothesized that ER stress and the resulting UPR may be associated with their onset. In order to test this hypothesis a bank of KCOTs specimens were analyzed by immunohistochemistry for the expression of BiP/GRP78 and calnexin, two widely used chaperones that are considered diagnostic for cells undergoing ER stress [19-21,23]. The expression of BiP/GRP78 and calnexin in the KCOTs were compared to that in PACs that are cysts with distinct pathologic features and pathogenetic mechanism from that of KCOTs as well as in FBs at which the cell type affected does not involve the epithelium but rather the stroma. Our results show a strong overexpression of the ER stress markers BiP/GRP78 and calnexin in the KCOTs but not in the PACs and the FBs. Furthermore, these two chaperones were frequently co-expressed in the same specimens, an observation that implies that the overexpression of

BiP/GRP78 and calnexin was not coincidental but rather indicative for ER stress induction and execution of the UPR [23].

A distinct diagnostic feature of the KCOTs is the keratinization of the epithelium [1,3,4]. It is conceivable that this feature of the KCOTs, namely the misexpression of keratin, is causatively associated with ER stress. For reasons not yet well understood commitment to this keratinocyte differentiation program, may induce ER stress and activate the UPR [24,25]. Whether this is due to the ectopic overexpression of a specific protein such as keratin(s) or it is related to the perturbation of tissue homeostasis due to aberrant differentiation remains unclear. However, since neither PACs nor FBs display evidence of ER stress it is likely that the latter is linked to KCOTs' pathogenesis. Consistently with this notion, recent findings showed that in the skin, at which keratinization represents a normal and physiological process, ER stress-related chaperones BiP/GRP78 and HRD1 was elevated in cells of normal human epidermis that contain keratinocytes undergoing differentiation [24]. These findings suggest that keratinization, either in its physiological context such as in the skin or in abnormal context such as in the KCOTs, are associated with ER stress induction. Furthermore, in the same study it has been demonstrated that pharmacological interference with the execution of the UPR affected the differentiation of keratinocytes *in vitro*, providing further clues regarding the causative link between ER stress and keratinocyte differentiation [24]. Our results are consistent with these findings and suggest that ER stress is induced in the odontogenic epithelium when cells are committed to the keratinocyte differentiation program, during KCOT development. This is also supported by the observation that especially

BiP/GRP78 and to some extent calnexin immunopositivity was frequently more intense in the upper layers of the epithelium at which keratinization is more prominent. Studies comparing the involvement of ER stress to parakeratinized normal tissues, hyperplastic and precancerous/dysplastic lesions of the oral epithelium would bestow insightful understanding if BiP/GRP78 or calnexin may be involved in parakeratinization. Indeed, a variety of diseases associated with aberrant keratinization, such as hereditary keratoses, including Darier's disease, keratosis linearis with ichthyosis congenita and keratoderma syndrome, erythrokeratoderma variabilis, and ichthyosis follicularis with atrichia and photophobia syndrome, have been linked to UPR [24]. It could be argued that keratinization and thus ER stress induction is irrelevant to the oncogenic stimulus that induces KCOTs' development. However, to the extent that keratinization reflects aberrant differentiation of the cells and considering that neoplastic development is indeed a disease of aberrant differentiation, ER stress is causatively linked to the disease development.

The results of the present study may provide clues regarding the pathogenesis of KCOTs. Which specific branches of UPR are activated during KCOT development and whether its inhibition is sufficient for the reversal of keratinization and regression of KCOTs remains to be explored. Furthermore, it would be of particular interest to investigate the involvement of epithelial to mesenchymal transition-associated markers in the pathogenesis of KCOT and their potential link to ER stress. In view of recent findings linking mutations in PTCH1 gene to KCOTs' development, and considering that the PTCH1 gene's product is a secreted ligand, an interesting hypothesis would be that its expression induces ER stress [26,27]. This is also supported by the ability of PTCH1 to act on post ER SMO and to modulate its activity without affecting its overall expression

levels [28].

These findings may have implications in the clinical practice at two major directions. The detection of ER stress and activation of the UPR may have diagnostic value for KCOT characterization especially in cases at which diagnosis is not clear especially in inflamed KCOTs [4] at which infiltration of the epithelium by inflammatory cells masks their typical histopathologic characteristics, raising issues of differential diagnosis. More importantly, considering that ER stress influences keratinocyte differentiation we may postulate that inhibition of UPR may have adjuvant therapeutic value for the management of KCOTs, particularly those with aggressive behaviour and often recurrences, at which surgery is the treatment of choice [29]. Indeed, recently developed chemical chaperones that can inhibit specific branches of the UPR may be beneficial for the therapy of KCOTs' patients.

## CONCLUSIONS

This is the first demonstration of the involvement of endoplasmic reticulum stress in the pathogenesis of keratocystic odontogenic tumours. Understanding the precise mechanism by which endoplasmic reticulum stress is involved the development of keratocystic odontogenic tumours may find application in the diagnosis and management of the disease.

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