Abstract. Tumors and cysts with odontogenic origin represent a family of lesions with specific histo-genetic and clinical characteristics. Among them, ameloblastomas are common benign neoplasms, predominantly detected in the anatomic areas of the jaws and also in the mandible and maxilla. Although they are characterized by a slow and stable growing pattern, a subset of them shows a tendency for local tissue invasiveness and partially increased recurrence rates after surgical excision. Furthermore, heat shock proteins (HSPs) are potentially implicated in ameloblastoma onset and progression. HSPs regulate the folding and refolding of proteins and are induced in response to oxidative stress. They are crucial members of the chaperone intracellular system and are categorized based on their molecular weight (i.e., HSP27, HSP60, HSP70, HSP90). In the current review, we describe HSPs origin and function, focusing on their deregulation mechanisms and impact predominantly on ameloblastomas and also on inflammatory and developmental odontogenic cystic lesions.

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transduction to the nucleus (15-17). In order HSPs’ functional activation to take place, over-expression of specific heat shock transcription factors – acting as modified stress sensors – is essential and mandatory (18-20). Interestingly, all of the main members of the HSP superfamily are over-expressed in different levels in specific types of malignancies. HSP 70/27 are activated in leukemias, lung, prostate, colon, breast, and head and neck squamous cell carcinomas, whereas HSP70 is also over-expressed in glioblastomas (21, 22). Similarly, HSP60 is activated in gastrointestinal malignancies including gastric, colon, and hepatocellular carcinomas and also strongly in prostate carcinoma, whereas HSP90 is also over-expressed in ovarian carcinoma (23-25). In the current review, we explored the role of HSPs’ different expression profiles in odontogenic ameloblastomas in comparison to odontogenic cystic lesions.

**HSPs in Ameloblastoma**

Ameloblastoma represents one of the most frequently observed epithelial tumors with odontogenic origin, predominantly detected in the anatomic areas of the jaws, especially in the mandible and maxilla (26). Interestingly, the majority of ameloblastomas are detected in the posterior mandibular area. Odontogenic cystic, enamel, and tooth residual epithelia, represent the substrate for its onset. Although benign regarding its pathological features, it demonstrates an increased tendency to invade locally in subgroups of patients that are characterized also by high recurrence rates (27, 28). It presents as a slow-growing painless swelling. Concerning its histological categorization, classical (conventional), extra osseous or peripheral, unicystic, and metastasizing are the prominent subtypes of the neoplasm (29). Especially the conventional ameloblastoma demonstrates specific histopathological variants and patterns such as granular, desmoplastic, plexiform, and follicular. Basal cell (ameloblasts) population in the periphery combined with suprabasal epithelial cells in the center of the lesion and abundant connective tissue are the main microscopic images of the tumor. Because ameloblastomas share similar radiographic features with other tumors and inflammatory lesions derived from the same anatomic regions, differential and final diagnosis is based exclusively on the corresponding biopsy analysis. In fact, lesions including osteomyelitis, cystic fibrous dysplasia, ossifying fibroma, ameloblastic carcinoma, sarcoma, and even myeloma could mimic ameloblastoma (30). Additionally, adenomatoid odontogenic tumour is an interesting and rare neoplastic lesion mimicking ameloblastoma (31, 32).

There are limited but interesting published data regarding the impact of altered HSPs’ expression on ameloblastomas. A protein study based on a comparative proteomic algorithm and a novel spectrometry assay implementation showed that HSPs were over-expressed (33). They suggested that they may be potential biomarkers of aggressive ameloblastic carcinoma. Another study analyzed the expression levels of HSP27 in a series of ameloblastomas with a plexiform and follicular histological pattern, as shown by immunohistochemistry. They reported a strong over-expression of the marker in plexiform variants combined with cytokeratin 8 (CK8) activation (34). Similarly, another comparative protein analysis between ameloblastomas and ameloblastic carcinomas showed high levels of nitric oxide and nitric oxide synthase concentration in the malignant tissues. This event was correlated with a slight HSP27, HSP60, and HSP70 over-expression in the same tissues (35). Although not statistically significant, HSPs activation seems to trigger the neoplastic transformation in the corresponding odontogenic tissues as a strong response to increased oxidative stress. Additionally, another study based on the combination of immunohistochemistry and western blotting showed HSP60 over-expression in a series of ameloblastomas. Interestingly, the immunostaining was not selectively detected in the plasma membrane of the corresponding tissues, but also in their nuclei, especially in the plexiform variant (36).

**HSPs in Odontogenic Cysts**

Odontogenic cysts -developmental and inflammatory- are categorized as multi- or mono-unicolar lesions that can mimic odontogenic tumors based on their similar radiographic characteristics (37). Periapical, paradental, and residual represent the main inflammatory cysts. A subset of these cystic lesions are characterized by increased neo-angiogenesis leading to a neoplastic-like tissue formation. In these cases, cluster differentiation 34 (CD34) protein expression combined with micro vessel density (MVD) measurement are eligible biomarkers in order for neo-angiogenesis levels to be estimated (38, 39). Concerning the HSPs expression profiles in odontogenic cysts in comparison to ameloblastomas, there are limited data. A study group co-analyzed odontogenic cysts (keratocysts and dentigerous) and ameloblastomas of the unicystic type, implementing a HSP70 based immunohistochemistry assay (40). They reported high expression levels of the marker both in ameloblastomas and keratocysts, concluding that this specific protein may be implicated in the aggressive progression of neoplasms as well inducing recurrence of the cysts. In addition, another study explored the role of HSP27 expression in a series of periapical lesions (cysts and granulomas) by applying immunohistochemistry. The study group detected high HSP27 levels in both radicular cysts and periapical granulomas (41). Interestingly, HSP27 over-activation prevented apoptosis and necrosis in these lesions, inducing also local cell migration. Furthermore, the co-expression of HSPs and nitric oxide synthase (iNOS) in periapical cysts seems to be significant for the progression of inflammation. A study group identified over-expression of iNOS, HSP27, HSP60, and HSP70 in a series of periapical inflammatory cysts (radicular) and granulomas (42). More specifically, there was selective
Protein expression of HSP27, HSP60, and HSP70 in the lining epithelia, endothelial cells, and lymphocytes.

In conclusion, odontogenic cysts and tumors including ameloblastomas demonstrate challenges regarding their differential diagnosis based on marginal in many cases and diverse morphology. Interestingly, maxillary and odontogenic ameloblastomas are characterized by a variety of subhistotypes and differences in their local or distant metastatic potential (43). HSPs are major biomarkers for estimating cell response rates to oxidative stress. Their over-expression is correlated to a progressively aggressive phenotype in ameloblastomas – that are transformed in some cases to ameloblastic carcinomas – and to hyperplasia and high recurrence rates in odontogenic cysts, respectively (Figure 1). HSPs 70/90/60/27 are over-expressed in different levels in these lesions and demonstrate specific staining patterns in the corresponding non- or neoplastic epithelia (44). Their over-activation -as a result of cell response to increased stress exposure – is implicated in odontogenic epithelial cells’ neoplastic transformation. Concerning the multiple roles of the HSP family in the metabolic and stress response pathways regulation, they should be considered significant targets for specific chemotherapeutic strategies.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors’ Contributions

VM, ET: design of the study, ET, VM: manuscript writing, IT, DP, ACL, NK, SM: academic advisors; SM, PS, TKI: collection and management of references’ data. All Authors read and approved the final manuscript.

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