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Derleme/ Review

THE USE OF PROLIFERATION MARKERS OF THE INFAMATUAR AND DEVELOPMENTAL ODONTOGENIC CYSTS

GELİŞİMSEL VE İNFAMMATUVAR ODONTOJENİK KİSTLERDE PROLİFERASYON MARKERLARI

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ABSTRACT

Understanding of the pathogenesis of developmental and inflammatory cysts is important to determine surgical approach and important for the identifcation and prediction of prognosis of the cyst of the oral and maxillofacial region. The immunohistochemically histologic examinations gives information about the potential proliferation of cyst epithelium. Subsequently facilitates the identifcation and choice of treatment options. In this review, with the use of proliferation markers in the prognosis of developmental and inflammatory cysts examined immunohistochemically evaluated in light of the current literature.

Key Words: odontogenic cyst, proliferation markers

ÖZET

Ağız, Çene ve yüz bölgesinde gelişen gelişimsel veya inflammatuvar odontojenik kistlerin patogenezinin anlaşılması , cerrahi yaklaşımını belirlenmesi ve kistin prognozunun öngörülmesi açısından önemlidir . İmmunohistokimyasal yöntemlerle yapılan histolojik incelemeler kist epitelinin proliferasyon potansiyeli hakkında bilgi vermektedir ve bununla birlikte proliferasyonun belirlenmesini ve tedavi seçeneklerinin tercihini kolaylaştırmaktadır. Bu derlemede proliferasyon markerlarının gelişimsel ve inflammatuvar odontojenik kistlerde immunohistokimyasal yöntemlerin kullanımı ile prognozun incelendiği güncel literatür bilgileri değerlendirilmiştir.

Anahtar kelimeler: odontojenik kist, proliferasyon markerları

The Use of Proliferation Markers of The Infla matuar and Developmental Odontogenic Cysts

Odontogenic cysts originate from the dental follicles or the epithelial rests of odontogenic epithelium during the odontogenesis. From a histological point of view, epithelial layer is not observed in the surrounding fibrous connective tissue but it may be observed in some of the follicles.[1-3] Such epithelial islands and chains which exist around and in the folicles are originating from different kinds of epithelium. Various kinds of such epithelia have been documented to include are reduced enamel epithelium, epithelial rests of Serres which refer to soft tissue remnants of dental lamina, rests of Hertwig's epithelial sheath or epithelial rests of Malessez. In addition, gingival epithelium has been reported to have a lifelong capability to differentiate in to odontogenic epithelium.[4,5]

It is known that the epithelial linings of odontogenic cysts are primarily composed of squamous epithelium, and various forms of metaplasia and degeneration are observed in these epithelial linings; such as, mucous cells, ciliated cells, parakeratinization and/or orthokeratinization and formation of hyaline bodies. It has been reported that the longer the tooth remains impacted the risk of cyst or tumor development increses. Malignancies such as carcinomas may also arise from cystic epithelium and such malign transformations have an incidence of 1% to 2%. Variations in proliferation rates of odontogenic epithelial cells are suggested to have a paramount role in cyst and tumor pathogenesis.[6,7]

Recently a number of studies in this field are ongoing because there is a lack of detailed histopathological or immunohistochemical data about these

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lesions although odontogenic epithelium has an abnormal transformation potential. Today, as a result of previous studies odontogenesis is a well known prosses. On the other hand, etiology and pathogenesis of most lesions except for a few cystic lesions which are known to develop in consequence with inflammatory events are not well known yet and being searched.[8] It is, however, reported that some odontogenic cysts manifest clinically aggressive courses while some other histomorphologically immature odontogenic tumors have relatively milder aggressive characteristics in clinic. Why these lesions developing from the tissue rests in odontogenesis with a common histogenesis exert different clinico-pathologic features from each other cannot be explained and still controversial. The literature points out that the research so far has focused on the pathogenesis of these lesions rather than their etiology. Although various approaches are being followed to investigate pathogenesis of lesions with an unknown etiology, immuhistochemical methods searching embryohistogenesis or proliferative characteristics of lesions stand for the majority of researches about odontogenic cysts and tumors. Current genetic and molecular researches report that treatment options might be managed by analyzing proliferation markers of aggressive neoplasms.[9]

Immunohistochemical methods are developed with the purpose of examining proliferating cell phenotypes through double staining techniques of cell-cycle related antigens.[10] Cellular proteins such as cyclins, proliferating cell nuclear antigens and histones having direct or indirect influence on cell proliferation have been identified. Such proteins, required by the DNA polymerase-α subunit and completion of cell-cycle, have been reported to have an increased synthesis during interphase stage and disappear at the end of the mitosis.[11,12] It has been proposed that such proteins might serve as markers about cell proliferation mechanisms.[13] (There are immunohistochemical studies in which proliferation markers are used to investigate proliferative potentials of odontogenic cells. In this review we aim to analyze use and effecttiveness of commonly used proliferation markers such as Ki-67, p53, PCNA, minichromosome maintenance proteins (MCM). To this end we conducted an online search in Turkish and English publications from 1998-2011 available on Pubmed (National library of medicine, (www.pubmed.com) and Google (www.google.com) websites. In addition, manual search was implemented on relevant books, periodicals and printed materials available at the Library of Yeditepe University, Dentistry Faculty.

Ki-67

A proliferation marker used to demonstrate the proliferative cell number within the tumors, Ki-67, was initially utilized by Gerdes et al. in 1983. It has a wide usage as it is detectable by simple histopathological methods.[14] Ki-67 recognizes the antigen within the proliferating cell nuclei and is indicative of division activity.[15]

While Ki-67 binding can be observed during the G1, S, G2, and M phases of cell-cycle it can not be detected at the early G1 phase.[14] Expression of this marker reaches to its maximum level during the G2 and M phases. The detection of Ki-67 in tumor tissues refer to the rate of cells in cycle.[16] Development of microwave technique in 1992 revealed MIB-1is an antigen equivalent to Ki-67. With the use of this technique, Ki-67, its use was limited only to fresh and frozen tissues, can be used on paraffin blocks as well.[17] In their study comparing immunohistochemical values of monoclonal and polyclonal Ki-67, PC10, MIB-1, and JC1 antibodies in malign and normal tissue samples Rose et al. described MIB-1 and polyclonal Ki-67 as proliferation markers with possible routine practice.[18] Ki-67 is a widely used marker to identify the proliferative activities and transformation processes of cells into carcinoma in premalign, dysplastic or tumoral formations of oral cavity.[19,20] It has been concluded that the increased Ki-67 expression may be an early stage sign of the changes in oral mucosa.[21] Moreover, a higher expression in inflammatory follicles and in turn an elevated cell turnover of DF epithelial structures can be evaluated.[22] Importance of Ki-67 expression in tumor prognosis is a subject of debate.[23] In literature there are some studies which demonst- rate a poor prognosis in tumors with a high proliferation rate. But there are also other researches which indicate that Ki-67 expression is not a good indicator for tumor prognosis.[24] Some authors have stated a significant correlation between malign transformation and Ki-67 expression.[25] In addition to that Ki-67 was reported to have usage both in diagnosis and determination of

treatment efficiency and capability to demonstrate susceptibility of tumor to chemotherapy and radiotherapy.[26] Toi et al. assessed Ki-67 index of the cancerous tissue during the treatment period concluding that the change in Ki-67 expression in comparison to basal levels is a determinative factor to offer customized treatments and as a result more effective treatments might be administered.[27] Ki-67 expression was pointed out as an important factor in finding out the recurrence.[28] Kropveld et al.[29] have shown T2 laringeal carcinoma tumor cells detected to express high levels of Ki-67 have a very well response to radiotherapy and a low recurrence in these cells In their study on keratocystic odontogenic tumor (KOT) Mendes et al. highlighted that relapse potential of KOTs cannot be clearly decided using surgical methods and have associated proliferation markers such as PCNA, Ki-67 and p53 with recurrence as well as progression rate of KOT.

In spite of its use in many lesions it is also stated that remember Ki-67 proliferation marker has a low efficiency in certain lesions. Souza et al. have concluded that despite it presents a more aggressive clinical picture central giant cell lesion has a lower proliferative activity in comparison to peripheral giant cell lesion and therefore the tissue biology of central giant cell lesion can not be based on the this marker.[30] Lack of Ki-67 expression in G0 phase of cell proliferation whereas it is active in G1, S, and G2 phases has been underlined as an important indicator by Bullwinkell et al.[31] It is therefore suggested that it might not be possible to detect the proliferation of cells at the G0 stage using this marker.

p53 Tumor Suppressor Gene

p53 gene was described for the first time in 1979 by Arnold Levine at University of Princeton. It is a phosphoprotein made up of 393 amino acids weighing 53 kilodaltons. p53 was believed to be an oncogene until 1989. In 1989 Bert Vogelstein reported that it functions as a tumor suppressor gene while mutant form of p53 acts in tumor formation.[32]

In following years p53 gene was reported to have an essential role in a number of cellular events such as cell cycle control, DNA repair, genome stability, apoptosis, differentiation and angiogenesis.[33] Called as the guardian of genome, p53 protein is shown to inhibit proliferation of cells with DNA damage. The reported ways of exerting this action is either to cease cell cycle until DNA damage is repaired or to target the cell to enter apostosis in case the cell fails to repair.[33]

Wild type p53 gene is located in human chromosome 17 and it is reported as the most frequently mutated gene in cancer.[32] Suppressing the cell's growth and transformation, this gene is a leading proliferation control factor.[33] Immunohistochemical detection of p53 gene is argued to be difficult as it exists in low quantities in health tissues with a short half-life, 6-20 minutes.[32] On the other hand, while wild type p53 gene acts as a tumor suppressor, mutant form has a tumorigenic activity.[34] Therefore, in immunohistochemical studies, mutant p53 expression is more usable.

Since p53 is the most frequently mutated gene in human cancers, it is known to be effective in disruption of the normal cell growth control through leading the accumulation of genetic alterations. Researches associate a positive p53 gene result to tumor development. p53 gene expression have been shown in squamous cell carcinomas of head, neck and mouth[35], osteosarcomas of jaw[36], malign oral mucosal lesions[37], oropharyngeal squamous cell cancers, lymphomas, reactive lymph nodes, and lymphatic malignancies[38], KOT and ameloblastomas.[39] Shear have detected p53 in 11 of 13 KOTs, 6 of 9 ameloblastomas, and both of 2 odontogenic carcinomas while no p53 detection is reported in any of the dentigerous or radicular cyst samples.[40] These results are also supported by other studies.[41] Nevertheless it was also reported that p53 protein is only detectable in KOTs among the jaw cysts along with a higher PCNA existence dentigerous or radicular cysts compared to KOTs.[42] Öktemer, reports higher expression of this marker may help us explain the aggressive course of KOT in comparison to other odontogenic cysts.[39]

Proliferating Cell Nuclear Agent (PCNA)

PCNA was identified in 1978 by Miyachi et al. in the sera from a systemic lupus erythematosus patient. It has been named after its intense detection in proliferating cell nuclei. PCNA is formed by 262 amino acids.[43] Mathews et al. have revealed out that PCNA and cyclin are actually the same protein.[44]

PCNA is observable during the late G1 phase of the cell-cycle and reaches a peak S-phase. Later in M phase and quiescent state immunohistochemically PCNA expression is not found and PCNA half-life is

reported to be 20 hours.[45]

PCNA expression is associated both with the active DNA replication and with DNA damage resulting in the carcinogenesis which leads the interpretation that PCNA expression might be used as a marker of irregular cell proliferation. However, it may exert higher rate of unassociated deviations when compared to other proliferation markers. In comparison to Ki-67, PCNA specifically gains attention during the S phase.[45] Decrease in its expression during the S phase[46] stands for a reduced proliferative activity.[46]

In a similar manner to its use in hematological malignancies, malignancies of gastrointestinal tract; breast skin, and urinary system malignancies, PCNA find its use as a proliferation marker in maxillofacial region, as well.[47-49] Shear has associated PCNA with cellular replication reporting that it is stimulated by growth factors and exists in higher quantities in KOTs than in dentigerous cysts and radicular cysts . In line with this he discusses its expression is associated with the aggressiveness of the lesion.[40] On the other hand, while p53 and Ki-67 expressions were reported to be useful in differential diagnosis of glandular odontogenic cyst, PCNA expression is not useful.[50]

Minichromosome Maintenance Proteins

In all eukaryotic cells, initiation of DNA synthesis occurs at defined replication sites.[51] Proteins forming the pre-replicative complex are required so that the DNA synthesis can take place.[52] Initially described in the yeast *Saccharomyces cerevisiae* the new proliferation marker, MCM proteins take part in the formation of the pre-replicative complex and therefore they are necessary proteins to initiate and regulate DNA synthesis.[51,53] MCM 2–7 proteins are structurally similar to each other and have similar action mechanisms to other markers in the cell cycle.[54] MCM binds to the DNA regions to which Cdc6 proteins and origin recognition complex have already bond sequentially forming altogether the pre-replication complex.[55] Allowing the DNA synthesis this complex also restricts DNA replication irreversibly to once per cell cycle thus ensuring the genome stability.[55,56] However, failure to regulate the activity of MCM proteins indicates a disruption in cell's genome stability and occurrence of an abnormal increase in proliferation.[57]

Existence and activity of MCM proteins during the cell cycle are well defined. It is reported that the protein is observed at all phases of cell-cycle but it disappears once the cell-cycle is completed or the cells undergoes differentiation. On the other and these proteins are not observable in cells with DNA repair mechanisms[51].

Recent studies highlights MCM proteins as one of the best proliferation markers to estimate tumor formation[58] Taking these properties into consideration MCM proteins are documented to have a possible use as specific markers of proliferative cells[59], their immunoreactivity is of potential clinical significance in certain malign tumors[59], and they might be useful in determination of prognosis in lung and prostate cancer.[60,61] They are also stated to be important in identification of high risk groups in some cancer types such as stage T1 bladder cancer.[62] The marker is also reported to provide reliable and objective findings in histopathological classification of larynx lesions. Chatrath et al. found increasing Ki–67 and MCM-2 expression in epithelia in: normal larynx, laryngeal dysplasia and laryngeal squamous cell carcinoma (SCC) respectively. They argued that MCM–2 expression can be used safely.[63] Proliferation marker MCM–2 has been investigated in healthy dental follicles. Cabbar et al. revealed out an higher proliferation rate in dental follicles of the asymptomatic impacted third molars when compared to healthy gingiva reporting MCM–2 expression indicates that odontogenic cells of asymptomatic dental follicles are likely to be actively proliferating. They also observed a greater expression in inflammatory follicles and discussed this elevation is supporting the view that epithelial structures in DF have an increased cell turnover.[64] Another research investigating the levels of markers Ki-67 ve MCM-2, has explained the high expression of MCM-2 by lack of Ki- 67 expression during the early G0 and early G1 phases of cell-cycle.[65] Therefore MCM–2 expressions are reported to provide more precise results in cytological diagnosis.[66]

DISCUSSION AND CONCLUSION

Variations in the proliferation rates of oral epithelium have an important role in the pathogenesis of cysts and tumors derived from odontogenic epithelial rests, dental follicles and epithelial lining of the oral mucosa.[67] For that reason, determination of the proliferation potentials of these epithelial cells

gains importance in treatment and prognosis of these lesions. Immunohistochemical researches employing proliferation markers such as Ki–67, p53, PCNA, and MCM-2 have been conducted in order to specify proliferative potential of epithelia. But these researches are reporting controversial results.

Considering Ki–67 proliferation marker which is already in routine use and is a possible indicator of genetic abnormalities co-existing with the premalignant and malignant lesions of oral cavity.[40,68] In literature there are some studies which demonstrate a poor prognosis in tumors with a high proliferation rate. But some authers indicate that Ki-67 expression is not informative about tumor prognosis. In addition to that Ki-67 was reported to have usage both in diagnosis and determination of treatment efficiency and capability to demonstrate susceptibility of tumor to chemotherapy and radiotherapy.[24] It is routinely in use for the jaw cysts but it should be taken into consideration that Ki-67 expression cannot be detected in G0 phase. So it might cause false negative results if the proliferating cells are in this stage[31]. In a recent study, Ki-67 was studied in tooth germs and it is shown that proliferating cells most likely influence the tooth germ.[69]

Since p53 is the most frequently mutated gene in human cancers, it is established to be effective in disruption of the normal cell growth control through leading the accumulation of genetic alterations. Researches associate a positive p53 gene result to tumor development but unfortunately not for the jaw cysts[35]. Proliferation rates of odontogenic epithelia of jaw cysts are also studied with this marker. It is reported that p53 is only detectable in KOTs among the jaw cysts and it is probaply because of the KOTs tumorogenic origin[40]. Regarding this data p53 is not a referred marker for jaw cysts.

PCNA expression is reported to have a possible use of irregular cell proliferation. PCNA expression is associated both with the active DNA replication and with DNA damage resulting in the carcinogenesis. In the studies which investigated the effect of this marker, has reported that PCNA expression is associated with cellular replication in dentigerous cyst, radicular cyst and glandular odontogenic cyst and it is related with the aggressiveness of the lesions but has no use for the differential diagnosis.[50,40] However, higher rate of deviations were shown compared to other proliferation markers.[45] Taking part in the formation of pre-replicative complex, MCM proteins are required to initiate and regulate DNA eukaryotic synthesis. Failure to regulate the activity of MCM proteins have been associated with a disruption in cell's genome stability and occurrence of an abnormal increase in proliferation.[55-57] Recent studies highlights MCM proteins as one of the best proliferation markers to estimate possible tumor formation.[53] Taking these properties into consideration MCM proteins are documented to have a possible use as specific markers of proliferative cells their immunoreactivity is reported to have a potential clinical significance in certain malign tumors.[59] It is reported that the MCM-2 expression is higher in follicles with squamous metaplasia which is indicating cystic transformation. Therefore authors suggested that MCM-2 is a valuable diagnostic tool for cystic transformations.[64-66]

As a result of the literature review, the need of implementing histopathological, immunohistochemical, and clinical studies examining larger number of cases arises as a common view. These should investigate the proliferative potential of developmental and inflammatory cysts directed to improve the diagnosis and prognosis of lesions through association of findings with the clinical parameters.

Ki-67 proliferation marker is already in routine use while action mechanisms and safety of other proliferation markers have to be determined and/or reliable markers must be developed to obtain more accurate results by their use.

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