Original Article

The anecdote of viral etiopathogenia in ameloblastoma and odontogenic keratocyst: Why don't we let it go?

Bacem A.E.O. Khalele*

Ministry of Health, Cairo, Egypt

ARTICLE INFO

Article history:

Received 1 December 2016

Received in revised form 19 February 2017

Accepted 5 April 2017

Available online 14 April 2017

Keywords:

EBV LMP-1

HPV

Ameloblastoma

KCOT

Odontogenic tumors

OKC

ABSTRACT

Background: Ameloblastoma (AM) and odontogenic Keratocyst (OKC) are destructive odontogenic lesions of the gnathion. Although their exact pathogeneses are not yet totally understood, the viral etiopathogenesis in AM and KCOT has been proposed. True to syndromic keratocystic odontogenic tumor (sKCOT) and non-syndromic OKC is the high recurrence rate.

Objectives: Given that shared pathways trailed by AM and by sKCOT/OKC have been suggested, this study, however, contrasts the expression of AM and OKC for viral antibodies.

Method: A total of archival 80 paraffin blocks of cases of parakeratinized odontogenic keratocyst (non-syndromic KCOTs) and of ameloblastomas (n = 40 for each) were included in this study to be sectioned and stained for two immunohistochemical markers: anti-human papillomavirus and Epstein-Barr virus-encoded latent membrane protein.

Results: All the submitted cases of AM and parakeratinized OKC were negative for both markers: anti-HPV and anti-LMP-1.

Conclusions: Although results could have been biased, given the same ethnic group and territory examined in this study, all cases were negative for both markers. Therefore, the viral contribution to the etiopathogenesis in AM and OKC could not be established in this study.

© 2017 Craniofacial Research Foundation. All rights reserved.

1. Introduction

Ameloblastoma (AM) usually affects young adults in the fourth and fifth decades of life, causing local discomfort and jaw expansion. AM is characterized by a benign clinical behavior, possibly leading to local recurrences.¹ Keratocystic odontogenic tumor (KCOT), solitary or multiple, develops in the mandible or maxilla, and occasionally on the gingiva as a peripheral counterpart.² Multiple KCOT is usually one of the stigmata of the inherited nevoid basal cell carcinoma syndrome (NBCCS). KCOT may evince a syndromic association (henceforth sKCOT) or non-syndromic incidence (henceforth OKC). Irrespective of the subclinical excetra of gnathic keratocystic lesions, the potential for local destruction, relatively high recurrence rate and tendency to multiply, particularly when associated with the NBCCS, are conspicuous.³

Both AM and sKCOT are characterized by a benign, yet locally invasive, behavior with a high risk of recurrence. Both can

demonstrate an involvement of adjacent soft tissues, infiltration into the cancellous bone, and destructive growth. Recently, there is mounting evidence as regards the activation of the mitogen-activated protein kinase pathway—posing a prominent role in the pathogenesis of AM and sKCOT/OKC. The discovery of recurrent activating mutations in FGFR2, BRAF, and RAS in a large majority of AM has highlighted a dysregulation of mitogen-activated protein kinase signaling; signifying a potential role as a diagnostic marker.⁴ Somatic mutations affecting the sonic hedgehog (SHH) pathway, specifically Smoothed (SMO), have been suggested to be in the etiopathogenesis of ameloblastic lesions. SMO pathway was claimed to be characteristic of maxillary AM while it might serve as either an alternative pathogenetic mechanism or as secondary mutations in mandibular ameloblastic lesions.⁵

Pertinently, mutations in the PTCH result in an aberrant activation of SHH signaling pathway in sporadic and syndromic KCOTs. Zhang et al.⁶ postulated that any strategy to develop antagonists of active receptor, transcriptional factors of SHH signaling pathway could induce effective treatment for KCOT. A close clinicopathological association of sKCOT and AM has been reported.⁷ Gurgel et al.⁸ concluded transcriptional profiles of SHH

* Corresponding author.

E-mail address: bacemottoman@gmail.com (B.A.E.O. Khalele).

pathway genes in sKCOT/OKC (5 and 18 cases respectively) and in 11 cases of mandibular AM. Recruiting qPCR and immunohistochemistry, they detected an overexpression of upstream (PTCH1 and SMO) and downstream (GLI1, CCND1 and Bcl-2) genes in the SHH pathway which proposed a constitutive activation of this pathway in sKCOT/OKC and in AM. This also prospected a shared mechanism for the development of these lesions.

The involvement of viral etipathogenesis in AM and in sKCOT/OKC has been postulated and propagated by several studies. This holds true especially when it comes to naming human papilloma and Epstein-Barr viruses.^{9–13} Therefore, this study uses a pair of immunohistochemical markers, which are expected to scrutinize the applicability of this hypothesis in AM and OKC. Moreover, this paper shall tackle re-allocating non-syndromic KCOTs back to odontogenic keratocyst (OKC) given the WHO's controversial promotion of all OKC to KCOT in 2005.

2. Material and method

A total of eighty archival cases of odontogenic parakeratinized keratocyst (*non-syndromic KCOTs*) and of ameloblastomas ($n = 40$ for each) were included in this study. All cases were stained for two immunohistochemical markers: anti-human papillomavirus and Epstein-Barr virus-encoded latent membrane protein (LMP-1). Lesional slides were contrasted to twenty archival cases of normal mucosa and tooth follicles. Of the 40 cases of AM, there were 7 unicystic, 3 desmoplastic and 30 solid/multicystic AMs (9 plexiform, 8 follicular, 5 basaloid, 4 acanthomatous, 3 granular and 1 adenoid). All the submitted cases of KCOT were non-syndromic parakeratinized KCOTs; yet, they revealed variable histological features.

From the archival formalin-fixed paraffin tissues blocks, 4 μ m sections were cut and mounted on positively charged glass slides. Sections were deparaffinized with xylene and rehydrated in graded ethyl alcohol. Sections were then heated using the microwave with citrate buffer (pH 6.0) for 7 minutes to retrieve antigens. For immunostaining, a universal kit (R&D Systems; USA) was used. Endogenous peroxidase was blocked with 3% H_2O_2 . Slides were

next washed by Tris-buffered saline for 15–30 minutes and were subsequently incubated with Epstein-Barr virus-encoded latent membrane antibody (CS1-4 clone:anti-LMP1; dilution of 1:100, Dako, Carpinteria, CA) and with mouse monoclonal anti-HPV antibody (clone K1H8, dilution of 1:50, DAKO, Carpinteria, CA). Diamino-benzidine, after rinsing with PBS, was used as a chromogen. Sections were then dehydrated in graded alcohol, and were cleared in xylene to be mounted and examined.

3. Results

Staining the normal mucosa and tooth follicles for anti-HPV and for anti-LMP1 showed no immuoreactivity. Moreover, all cases of AM, KCOT/OKC and of control group were negative both for anti-LMP1 and for anti-HPV. Even a brownish ting of nuclear expression could not be detected in the studied samples. Of the 40 cases of AM, there were 7 unicystic, 3 desmoplastic and 30 solid/multicystic AMs (9 plexiform, 8 follicular, 5 basaloid, 4 acanthomatous, 3 granular and 1 adenoid) (Fig. 1). All the submitted cases of KCOT were non-syndromic parakeratinized KCOTs (sporadic OKC); yet, they revealed variable histological features (Fig. 2). All AMs evinced negative immunoreactivity for anti-HPV and for anti-LMP1 (Fig. 3) and so did the submitted cases of OKCs (Fig. 4).

4. Discussion

Basically, odontogenic tumors comprise an unusually diverse group because odontogenesis is a complicated process in which cells, in various stages of differentiation, contribute to the numerous phenotypes of histological variants in the odontogenic lesions.¹⁴ Although odontogenic lesions share the same sources of odontogenic epithelium, they exhibit different degrees of local aggressiveness as regards their biological behavior. Odontogenic cysts are generally expansile lesions with favorable prognosis whereas odontogenic tumors are destructive lesions with variable prognosis.¹⁵

Comparing AM with sKCOT/OKC was generally justified because of their high rate of incidence and recurrence. The controversy

Fig. 1. Photomicrograph of H&E stained slides displaying different types and subtypes of the included AMs. (a) Unicystic AM showing a characteristic budding [40x]; (b) Desmoplastic AM revealing a rich collagenous stroma and reduced ameloblast-like cells [20x]; Solid/Multicystic AM: (c) Acanthomatous pattern revealing areas of squamous metaplasia and remarkable keratinization [20x]; (d) Basaloid pattern showing typical basal cell arrangements [20x]; (e) Granular pattern characterizing a granular cytoplasm in an ameloblastomatous follicle [40x]; (f) Follicular pattern with an area of cystic degeneration [40x]; (g) Plexiform pattern showing anastomosing cords of ameloblast-like cells and a myxomatous degeneration in the connective tissue where some condensing osteoclast-like cells recapitulated a chondroid-like appearance "upper left" [20x]; and (h) Adenoid pattern demonstrating a duct-like structures interspersed with the ameloblastic follicles. All show tall columnar epithelial cells [40x].

Fig. 2. Photomicrograph of H&E stained slides various features of the included KCOTs. (a) Keratocystic wall, with variable thickness, overlying a fibrous stroma [20×]; (b) Typical palisading basal cells of KCOT and luminal keratin formation; (c) KCOT showing mild suprabasal dysplasia; and (d) KCOT demonstrating splitting at the epithelial-CT interface as well as corrugated thickened keratin layer.

about KCOT, either a cyst or neoplasm, has been keeping fierce. In advocating its cystic nature, the shrinkage of size after being treated by marsupialization is a basic clue. It is also evident that the intracystic fluid levels of IL-1 α , before marsupialization, were significantly higher than those of IL-6 and TNF- α in OKCs after marsupialization and so was the Ki-67 labeling index of the epithelial cells.¹⁶

The same point was also rejected because studies on their behavior, histopathology and molecular biology lead one to believe

that retention of part of the cyst lining denotes remaining lesional tissue with potential for further growth and infiltration.¹⁷

In advocating the neoplastic nature of KCOT, Agaram et al.¹⁸ in their molecular analysis, using a microdissection and semiquantitative genotyping analysis, suggested that sKCOT are neoplastic based on detecting clonal loss of heterozygosity of common tumor suppressor of genomic DNA in ten cases of OKCs. However, the parakeratinized sKCOTs have shown greater mitotic figures in the basal and suprabasal layer than in sporadic OKCs.¹⁹ Other findings

Fig. 3. Photomicrograph of AM revealed negative immunoreactivity for (a) anti- HPV and for (b) anti-LMP1 [Original magnification: 40×, 20× respectively];.

Fig. 4. Photomicrograph of OKC revealed negative immunoreactivity for (a) anti- HPV and for (b) anti-LMP1 [Original magnification: 40 $\times$, 20 $\times$ respectively].

show differences between the immunohistochemical expression of tenascin, fibronectin and collagen IV in syndromic and non-syndromic KCOT which, again, might promote the neoplastic nature of syndromic sKCOT but not that of sporadic OKCs.²⁰ Pursuing the neoplastic nature further, survivin may contribute to the local aggressive behavior of sKCOT/OKC, and thus support the emerging opinion of their neoplastic nature.²¹ Stressing the risky nature of OKCs, Kamarthi et al.²² have reported an intraosseous verrucous carcinoma ex-orthokeratinized OKC. The clonal nature of sKCOTs, which was further assessed by a phenotypic assay, revealed its monoclonal pattern in few cases. This suggests that sKCOTs originate from one altered clone of odontogenic cells.²³ There, it is worthy to observe that most of studies which reported genomic DNA mutations, other than PTCH gene, are confined to syndromic KCOT. The other studies which reported mutations in sporadic KCOT (OKC) have recruited too small a scale of archival cases.

Moreover, non-syndromic KCOTs, or sporadic OKCs, fail, at the molecular level, to establish any consistent mutation profiles. Also, cryotherapy (freezing) with liquid nitrogen and the use of the fixative Carnoy's solution placed in the cystic cavity of OKC have proven effective in treating such locally aggressive lesions. Taken together, the neoplastic nature of non-syndromic KCOTs cannot be assessed.²⁴ More important, the shrinkage of size after treating non-syndromic KCOTs by marsupialization, which is attributed to decreasing IL-1a and reducing the epithelial cell proliferation, is considered compelling evidence of the cystic nature of these lesions.²⁵

Epstein-Barr virus, a ubiquitous lymphotropic herpes virus, is implicated in several human tumors. Its involvement was suggested as a possible etiologic factor and so was the proposal of HPV; secondary to the remarkable koilocytosis which was appreciated approximately in one fifth of sKCOTs.²⁶ HPV may provide oncogenic phenotypes and create a scenario that supports genomic structural aberrations and mutations. This, in turn, can trigger ERK1/2, MAPK through EGFR-independent signaling cascades.²⁷ Because of the hypothetical possibility of evoking MAPK pathway, which plays an effective role in the pathogenesis, or even proliferation, of AM and sKCOT/OKC, HPV and EBV involvement in the etiopathogenesis of such odontogenic lesions has been advocated.

Underpinning the literature, Alsaegh et al.²⁸ detected HPV-L1 protein, which is usually expressed in the active phase of the viral infection and is necessary for viral cellular cycle completion, in thirteen cases of OKCs (out of 19 studied cases). In revisiting the etiology, pathogenesis and treatment options of OKCs, Menon²⁶

has found, in a retrospective study of 183 OKC cases, that 17.1% of the cases showing koilocytosis. Given that koilocytosis is a histologic feature of viral infections, HPV etiopathogenesis was suggested. This was a misreading because what Alva et al.²⁹ have concluded was different. The 17.1% of the cases showing koilocytosis in OKCs did not stain positive for HPV. Actually, Alva et al.²⁹ emphasized that they traced a single positive case for HPV but they think, based on archaic findings in cervical cancer, that this may also be the case with OKCs.

In AM, several studies have regarded the presence of HPV in their studied AM samples as a secondary contamination, from the mucosal epithelium, induced by the surgical manipulation. Therefore, they did not consider HPV a causative factor in the pathogenesis of AM.^{30–33} This holds true especially when Verduin et al.³⁴ studied 29 cases of AM of which a single case demonstrated a low-risk HPV subtype in a peripheral lesional expansion. Such a case was observed in a patient with an HIV-infection whose maxillary ameloblastoma was recurred multiple times, necessitating at least six surgical procedures, with tumor locations ranging from the maxillary sinus to the adjacent skin and soft tissue. Thus, they jettisoned the assumption of HPV etiopathogenic role in gnathic and peripheral AMs. Moreover, a recent systematic review of immunohistochemical markers of AM has discarded the idea of any viral involvement in the oncogenesis of AM.³⁵

Several EBV proteins, including LMP1, LMP2, BZLF1 and the tegument protein BGLF2, can trigger mitogen-activated protein kinase signaling, through its induction of Fra-1 and c-Jun genes as well as through its activation of AP-1 and NF- κ B reporters.^{36–38} In cases of sKCOT, the PTCH1 gene, located on chromosome 9q (9q22.3), acts as negative regulator of the hedgehog signaling pathway through binding sonic hedgehog, one of three ligands in the hedgehog signaling pathway, and inhibition of SMO receptor. Although it is technically possible for EBV, through its proteins, to trigger the MAPK pathway, which is involved to some extent in AM, and sKCOT/OKC, this study could not define any involvement of LMP1, immunohistochemically, in 80 cases of AMs and sporadic parakeratinized OKCs.

Thus, this study goes hand in hand with overwhelming consensus^{29–33} concerning the lack of viral pathogenic role in AM and does defy the allegation, proposed by Alsaegh et al.,²⁸ of the viral involvement in the pathogenesis of OKC. Not a single positive case could be detected in the present study, either for HPV or for EBV in AM and OKC. Therefore, we recommend jettisoning the anecdote of viral etiopathogenesis in AM and OKC. The sporadically reported cases of OKC which showed positive immunoreactivity for viral inclusion were observed in a small

sample of Chinese population. In a large populated area like China, less-than-twenty positive cases cannot be even suggestive of any viral etiopathogenesis in odontogenic AM or OKC.

5. Conclusions

Contrasting the expression of AM and OKCs for anti-human papillomavirus and Epstein-Barr virus-encoded latent membrane protein (LMP-1), this study found no positive immunoreaction in the submitted 80 cases for the HPV or EBV antibodies to the pathogenesis of such odontogenic lesions. Therefore, the assumption of viral pathogenicity in AMs and OKCs is not valid within the studied sample of the Cairene population in Egypt. Moreover, the non-syndromic KCOTs should be reclassified as OKCs. Reinstating the vast majority of sporadic KCOTs back to OKCs will return statistics on odontogenic neoplasms back to where it had been before the WHO's controversial reclassification in 2005. There, only cases of sKCOT, where PTCH gene mutation is evident, should be considered neoplastic.

Conflict of interest

None.

Funding sources

None.

Ethics committee approval

Not required.

Acknowledgment

None.

References

- Mendenhall W, Werning J, Fernandes R, Malyapa S, Ameloblastoma Mendenhall N. *Am J Clin Oncol*. 2007;30(6):645–648.
- Yamamoto K, Matsusue Y, Kurihara M, Takahashi Y, Kirita T. A keratocyst in the buccal mucosa with the features of keratocystic odontogenic tumor. *Open Dent J*. 2013 Nov;13(7):152–156.
- Myoung H, Hong SP, Hong SD, Lee JI, Lim CY, Choung PH, et al. Odontogenic keratocyst: review of 256 cases for recurrence and clinicopathologic parameters. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;91:328–333.
- Brown N. Ameloblastoma: A Review of Recent Molecular Pathogenetic Discoveries. *Biomark Cancer*. 2015;7(Suppl 2):19–24.
- Kumamoto H, Ohki K, Ooya K. Expression of Sonic hedgehog (SHH) signaling molecules in ameloblastomas. *J Oral Pathol Med*. 2004;33(3):185–190.
- Zhang L, Sun Z, Zhao Y, Bian Z, Fan M, Chen Z. Inhibition of SHH signaling pathway: molecular treatment strategy of odontogenic keratocyst. *Med Hypotheses*. 2006;67(5):1242–1244.
- Neuman A, Montague L, Cohen D, Islam N, Bhattacharyya I. Report of Two Cases of Combined Odontogenic Tumors: Ameloblastoma with Odontogenic Keratocyst and Ameloblastic Fibroma with Calcifying Odontogenic Cyst. *Head Neck Pathol*. 2015;9(3):417–420.
- Gurgel C, Buim M, Carvalho K, Sales C, Reis M, de Souza R, et al. Transcriptional profiles of SHH pathway genes in keratocystic odontogenic tumor and ameloblastoma. *J Oral Pathol Med*. 2014;43(8):619–626.
- Cox M, Eveson J, Scully C. Human papillomavirus type 16 DNA in an odontogenic keratocyst. *J Oral Pathol Med*. 1991;20(March (3)):143–145.
- Fujita S, Shibata Y, Takahashi H, Tsuda N, Okabe H. Latent infection with Epstein-Barr virus in odontogenic disorders: comparison among ameloblastoma, dentigerous cyst and odontogenic keratocyst. *Pathol Int*. 1997;47(July (3)):449–453.
- Jang HS, Cho JO, Yoon CY, Kim HJ, Park JC. Demonstration of Epstein-Barr virus in odontogenic and nonodontogenic tumors by the polymerase chain reaction (PCR). *J Oral Pathol Med*. 2001;30(November (10)):603–610.
- Khojasteh A, Khodayari A, Rahimi F, Ghaderian MH, Jafarian M, Nayeibi A, Akbarzadeh Najari R, Tabatabayippanah A, Jahangirnia A. Hypermethylation of p16 tumor-suppressor gene in ameloblastic carcinoma, ameloblastoma, and dental follicles. *J Oral Maxillofac Surg*. 2013;71(January (1)):62–6510.1016/j.joms.2012.04.033.
- Suzuki H, Sugimura H, Kitayama Y, Uchiyama Y, Masumoto K, Tanaka H, et al. Expression of p16INK4A in ameloblastoma: Immunohistochemical and FISH analysis. *Oral Med Pathol*. 2010;14:99–105.
- Anneroth G, Hansen LS. Variations in keratinizing odontogenic cysts and tumors. *Oral Surg Oral Med Oral Pathol*. 1982;54(5):530–546.
- Sapp JP, Eversole LR, Wysocki GP. Contemporary Oral and Maxillofacial Pathology. In: Rudolph P, ed. 2nd ed. USA: Mosby-Year book, Inc.; 2004.
- Ninomiya T, Kubota Y, Koji T, Shirasuna K. Marsupialization inhibits interleukin-1alpha expression and epithelial cell proliferation in odontogenic keratocysts. *J Oral Pathol Med*. 2002;31(October (9)):526–533.
- Tarakji B, Baroudi K, Hanouneh S, Azzeghaiby SN. Possible recurrence of keratocyst in nevoid basal cell carcinoma syndrome: A review of literature. *Eur J Dent*. 2013;7(Suppl 1):126–223.
- Agaram NP, Collins BM, Barnes L, Lomago D, Aldeeb D, Swalsky P, et al. Molecular analysis to demonstrate that odontogenic keratocysts are neoplastic. *Arch Pathol Lab Med*. 2004;128(3):313–317.
- Shear M, Speight P. *Cysts of the oral and maxillofacial regions*. John Wiley & Sons; 2008:15 2008 Apr 15.
- Amorim R, Godoy GP, Galvão HC, Souza LB, Freitas RA. Immunohistochemical assessment of extracellular matrix components in syndrome and non-syndrome odontogenic keratocysts. *Oral Dis*. 2004;10(5):265–270.
- Andric M, Dozic B, Popovic B, Stefanovic D, Basta-Jovanovic G, Djogo N, Andjus P, Milasin J. Survivin expression in odontogenic keratocysts and correlation with cytomegalovirus infection. *Oral Dis*. 2010;16(March (2)):156–159.
- Kamarthi N, Palakshappa S, Wadhwan V, Mohan RS. Intraosseous verrucous carcinoma arising from an orthokeratinized odontogenic keratocyst: A report of a rare entity. *Contemp Clin Dent*. 2016;7(July–September (3)):416–41910.4103/0976-237X.188586.
- Gomes CC, Oliveira Cda S, Castro WH, de Lacerda JC, Gomez RS. Clonal nature of odontogenic tumours. *J Oral Pathol Med*. 2009;38(4):397–400.
- Sharif FN, Oliver R, Sweet C, Sharif MO. Interventions for the treatment of keratocystic odontogenic tumours. *Cochrane Database Syst Rev*. 2015;5 (November (4)):CD00846410.1002/14651858.cd008464.pub3.
- Ninomiya T, Kubota Y, Koji T, Shirasuna K. Marsupialization inhibits interleukin-1alpha expression and epithelial cell proliferation in odontogenic keratocysts. *J Oral Pathol Med*. 2002;31(9):526–533.
- Menon S. Keratocystic Odontogenic Tumours: Etiology, Pathogenesis and Treatment Revisited. *J Maxillofac Oral Surg*. 2015;14(3):541–54710.1007/s12663-014-0734-5.
- Crusius K, Rodriguez I, Alonso A. The human papillomavirus type 16 E5 protein modulates ERK1/2 and p38 MAP kinase activation by an EGFR-independent process in stressed human keratinocytes. *Virus Genes*. 2000;20(1):65–69.
- Alsaegh M, Miyashita H, Zhu SR. Expression of human papillomavirus is correlated with Ki-67 and COX-2 expressions in keratocystic odontogenic tumor. *Pathol Oncol Res*. 2015;21(1):65–7110.1007/s12253-014-9789-3.
- Gonzalez-Alva P, et al. Keratocystic odontogenic tumour: a retrospective study of 183 cases. *J Oral Sci*. 2008;50(2):205–212.
- van Heerden WF, van Rensburg EJ, Raubenheimer EJ, Venter EH. Detection of human papillomavirus DNA in an ameloblastoma using the in situ hybridization technique. *J Oral Pathol Med*. 1993;22:109–112.
- Correnti M, Rossi M, Avila M, Perrone M, Rivera H. Human papillomavirus in ameloblastoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2010;110:e20–e24.
- Sand L, Jalouli J, Larsson PA, Magnusson B, Hirsch JM. Presence of human papilloma viruses in intraosseous ameloblastoma. *J Oral Maxillofac Surg*. 2000;58:1129–1134.
- Migaldi M, Pecorari M, Rossi G, et al. Does HPV play a role in the etiopathogenesis of ameloblastoma? An immunohistochemical, in situ hybridization and polymerase chain reaction study of 18 cases using laser capture microdissection. *Mod Pathol*. 2005;18:283–289.
- Verduin L, Bishop J, Mills SE. Gnathic and peripheral ameloblastomas lack human papillomavirus DNA. *Ann Diagn Pathol*. 2015;19(5):306–30910.1016/j.anndiagpath.2015.06.006.
- Khalele BA, Al-Shiaty RA. A novel marker of ameloblastoma and systematic review of immunohistochemical findings. *Ann Diagn Pathol*. 2016;22:18–2410.1016/j.anndiagpath.2016.01.005.
- Li B, Wan Z, Huang G, Huang Z, Zhang X, Liao D, Luo S, He Z. Mitogen- and stress-activated Kinase 1 mediates Epstein-Barr virus latent membrane protein 1-promoted cell transformation in nasopharyngeal carcinoma through its induction of Fra-1 and c-Jun genes. *BMC Cancer*. 2015;10(May (15)):39010.1186/s12885-015-1398-3.
- Liu X, Cohen JI. Epstein-Barr Virus (EBV) Tegument Protein BGLF2 Promotes EBV Reactivation through Activation of the p38 Mitogen-Activated Protein Kinase. *J Virol*. 2015;11(November (2)):1129–113810.1128/JVI.01410-15.
- Ren C, Amm HM, DeVilliers P, Wu Y, Deatherage JR, Liu Z, MacDougall M. Targeting the sonic hedgehog pathway in keratocystic odontogenic tumor. *J Biol Chem*. 2012;287(32):27117–2712510.1074/jbc.M112.367680.