Short Communication

The Changing Clinicopathological Profile of Ameloblastoma: An update

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Ameloblastoma (AM) is a locally aggressive benign expansible odontogenic tumor that shows a variety of clinicopathological features. AM reveals a slight preference for affecting males near their third decades with a high rate of local recurrence after resection [1]. Histologically, there are four phenotypes of AM: solid/multicystic, peripheral, desmoplastic and unicystic types. Solid/multicystic shows diverse subtypes. Although evidence on the molecular involvement of BRAF V600E mutant gene in the oncogenesis of mandibular AM and SMO in maxillary AM can be accepted now, surgical resection is the standard treatment because molecular-based therapy is still lagging [2–4]. Synchronous association of AM with other syndromes were observed in Gorlin syndrome, Gardner syndromes, epidermal nevus syndrome, Simpson-Golabi-Behmel Syndrome and Williams' syndrome[5, 6].

Malignant transformation of AM into primary intraosseous carcinoma, squamous cell carcinoma has been reported. There are high hopes for finding a molecular signature malignant ameloblastoma (either metastasizing ameloblastoma or ameloblastic carcinoma) or an immunohistochemical marker that would be of high sensitivity and specificity to distinguish the diverse ameloblastomatous lesions (with intraoral and extraoral onsets). The absence of any distinguishing histological features or immunohistochemical markers for malignant AM, when compared to benign AM, challenges its early detection[3, 7].

The controversy on the best surgical treatment approach for managing AM is attributed to several factors. First, the solid/multicystic, peripheral, desmoplastic and unicystic types demonstrate a different clinical behavior in terms of aggressiveness, response to conservative treatment (e.g., enucleation with Carnoy's solution) and recurrence. However, the many phenotypes solid/multicystic reveals, including follicular, plexiform, acanthomatous, hemangiomatous, adenoid, granular, basal, mucinous, keratoameloblastoma, adenoid and hybrid AMs do not demonstrate any significant clinicopathological behavior [3]. Second, several clinical parameters, such as the age of the patient, date of diagnosis, quality of bone, concomitant systematic disease, syndromic association with other lesions, and general health of the patient are reported to affect the invasiveness of AM. The most recent systematic review on the surgical management of AM recommends the radical treatment for both unicystic and solid or multicystic AM, although the included studies do not consider any of the clinical parameters mentioned above[8]. Third, Although recent molecular pathogenetic discoveries have proven promising in mitigating the aggressiveness of several cases when used as adjunctive therapy to reduce the size of AM, maxillofacial surgeons tend to treat the tumor by surgical resection [7].

Approximately 1,800 research articles and reviews were published about AM over the past ten years. Most of these publications delve into discussing the histological nuance of the subtypes of the conventional AM and call for new pathological taxonomies. However, only 10-20 % of these articles contribute to the effective treatment of AM [2, 9–12]. The genomic findings that may explain the molecular oncogenesis is shown in Table 1.

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Table 1. Genes commonly involved in the pathogenesis of ameloblastoma

Gene	Chromosome	Aliases
PTGS2	1	COX-2, COX2, GRIPGHS, PGG/HS, PGHS-2, PHS-2, hCox-2
CDC42	1	CDC42Hs, G25K, TKS
HSPG2	1	HSPG, PLC, PRCAN, SJA, SJS, SJS1
SDC1	2	CD138, SDC, SYND1, syndecan
IL1A	2	IL-1 alpha, IL-1A, IL1, IL1-ALPHA, IL1F1
HSPD1	2	CPN60, GROEL, HLD4, HSP-60, HSP60, HSP65, HuCHA60, SPG13
BMPR2	2	BMPR-II, BMPR3, BMR2, BRK-3, POVD1, PPH1, T-ALK
RHOB	2	ARH6, ARHB, MST081, MSTP081, RHOH6
WIPF1	2	PRPL-2, WAS2, WASPIP, WIP
RHOA	3	ARH12, ARHA, EDFAOB, RHO12, RHOH12
MME	3	CALLA, CD10, CMT2T, NEP, SCA43, SFE
BAP1	3	HUCEP-13, UCHL2, hucep-6
PIK3CB	3	P110BETA, PI3K, PI3KBETA, PIK3C1
DAG1	3	156DAG, A3a, AGRNR, DAG, LGMDR16, MDDGA9, MDDGC7, MDDGC9
GNL3	3	C77032, E2IG3, NNP47, NS
CXCL8	4	GCP-1, GCP1, IL8, LECT, LUCT, LYNAP, MDNCF, MONAP, NAF, NAP-1, NAP1, SCYB8
SPARC	5	BM-40, OI17, ON, ONT
PPP2CA	5	NEDLBA, PP2Ac, PP2CA, PP2Calpha, RP-C
TERT	5	CMM9, DKCA2, DKCB4, EST2, PFBMFT1, TCS1, TP2, TRT, hEST2, hTRT
FGF10	5	
CDKN1A	6	CAP20, CDKN1, CIP1, MDA-6, P21, SDI1, WAF1, p21CIP1
BRAF	7	B-RAF1, B-raf1, NS7, RAFB1, BRAF
EGFR	7	ERBB, ERBB1, ERRP, HER1, NISBD2, PIG61, mENA
IL6	7	BSF-2, BSF2, CDF, HGF, HSF, IFN-beta-2, IFNB2, IL-6
SHH	7	HHG1, HLP3, HPE3, MCOPCB5, SMMCI, ShhNC, TPT, TPTPS
SMO	7	CRJS, FZD11, Gx, PHLSH, SMO
TWIST1	7	ACS3, BPES2, BPES3, CRS, CRS1, CSO, SCS, SWCOS, TWIST, bHLHa38
WASL	7	N-WASP, NWASP, WASPB
PTK2	8	FADK, FADK 1, FAK, FAK1, FRNK, PPP1R71, p125FAK, pp125FAK
SNAI2	8	SLUG, SLUGH, SLUGH1, SNAIL2, WS2D
PTCH1	9	BCNS, NBCCS, PTC, PTC1, PTCH
NOTCH1	9	AOS5, AOVD1, TAN1, hN1
RECK	9	ST15
IL33	9	C9orf26, DVS27, IL1F11, NF-HEV, NFEHEV
ENG	9	END, HHT1, ORW1
PLIN2	9	ADFP, ADRP
PTEN	10	10q23del, BZS, CWS1, DEC, GLM2, MHAM, MMAC11, PTENbeta, TEP1, PTEN
MKI67	10	KIA, MIB-, MIB-1, PPP1R105
ITGB1	10	CD29, FNRB, GPIIA, MDF2, MSK12, VLA-BETA, VLAB
FGFR2	10	BBDS, BEK, BFR-1, CD332, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25

Gene	Chromosome	Aliases
BMPR1A	10	10q23del, ACVRLK3, ALK3, CD292, SKR5
YAP1	11	COB1, YAP, YAP2, YAP65, YKI
NCAM1	11	CD56, MSK39, NCAM
CTTN	11	EMS1
MAML2	11	MAM-3, MAM2, MAM3, MLL-MAML2
MDM2	12	ACTFS, HDMX, LSKB, hdm2
KRAS	12	'C-K-RAS, C-K-RAS, CFC2, K-RAS2A, K-RAS2B, K-RAS4A, K-RAS4B, K-Ras, K-Ras 2, KI-RAS1, KRAS2, NS, NS3, OES, RALD, RASK2, c-Ki-ras, c-Ki-ras2, KRAS
CDKN1B	12	CDKN4, KIP1, MEN1B, MEN4, P27KIP1
TNFRSF1A	12	CD120a, FPF, TBP1, TNF-R, TNF-R-I, TNF-R55, TNFAR, TNFR1, TNFR55, TNFR60, p55, p55-R, p60
GLI1	12	GLI, PAPA8, PPD1
HOXC13	12	ECTD9, HOX3, HOX3G
HOXC13-AS	12	HOXC-AS5
TNFSF11	13	CD254, ODF, OPGL, OPTB2, RANKL, TNLG6B, TRANCE, hRANKL2, sOdf
POSTN	13	OSF-2, OSF2, PDLPOSTN, PN
MMP14	14	MMP-14, MMP-X1, MT-MMP, MT-MMP 1, MT1-MMP, MT1MMP, MTMMP1, WNCHRS
FAM30A	14	C14orf110, HSPC053, KIAA0125
HIF1A	14	HIF-1-alpha, HIF-1A, HIF-1alpha, HIF1, HIF1-ALPHA, MOP1, PASD8, bHLHe78
BMP4	14	BMP2B, BMP2B1, MCOPS6, OFC11, ZYME
FOS	14	AP-1, C-FOS, p55
FGF7	15	HBGF-7, KGF
PLIN1	15	FPLD4, PERI, PLIN
CDH1	16	Arc-1, BCDS1, CD324, CDHE, ECAD, LCAM, UVO
MMP2	16	CLG4, CLG4A, MMP-2, MMP-II, MONA, TBE-1
CALB2	16	CAB29, CAL2, CR
TP53	17	BCC7, BMFS5, LFS1, P53, TRP53
TIMP2	17	CSC-21K, DDC8
FASN	17	FAS, OA-519, SDR27X1
BCL2	18	Bcl-2, PPP1R50
HRAS	18	H-RAS
XRCC1	19	RCC, SCAR26
TGFB1	19	CED, DPD1, IBDIMDE, LAP, TGF-beta1, TGFB, TGFbeta
CCNE1	19	CCNE, pCCNE1
MIR524	19	MIRN524, hsa-mir-524, mir-524
MMP9	20	CLG4B, GELB, MANDP2, MMP-9
BMP2	20	BDA2A, SSFSC, SSFSC1, BMP2
SNAI1	20	SLUGH2, SNA, SNAH, SNAIL, SNAIL1, dJ710H13.1
JAG1	20	AGS, AGS1, AHD, AWS, CD339, DCHE, HJ1, JAGL1
MCM5	22	CDC46, MGORS8, P1-CDC46
TMSB4X	X	FX, PTMB4, TB4X, TMSB4

To conclude, the clinicopathological profile of AM has differed as regards its malignant transformation, extra-oral incidence, synchronous occurrence with other systematic syndromes, and response to conservative and adjunctive therapeutics.

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