Cellular & Molecular Biology
Cell. Mol. Biol. 2015; 61 (6): 9-16
Published online October 30, 2015 (http://www.cellmolbiol.com)
Received on October 2, 2015, Accepted on October 8, 2015.
doi : 10.14715/cmb/2015.61.6.3

Association of NOTCH with different microRNAs in head and neck cancer

N. Masood[1]✉, M. Z. Qureshi[2] and A. Yasmin[1]

[1] Environmental Sciences Department, Fatima Jinnah Women University, Rawalpindi, Pakistan
[2] Department of Chemistry, GCU, Lahore, Pakistan

Corresponding author: Nosheen Masood, Environmental Sciences Department, Fatima Jinnah Women University, Rawalpindi, Pakistan. E-mail: nosheenmasood@hotmail.com

Abstract

Head and neck cancer is the sixth most common cancer worldwide with an alarming increase in Asian countries. Overwhelmingly increasing cell culture and pre-clinical studies are identifying wide ranging mechanisms which are instrumental in disease development, progression and resistance against different therapeutics. The scientists are unable to differentiate whether expressional mutation is a cause or a consequence of some other alterations occurring in the body. We partition this review into how NOTCH1 and p16 contribute in cancer development and how microRNAs quantitatively control NOTCH1 expression. Future studies must converge on identification of miRNAs which negatively regulate p16 and targeted inhibition of p16 targeting miRNAs will be helpful in inhibiting tumor growth, cell proliferation and induction of apoptosis. Detailed mechanistic insights related to miRNA mediated Notch regulation will also be useful in delivery of tumor suppressor miRNAs or mimics to effectively inhibit cancer.

Key words: microRNA, NOTCH1, p16, head and neck cancer, mutations.

Introduction

Head and neck cancer (HNC) is multifaceted and genomically complex disease and rapidly emerging experimental evidence is shedding light on wide ranging molecular mechanisms that underpin its development and progression. HNC is associated with tumor formation in oral cavity, nasopharynx, oropharynx, larynx, hypopharynx, paranasal sinuses and salivary glands. More than 500,000 people in the world are affected by head and neck cancer. It is reported to be the sixth most common type of cancer worldwide with 4% of cancers in men and 2% cancers in women (1). Use of tobacco, alcohol (2) and infection with human papillomavirus are believed to be the important causes of HNC. Similarly different genetic and immunological factors also contribute to the prevalence of this disease (3). Different genetic polymorphisms are frequently reported to be associated with the etiology of head and neck cancer and still many more are being discovered (4, 5). Two most important genes (NOTCH1 and p16) have been discussed here in reference to their association with micro RNAs.

MicroRNAs and head and neck cancer

MicroRNAs (miRNA) were studied recently to a larger extent in order to find out their role in the development of tumorigenesis. Continuous growth and expansion was observed in the microRNA gene family with the discovery of new members and advances in genome technologies. To date, 2042 microRNA species are known in humans. They are noncoding, highly conserved and double stranded RNA molecules comprising of 18 – 25 nucleotides. miRNAs are capable of regulating expression of different genes in biological processes like apoptosis, differentiation and proliferation at the post transcriptional level (6). Characteristically, miRNAs are categorized broadly into oncogenic and tumor suppressor miRNAs.

Dysregulation (which can be in the form of overexpression or loss of expression) of miRNA is associated with different types of human cancers, as miRNA affects cell proliferation, differentiation and apoptosis. Expression profiles of miRNA have been reported to be altered for HNC in comparison with normal tissues (7-13). Micro RNAs possess the ability to behave as proto-oncogenes, can affect different tumor suppressors and can act as tumor suppressors as well. Different types of miRNA are expressed differently in HNC expression profiles, some miRNAs were found to be upregulated and others downregulated in HNC cell lines (8,14). Micro RNA let-7g, miRNA-34a, miRNA-23a and miRNA-139 have been shown to be down regulated in oral squamous cell cancer cell lines as detected by RT PCR (15). Tongue squamous cell carcinoma also showed reduced expression of miRNA-139 and increased expression of miRNA-30a (16). Microarray analysis of head and neck cancer cell line reveal reduced expression of miRNA-449 and miRNA-24 and increased expression of miRNA-23a (8). Micro RNA expression analysis through microarray on animal model (hamster) of oral squamous cell carcinoma showed reduced expression of miRNA-26a (17). Major breakthroughs in miRNA biology have considerably improved our understanding of the mechanisms which underlie cancer and there is a rapidly expanding list of miRNAs which are currently being targeted in preclinical studies to inhibit cancer progression, reverse drug resistance and induce apoptosis.

p16 and head and neck cancer

CDKN2A gene produces 2 major proteins: p14(ARF), which binds p53-stabilizing protein MDM2

and p16(INK4), a CDK inhibitor . HNC is associated with many dynamic alterations in genome and these changes included activation of the proto-oncogenes and/or suppression of the tumor suppressor genes. Cdkn2a/p16 which is located on chromosome 9p21 is a gene involved in tumor suppression. It has been reported that many human cancers are caused because of the functional loss of p16 gene which is mostly due to hypermethylation and less commonly by homozygous deletion and point mutations. Inactivation of p16 accounts for about 80% of molecular abnormalities in HNC and p16 is mostly downregulated in HNC which causes proliferation and tumor formation. Molecular mechanism involved in suppression of tumor formation by p16 gene is that p16 protein binds to CDK4 or CDK6 (cyclin dependent kinases) and thus blocks the proliferation and this process occurs during G1-S phase of cell cycle. P16 gene expression is not found to be associated with age, sex or level of proliferation nevertheless it is associated with location of tumor formation i.e. more decreased expression of p16 in HNC in larynx as compared to HNC in pharynx (19, 20). p16 gene was epigenetically silencedin HNC due to factors like hypermethylation of promoter (20).

NOTCH1 and head and neck cancer

Notch is expressed as a heterodimer on cell surface, consisting of an extracellularly located ligand binding domain that is linked noncovalently with a transmembrane polypeptide. Signals are transduced intracellularly by interaction of Notch with Jagged or Delta-like ligands (DLLs) that induced a conformational change in Notch and exposed a previously protected site to proteolytic cleavage (21). It has previously been studied that proteolytic cleavage of Notch was triggered by different enzymes including ADAM (a disintegrin and metalloproteinase)-family protease and a γ-secretase complex (22, 23).

Ligand binding consequently induced sequentially cleaved form of Notch, processed initially by an ADAM and afterward by a γ-secretase complex. Final cleavage sequestered Notch intracellular domain (NICD) away from cell membrane and consequently nuclear accumulation of NICD was noted. Mechanistically, NICD facilitated positioning of specific coactivators to transcriptionally upregulate expression of target genes.

There is a direct piece of evidence suggesting considerably downregulated levels of miR-200a-3p, miR-200b-3p, miR-34b-5p, miR-34c-5p and/or miR-200c-3p in Head and neck paragangliomas that often co-occurred with genomically amplified of NOTCH pathway genes (24). Circumstantial evidence also revealed frequently mutated Notch pathway in 35.2% of oesophageal squamous cell cancer cases. 8 cases were found to be mutated for NOTCH1, 4 mutations in NOTCH2 and 2 mutations in NOTCH3 have also been reported. The mutation and amplified NOTCH1, NOTCH2 and NOTCH3 were detectable in 16.4% of cases (25).

NOTCH pathway plays an important as tumor sup-

Table 1. Different microRNAs and most commonly effected pathways involved in their role in carcinogenesis.

Cancer/Cancer cell lines/Cancer cells	MicroRNA(s)	Output/targets	References
Head and Neck squamous cell carcinoma (HNSCC)	Let-7A, miR-1, miR-206, miR-153, miR-519A and miR-506	HNSCC prevention by targeting CYP46A1, BPNT1, MCM7 and COL5A1	(61)
Nasopharyngeal carcinoma (NPC)/radio-resistant cell lines	miR-504	miR-504 over-expression; Nuclear respiratory factor 1 (NRF1), Mitochondrial transcription factor A (TFAM) and Oxidative phosphorylation (OXPHOS) complex III ↓	(62)
Laryngeal squamous cell carcinoma (SCC)	miR-223, miR-142-3p, miR-21, and miR-375	Patients with T3-4 tumors exhibited a significant upper-expression of miR-21/miR-375 level. Expression ratio of miR-21/miR-375 in patients with stage (III-IV) tumors was significantly higher.	(63)
Nasopharyngeal carcinoma (NPC)/radio-resistant NPC cell line (CNE-2-1)	miR-21	Down-regulation of miR-21 results in enhanced radio-sensitivity in the CNE-2-1 cells Higher miR-21 expression; CNE-2-1 cells proliferation at the G1 phase of the cell cycle ⊥	(64)
LSCC cell lines/laryngeal squamous cell carcinoma	miR-24	Growth and colony formation , XIAP protein expression ⊥, Apoptosis ↑	(65)
Head and Neck squamous cell carcinomas (HNC)/Tumor initiating cells (TICs)	miR-494	Bmi1, ADAM10 ↓ Stemness,Tumor aggressiveness ↓	(66)
Oral squamous cell carcinoma (OSCC)	miR-15a, miR-29a and miR-34a	Downregulated expression of miR-15a, miR-29a and miR-34a	(67)
Esophageal cancer cells	miR-124	Downregulated miR-124 STAT3 ↓, Cell proliferationandG1/S phase transition ⊥, Apoptosis ↑	(68)
Squamous cell carcinoma (SSC) cells of larynx and tongue	miR-101-3p	RIPK1↓, Drug resistance	(69)
Head and Neck squamous cell cancer (HNSCC) oropharyngeal/ laryngeal/hypopharyngeal carcinomas	miR-21, miR-200c, miR-34a and miR-375	miR-21↑, miR-200c↑, miR-34a ↑ miR-375↓	(70)

Head and Necksquamous cell carcinoma (HNSCC)	miR-196a	miR-196a+HOXB9 ↑↑ Knock-down of miR-196a expression decreases cell migration, invasion and adhesion to fibronectin Knock-down of HOXB9 expression decreased migration, invasion and proliferation	(71)
Tongue squamous cell carcinoma (TSCC) cells	miR-483-5p	Mitochondrial fission, Cisplatin sensitivity↓	(72)
Esophageal squamous cell carcinomas /EC109 and EC9706 cells	miR-889	DAB2IP↓, proliferation↑	(73)
Hypopharyngealcancer	miRNA-203	Cell proliferation, colony formation ↑, TP63, B3GNT5↓	(74)
Head and Neck squamous cell carcinoma (HNSCC)/ human HNSCC cell lines (JHU-13 and JHU-22)	miRNA-128	BMI-1, BAG-2, BAX, H3f3b, Paip2↓	(75)
Nasopharyngeal carcinoma (NPC)/paclitaxel-resistant CNE-1/Taxol, HNE-2/Taxol and 5-8F/Taxol cell sublines	miR-1204	Tumor growth ↓	(76)
Oesophageal cancer (EC)	miR-503	Tumor cell proliferation↑ Poor disease-free and overall survival	(77)
Head and Neck adenoid cystic carcinoma (HNACC)	hsa-miR-214, hsa-miR-125a-5p, hsa-miR-574-3p, hsa-miR-199a-3p/199b-3p and hsa-miR-199a-5p	(hsa-miR-214, hsa-miR-125a-5p, hsa-miR-574-3p, hsa-miR-199a-3p/199b-3p, hsa-miR-199a-5p)↑ hsa-miR-452↓	(78)
Nasopharyngeal carcinoma (NPC)	miR-143	Viability, colony formation, and anchorage-independent growth ⊥, KRAS ⊥	(79)
Oral squamous cell carcinoma (OSCC)	miR-26a/b	Lower expression of miR-26a and miR-26b; Cancercell migration and invasion ⊥, TMEM184B ⊥	(80)
Esophageal cancer (EC)	miR-21, miR-143, miR-196a, miR-203, miR-205 and miR-221	miR-205↑ (miR-143, miR-203 and miR-205) ↓	(81)
Head and Neck squamous cell carcinoma (HNSCC)	MicroRNA-93-5p (miR-93)	miR-93 overexpression leads tumour progression, metastasis and poor prognosis	(82)
Esophageal squamous cell carcinoma (ESCC)	miR-101 and miR-217	(MALAT1, migration and invasion)↓	(83)
Head and Neck squamous cell carcinoma (HNSCC)	miR-196a	Annexin A1 (Cell proliferation, migration and invasion and epithelial to mesenchymal transition) ↑	(84)
Anaplastic thyroid cancer (ATC)	miRNA miR30a	Lower expression of miR30a; LOX	(85)
Esophageal squamous cell carcinoma (ESCC)	miR-494	CLPTM1L↑ Cell proliferation, invasion↑	(86)

Up-regulation = ↑ , Down-regulation = ↓, Inhibition = ⊥, Combined up-regulation = ↑↑

pressor as well as oncogene in head and neck cancer that was revealed by exome sequencing and microarray studies (26, 27). Different mutations have been reported in NOTCH1 gene producing truncated proteins in head and neck cancer (28). Various mutations involving complete loss of functional phenotypes have also been found. A novel mutational spectrum was observed that mutations identified in NOTCH1 were basically present at or just close to the epidermal growth factor like ligand-binding domain (29). According to a multiplatform analysis NOTCH1 has been driving force behind cancer through gene expression, point mutation, methylation and copy number variations. Mutations were observed in NOTCH1 and NOTCH2 along with gain in copy number in JAG1 and JAG2 (30). So, it was thought that the amplifications of NOTCH ligands were supporting tumor suppressor role for NOTCH pathway in oral squamous cell carcinoma (OSCC). South and his colleagues suggested that NOTCH1 behaves as a gatekeeper because mutations in NOTCH1 were observed in the early developmental stages of cutaneous squamous cell carcinoma and down-regulation was detected in normal (looking) skin (31). NOTCH1 over-expression in head and neck cancer cell lines resulted in inhibition of the growth in vitro and tumor size was considerably reduced in mice xenografted withNOTCH1 over-expressing cancer cells (30). Treatment of head and neck cancerous cells with the inhibitor of γ-secretase in NOTCH pathway or knocking down of NOTCH1 resulted in significantly decreased cell proliferation and invasion suggesting an oncogenic role (32, 33).These findings clearly suggested diametrically opposed role of Notch induced signaling and future studies must converge on context dependent modulation of Notch signaling in head and neck cancer.

Association of mircoRNAs with NOTCH1

This section mainly deals with intricate modulation of NOTCH1 by different miRNAs. miR-34a is highly expressed in normal spleen, adrenal gland, testis and lung tissues and is one of the first and best-studied miRNAs related to carcinogenesis. miR-34a is commonly repressed in tumors like neuroblastoma, colon cancer

and non-small-cell lung cancer cell lines. Forced expression of miRNA-34a causes reduction in the ability of cell to invade in case of cervical cancer through reduced NOTCH1 expression (34).miRNA-139-5p is also reportedly downregulated in colorectal cancer. miRNA-139-5p inhibited cell proliferation, apoptosis, metastasis and also arrested G0/G1 phase of cell cycle through NOTCH1 repression (35). miRNA-449aquantitatively controlledNOTCH1 by binding to its 3′UTR and inhibiting its expression. Therefore if miRNA-449a expression is reduced it may lead to cancer formation through cell proliferation pathways (36).

Interplay of Notch and miRNAs in different Cancers

MITF has been shown to bind and transcriptionally repress miR-222/221, RBPJK-dependently. However, when melanoma cells are in contact with distal Notch ligands expressing differentiated keratinocytes, the activated NICD inhibits MITF positioning at promoter region of miR-222/221. De-repression of miR-222/221 induced invasive phenotype (49). There is evidence of miR-19a induced activation of Notch signaling and considerably enhanced cell proliferation, migration and invasive potential of cancer cells (50). Overexpression of Notch signaling was noted in miR-9 expressing breast cancer MDA-MB-231 cells. There results revealed that metastasizing potential of breast cancer cells can be inhibited by targeting of miR-9 (51).

F-box and WD repeat domain-containing 7 (Fbw7) is reportedly involved in targeting of Notch via proteasomal degradation. However, miR-223 mediated targeting of Fbw7 in drug resistant pancreatic cancer cells stabilized Notch1 protein levels. Targeting of miR-223 significantly enhanced Fbw7 levels and Notch levels were dramatically reduced (52).

However, it has recently been convincingly revealed that apoptotic activity reduced substantially in cancer cells simultaneously treated with antisense against miR-100 and Notch signaling inhibitor (53).

Association of microRNAs with p16

Micro RNA-24 has been known to be upregulated in human cancers of breast, oral, prostate, hepatic and lung, supporting the significance of miRNA-24 in cell proliferation (37-40). Cell proliferation of primary and cancer cells is controlled by p16 expression and inturn its expression is controlled by microRNA-24 (41). Another family of microRNAs known as let-7 is involved in many cancers via different molecular pathways. One of them, has-let-7g, plays an important role in inhibiting hepatocellular carcinoma via two pathways. One by inhibiting oncogene c-Myc and second is the activation of tumor suppressor gene p16. Increased expression of miRNA-23a and miRNA-30a increased expression of p16. However increased miRNA-26a directly correlated with p16 expression but surprisingly inhibition of miRNA-26a did not reduce p16 levels (42).

Hotair (Hox transcript antisense intergenic RNA) is a 2158-bp lncRNA located in the Hoxc gene cluster and reportedly upregulated in hepatocellular carcinoma. Intriguingly, p16 expression was notably enhanced in Hotair silenced cells (43).

Very little is known about miRNA regulation of Notch signaling in head and neck cancer, however, certain hints have emerged from renal cell carcinoma and hepatocellular carcinoma.

Clinical Trials of Notch Signaling Inhibitors

Confluence of information suggested testing of clinical efficacy of different Notch signaling inhibitors. RO4929097, a gamma secretase inhibitor (GSI) of Notch signaling has been noted to be ineffective against platinum resistant ovarian cancer (44). RO4929097 was also clinically insufficient against metastatic melanoma in this phase II clinical trial (45). Patients with advanced solid tumors combinatorially treated with R04929097 and Gemcitabine revealed a prolonged stable disease in 3 patients and notable response in 1 patient with nasopharyngeal carcinoma (46). Initial testing of MK-0752 was disappointing as evidenced by different reports. Toxicity management of Notch inhibitor MK-0752 in combination with dalotuzumab was challenging in advanced solid tumors and all of 12 evaluable patients experienced disease progression in the first radiological evaluation (47).

Anti-DLL4 agents are also being tested for efficacy however no recommended phase II schedules or doses have been optimized. Reportedly, complications associated with continuous antibody mediated Notch inhibition included development of neovascular tuft formation and angiomas (48). MEDI0639, a DLL4 (IgG1λ) monoclonal antibody that abrogated protein-protein interaction of DLL4 and Notch 1, is being evaluated for efficiency in patients with solid tumors(48). DLL4 antibody (Demcizumab or OMP-21M18), is another monoclonal being tested for clinical efficacy in ovarian, fallopian and peritoneal cancer, non-small-cell lung cancer, colorectal and pancreatic cancer (48).

It is interesting to mention that tumor suppressor miRNAs are frequently downregulated in cancer cells having deregulated Notch signaling. Different tumor suppressor miRNAs have shown considerable efficacy as tumor growth inhibitors in xenografted mice. Moreover, miR-34a is a tumor suppressor miRNA which has entered into clinical trials. Future studies must converge on combinatorial treatment using Notch signaling inhibitors with tumor suppressor miRNAs in preclinical studies.

Conclusion

Wealth of information is emphasizing on contributory role of miRNAs in cancer development, progression and metastasis (54, 55, 59, 60). Tumor suppressor miRNAs have attracted considerable attention and various strategies are currently being used to effectively deliver tumor suppressor miRNAs to target site (56, 57, 58). Head and neck cancer biology has undergone substantial broadening and confluence of information suggested wide ranging oncogenic and tumor suppressor proteins which contribute in cancer development and progression. miRNAs have also occupied central stage in molecular oncology and researchers have started to develop deeper understanding of the misrepresentation of miRNAs in head and neck cancer.

However, population specific data is still insufficient and future studies emphasizing on intra/inter ethnic variability in different genes in head and neck cancer will bridge the existing gaps. Notch and miRNA interplay needs closer analysis because of context and cell type specific behavior. Different tumor suppressor and oncogenic miRNAs have been evaluated in xenografted mice and comprehensive knowledge of different intracellular signaling cascades and interplay with miRNAs will be helpful in identification of true potential of therapeutics with minimal off target effects and significant clinical outcome.

Other articles in this theme issue include references (87-98).

References

1. Bose, P., Brockton, N.T. and Dort, J.C., Head and neck cancer from anatomy to biology. *Int.J.Cancer.* 2013,**133**: 2013-2023.
2. Maier, H., Dietz, A., Gewelke, U., Heller, W.,D. and Weidauer, H., Tobacco and alcohol and the risk of head and neck cancer. Clin. Investig. 1992, 70:320-327.
3. Liu, X., Chen, Z., Yu, J., Xia, J. and Zhou, X., MicroRNA profiling and head and neck cancer.*Comp.Func. Genom.* 2009, doi: 10.1155/2009/837514.
4. Toru, H., Masaharu, Y. and Shinji, T., Genetic polymorphisms and head and neck cancer risk . Int. J. Oncol. 2008, 32: 945-73.
5. McWilliams, J.,E., Evans, A.,J., Beer, T.,M., Andersen, P.,E., Cohen, J.,I., Everts, E.,C. and Henner, W.,D., Genetic polymorphisms in head and neck cancer risk. Head Neck. 2000, 22(6):609-17.
6. Chen, D., Cabay, J.R., Wang, A., Lu, Y., Khan, S.M. and Zhou, X.,MicroRNA deregulations in head and neck squamous cell carcinomas. *J. Oral.Maxillofac. Res.*2013, **4**: e2.
7. Bentwich, I., Avniel, A., Karov Y., Aharonov, R., Gilad, S., Barad, O., Barzilai, A., Einat, P., Einav, U., Meiri, E., Sharon, E., Spector, Y. and Bentwich Z., Identification of hundreds of conserved and nonconserved human microRNAs.*Nature Genetics.* 2005,**37(7)**: 766-770.
8. Tran, N., McLean, T., Zhang, X., Zhao, C.J., Thomson, J.M., Brien, C. and Rose, B., MicroRNA expression profiles in head and neck cancer cell lines. *Biochem.Biophy. Res. Comm.*2007, **358**: 12-17.
9. Avissar, M., Christensen, B.C., Kelsey, K.T. and Marsit, C.J., A MicroRNA Expression Ratio is Predictive of Head and Neck Squamous Cell Carcinoma. *Clin. Cancer Res.* 2009,**15(8)**: 2850-2855.
10. Liu, X., Jiang, L., Wang, A., Yu, J., Shi, F. and Zhou X., MicroRNA-138 suppresses invasion and promotes apoptosis in head and neck squamous cell carcinoma cell lines. *Cancer Lett.*2009, **286(2)**: 217-222.
11. Hui, A.B.Y., Lenarduzzi, M., Krushel, T., Waldron, L., Pintille, M., Shi, W., Ordonnez, B., Jurisica, I., Sullivan, B., Waldron, J., Gullane, P., Cummings, B. and Liu, F., Comprehensive microRNA profiling for head and neck squamous cell carcinomas.*Clin. Cancer Res.*2010, **16**: 1129-1139.
12. Orang, A.V., Safaralizadeh, R. and Kazemzadeh-Bavili, M., Mechanisms of miRNA-mediated gene regulation from common downregulation to mRNA-specific upregulation.*Int. J. Genom.* 2014, **2014**: 970607.doi: 10.1155/2014/970607.
13. Wald, A.I., Hoskins, E.E., Wells, S.I., Ferris, R.L. and Khan, S.A., Human papillomavirus alters microRNA profiles in squamous cell carcinoma of the head and neck (SCCHN) cell lines. *Head Neck.* 2011,**33(4)**: 504-512.
14. Hebert, C., Norris, K., Scheper, M.A., Nikitakis, N. and Sauk, J.J., High mobility group A2 is a target for miRNA-98 in head and neck squamous cell carcinoma. *Mol. Cancer.*2007, **6(5)**: 1-11.
15. Kozaki, K.I., Imoto, I., Mogi, S., Omura, K. and Inazawa, J., Exploration of tumor suppressive microRNAs silenced by DNA hypermethylation in oral cancer.*Cancer Res.*2008, **68(7)**: 2094-2105.
16. Wong, T.S., Liu, X.B., Wong, B.Y., Ng, R.W., Yuen, A.P., Wei, W.I., Mature miR-184 as potential oncogenic microRNA of squamous cell carcinoma of tongue. *Clin. Cancer Res.*2008, **14**: 2588–2592.
17. Yu, T., Wang, X.Y., Gong, R.G., Li, A., Yang, S., Cao, Y.T., Wen, Y.M., Wang, C.M., Yi, X.Z.,The expression profile of microRNAs in a model of 7,12-dimethyl-benz[a]anthrance-induced oral carcinogenesis in Syrian hamster. *J. Exp. Clin. Cancer Res.* 2009, **28**: 64.
18. Yeun, P.W., Man, M., Lam, K.Y. and Kwong, Y.L.,Clinicopathological significance of p16 gene expression in in the surgical treatment of head and neck squamous cell carcinomas.*J. Clin. Pathol.*2002, **55**: 58-60.
19. Perez-Ordonez, P.,Beauchemin, M. and Jordan R.C.K., Molecular biology of squamous cell carcinoma of the head and neck.*J. Clin. Pathol.*2009, **59**:445-453.
20. Patrick, K.H., Chang, S.S., Glazer, C.A., Califano, J.A. and Sidransky, D., Molecular techniques and genetic alterations in head and neck cancer.*Oral Oncol.*2009, **45(4)**: 335-339.
21. Tohda, S., NOTCH signaling roles in acute myeloid leukemia cell growth and interaction with other stemness-related signals.*Anticancer Res.* 2014, **34(11)**:6259-64.
22. Takebe, N., Miele, L., Harris, P.J., Jeong, W., Bando, H., Kahn, M., Yang, S.X. and Ivy, S.P.,Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update.*Nat Rev Clin Oncol.*2015, doi: 10.1038/nrclinonc.2015.61.
23. Flores, A.N., McDermott, N., Meunier, A. and Marignol, L.,NUMB inhibition of NOTCH signalling as a therapeutic target in prostate cancer.*Nat Rev Urol.* 2014, **11(9)**:499-507.
24. Cama, A., Verginelli, F., Lotti, L.V., Napolitano, F., Morgano, A., D'Orazio, A., Vacca, M., Perconti, S., Pepe, F., Romani, F., Vitullo, F., di Lella, F., Visone, R., Mannelli, M., Neumann, H.P., Raiconi, G., Paties, C., Moschetta, A., Tagliaferri, R., Veronese, A., Sanna, M. and Mariani-Costantini, R., Integrative genetic, epigenetic and pathological analysis of paraganglioma reveals complex dysregulation of NOTCH signaling.*Acta Neuropathol.* 2013, **126(4)**:575-94.
25. Song, Y., Li, L., Ou, Y., Gao, Z., Li, E., Li, X., Zhang, W., Wang, J., Xu, L., Zhou, Y., Ma, X., Liu, L., Zhao, Z., Huang, X., Fan, J., Dong, L., Chen, G., Ma, L., Yang, J., Chen, L., He, M., Li, M., Zhuang, X., Huang, K., Qiu, K., Yin, G., Guo, G., Feng, Q., Chen, P., Wu, Z., Wu, J., Ma, L., Zhao, J., Luo, L., Fu, M., Xu, B., Chen, B., Li, Y., Tong, T., Wang, M., Liu, Z., Lin, D., Zhang, X., Yang, H., Wang, J. and Zhan, Q., Identification of genomic alterations in oesophageal squamous cell cancer.*Nature.* 2014, **509(7498)**:91-5.
26. Agrawal, N., Frederick, M.J., Pickering, C.R., Bettegowda, C. and Chang, K., Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science.*2011, **333**: 1154–1157.
27. Leethanakul, C., Patel, V., Gillespie, J., Pallente, M., Ensley, J.F., Koontongkaew, S., Liotta, L.A., Emmert-Buck, M. and Gutkind, J.S., Distinct pattern of expression of differentiation and growth-related genes in squamous cell carcinomas of the head and neck revealed by the use of laser capture microdissection and cDNA arrays. *Oncogene.*2000, **19**: 3220–3224.
28. Stransky, N., Egloff, A.M., Tward, A.D., Kostic, A.D., Cibulskis, K., The mutational landscape of head and neck squamous cell carcinoma. *Science.*2011, **333**: 1157–1160.
29. Baldus, C.D., Thibaut, J., Goekbuget, N., Stroux, A., Schlee, C., Mossner, M., Burmeister, T., Schwartz, S., Bloomfield, C.D., Hoelzer, D., Thiel, E. and Hofmann, W.K., Prognostic implications of

NOTCH1 and FBXW7 mutations in adult acute T-lymphoblastic leukemia. *Haematologic*. 2009, **94**: 1383–1390.

30. Pickering, C.R., Zhang, J., Yoo, S.Y., Bengtsson, L., Moorthy, S., Integrative genomic characterization of oral squamous cell carcinoma identifies frequent somatic drivers. *Cancer Discov.*2013, **3**: 770–781.

31. South, A.P., Purdie, K.J., Watt, S.A., Haldenby, S., NOTCH1 mutations occur early during cutaneous squamous cell carcinogenesis. *J. Invest.Dermatol.*2014, **134**: 2630–2638.

32. Hijioka, H., Setoguchi, T., Miyawaki, A., Gao, H., Ishida, T., Komiya, S. and Nakamura, N., Upregulation of Notch pathway molecules in oral squamous cell carcinoma. *Int. J.Oncol.*2010, **36**: 817–822.

33. Yao, J., Duan, L., Fan, M. and Wu, X., Gamma-secretase inhibitors exerts antitumor activity via down-regulation of Notch and Nuclear factor kappa B in human tongue carcinoma cells. *Oral Dis.*2007, **13**: 555–563.

34. Pang, T.K., Leung, O.N., Ye, T.M., Liu, W., Chiu, P.N., Lam, K.W., Lee, K. andYeung, S.B., MicroRNA-34a suppresses invasion through downregulation of Notch1 and Jagged1 in cervical carcinoma and choriocarcinoma cells.*Carcinogenesis*. 2010, **31(6)**: 1037-1044.

35. Zhang, L., Dong, Y., Zhu, N., Tsoi, H., Zhao, Z., Wu, C., Wang, K., Zheng, S., Ng, S.M., Chan, F.K.L., Sung, J.Y. and Yu, J., MicroRNA-139-5p exerts tumor suppressor function by targeting NOTCH1 in colorectal cancer. *Mol. Cancer*. 2014, **13**:124.

36. Capuano, M., Iaffaldano, L., Tinto, N., Montanaro, D., Capobianco, V., Izzo, V., Tucci, F., Troncone, G., Greco, L. andSacchetti, L. MicroRNA-449a Overexpression, Reduced NOTCH1 Signals and Scarce Goblet Cells Characterize the Small Intestine of Celiac Patients. *PLoS ONE*. 2011,**6(12)**: 1-10.

37. Hatziapostolou, M., Polytarchou, C., Aggelidou, E., Drakaki, A., Poultsides, G.A. and Jaeger, S.A., Ogata H, Karin M, Struhl F K, Hadzopoulou-Cladaras M, Iliopoulos D. An HNF4a-miRNA inflammatory feedback circuit regulates hepatocellular oncogenesis. *Cell*2011, **147:**1233–1247.

38. Lin, S.C., Liu, C.J., Lin, J.A., Chiang, W.F., Hung, P.S. and Chang, K.W., miR-24 up-regulation inoral carcinoma: Positive association from clinical and in vitro analysis. *Oral Oncol*. 2010,**46**:204–208.

39. Wu, Q., Wang, C., Lu, Z., Guo, L. andGe, Q., Analysis of serum genome-wide microRNAs forbreast cancer detection. *Clin.Chim. Acta.*2012, **413**:1058–1065.

40. Nymark, P., Guled, M., Borze, I., Faisal, A., Lahti, L., Salmenkivi, K., Kettunen, E., Anttila, S. andKnuutila, S., Integrative analysis of microRNA, mRNA and aCGH data revealsasbestos- and histology related changes in lung cancer. *Gene.Chrom. Cancer.*2011, **50**:585–597.

41. Giglio, S., Cirombella, R., Amodeo, R., Portaro, C., Lavra, L. and Vecchione, A. MicroRNA miR-24 Promotes Cell Proliferation by Targeting the CDKs Inhibitors p27Kip1 and p16INK4a. *J. Cell. Physiol.* 2013, **228**: 2015–2023.

42. Lee, S., Jung, J.W., Park, S.B., Roh, K., Lee, S.Y., Kim, J.H., Kang, S.K. and Kang, K.S., Histone deacetylase regulates high mobility group A2-targeting microRNAs in human cord blood-derived multipotent stem cell aging. *Cell. Mol. Life Sci.* 2011,**68**:325–336.

43. Fu, W.M., Zhu, X., Wang, W.M., Lu, Y.F., Hu, B.G., Wang, H., Liang, W.C., Wang, S.S., Ko, C.H., Waye, M.M., Kung, H.F., Li, G. and Zhang, J.F.,Hotair Mediates Hepatocarcinogenesis through Suppressing MiRNA-218 Expression and Activating P14 and P16 Signaling.*J Hepatol.* 2015,. pii: S0168-8278(15)00343-8.

44. Diaz-Padilla, I., Wilson, M.K., Clarke, B.A., Hirte, H.W., Welch, S.A., Mackay, H.J., Biagi, J.J., Reedijk, M., Weberpals, J.I., Fleming, G.F., Wang, L., Liu, G., Zhou, C., Blattler, C., Ivy, S.P. and Oza, A.M., A phase II study of single-agent RO4929097, a gamma-secretase inhibitor of Notch signaling, in patients with recurrent platinum-resistant epithelial ovarian cancer: A study of the Princess Margaret, Chicago and California phase II consortia.*GynecolOncol.* 2015, **137(2)**:216-22.

45. Lee, S.M., Moon, J., Redman, B.G., Chidiac, T., Flaherty, L.E., Zha, Y., Othus, M., Ribas, A., Sondak, V.K., Gajewski, T.F. and Margolin, K.A., Phase 2 study of RO4929097, a gamma-secretase inhibitor, in metastatic melanoma: SWOG 0933.*Cancer.* 2015, **121(3)**:432-40.

46. Richter, S., Bedard, P.L., Chen, E.X., Clarke, B.A., Tran, B., Hotte, S.J., Stathis, A., Hirte, H.W., Razak, A.R., Reedijk, M., Chen, Z., Cohen, B., Zhang, W.J., Wang, L., Ivy, S.P., Moore, M.J., Oza, A.M., Siu, L.L. and McWhirter, E., A phase I study of the oral gamma secretase inhibitor R04929097 in combination with gemcitabine in patients with advanced solid tumors (PHL-078/CTEP 8575).*Invest New Drugs.* 2014, **32(2)**:243-9.

47. Brana, I., Berger, R., Golan, T., Haluska, P., Edenfield, J., Fiorica, J., Stephenson, J., Martin, L.P., Westin, S., Hanjani, P., Jones, M.B., Almhanna, K., Wenham, R.M., Sullivan, D.M., Dalton, W.S., Gunchenko, A., Cheng, J.D., Siu, L.L. and Gray, J.E., A parallel-arm phase I trial of the humanised anti-IGF-1R antibody dalotuzumab in combination with the AKT inhibitor MK-2206, the mTOR inhibitor ridaforolimus, or the NOTCH inhibitor MK-0752, in patients with advanced solid tumours.*Br J Cancer.* 2014, **111(10)**:1932-44.

48. Andersson, E.R. and Lendahl, U., Therapeutic modulation of Notch signalling--are we there yet?*Nat Rev Drug Discov.* 2014, **13(5)**:357-78.

49. Golan T, Messer AR, Amitai-Lange A, Melamed Z, Ohana R, Bell RE, Kapitansky O, Lerman G, Greenberger S, Khaled M, Amar N, Albrengues J, Gaggioli C, Gonen P, Tabach Y, Sprinzak D, Shalom-Feuerstein R, Levy C. Interactions of Melanoma Cells with Distal Keratinocytes Trigger Metastasis via Notch Signaling Inhibition of MITF. Mol Cell. 2015 Jul 29. pii: S1097-2765(15)00500-6.

50. Xiao W, Gao Z, Duan Y, Yuan W, Ke Y. Downregulation of miR-19a exhibits inhibitory effects on metastatic renal cell carcinoma by targeting PIK3CA and inactivating Notch signaling in vitro. Oncol Rep. 2015 Aug;34(2):739-46.

51. Mohammadi-Yeganeh S, Mansouri A, Paryan M. Targeting Of miR9/NOTCH1 Interaction Reduces Metastatic Behavior in Triple-negative Breast Cancer. Chem Biol Drug Des. 2015 May 11. doi: 10.1111/cbdd.12584.

52. Ma J, Fang B, Zeng F, Ma C, Pang H, Cheng L, Shi Y, Wang H, Yin B, Xia J, Wang Z. Down-regulation of miR-223 reverses epithelial-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. Oncotarget. 2015 Jan 30;6(3):1740-9.

53. Yang G, Gong Y, Wang Q, Wang Y, Zhang X. The role of miR-100-mediated Notch pathway in apoptosis of gastric tumor cells. Cell Signal. 2015 Jun;27(6):1087-101.

54. Fayyaz S, Farooqi AA. miRNA and TMPRSS2-ERG do not mind their own business in prostate cancer cells. Immunogenetics. 2013 May;65(5):315-32.

55. Farooqi AA, Nawaz A, Javed Z, Bhatti S, Ismail M. While at Rome miRNA and TRAIL do whatever BCR-ABL commands to do. Arch Immunol Ther Exp (Warsz). 2013 Feb;61(1):59-74.

56. Farooqi AA, Fayyaz S, Shatynska-Mytsyk I, Javed Z, Jabeen S, Yaylim I, Gasparri ML, Panici PB. Is miR-34a a Well Equipped swordsman to Conquer Temple of Molecular Oncology? Chem Biol Drug Des. 2015 Aug 11. doi: 10.1111/cbdd.12634.

57. Misso G, Di Martino MT, De Rosa G, Farooqi AA, Lombardi A, Campani V, Zarone MR, Gullà A, Tagliaferri P, Tassone P, Caraglia M. Mir-34: a new weapon against cancer? Mol Ther Nucleic Acids. 2014 Sep 23;3:e194.

58. Farooqi AA, De Rosa G. TRAIL and microRNAs in the treat-

ment of prostate cancer: therapeutic potential and role of nanotechnology. Appl Microbiol Biotechnol. 2013 Oct;97(20):8849-57.
59. Farooqi AA, Naqi A, Qureshi MZ, Rana A, Khan A, Riaz AM, Afzal SM, Rasheed N, Bhatti S. Prostate cancer is known by the companionship with ATM and miRNA it keeps: craftsmen of translation have dual behaviour with tailors of life thread. Cell Biochem Funct. 2012 Oct;30(7):611-7.
60. Farooqi AA, Qureshi MZ, Coskunpinar E, Naqvi SK, Yaylim I, Ismail M. MiR-421, miR-155 and miR-650: emerging trends of regulation of cancer and apoptosis. Asian Pac J Cancer Prev. 2014;15(5):1909-12.
61. An, F., Zhang, Z., Xia, M., and Xing, L. Subpath analysis of each subtype of head and neck cancer based on the regulatory relationship between miRNAs and biological pathways. Oncol Rep. 2015, 34:1745-1754, doi: 10.3892/or.2015.4150
62. Zhao, L., Tang, M., Hu, Z., Yan, B., Pi, W., Li, Z., Zhang, J., Zhang, L., Jiang, W., Li, G., Qiu, Y., Hu, F., Liu, F., Lu, J., Chen, X., Xiao, L., Xu, Z., Tao, Y., Yang, L., Bode, A.M., Dong, Z., Zhou, J., Fan, J., Sun, L., and Cao, Y. miR-504 mediated down-regulation of nuclear respiratory factor 1 leads to radio-resistance in nasopharyngeal carcinoma. Oncotarget, 2015, 6:15995-16018
63. Hu, A., Huang, J.J., Xu, W.H., Jin, X.J., Li,J. P., Tang, Y.J, Huang, X.F., Cui, H.J., Sun, G,B., Li, R.L., Duan, J.L., and Duan, J.L. MiR-21/miR-375 ratio is an independent prognostic factor in patients with laryngeal squamous cell carcinoma. Am J Cancer Res, 2015, 5:1775-1785
64. Zhu, H., Xiaoyuan, Z., Genyang, C., Minghui, Z., and Weihua, L. Downregulation of microRNA-21 enhances radiosensitivity in nasopharyngeal carcinoma. Exp Ther Med , 2015, 9: 2185-2189
65. Xu, L, Zhifeng, C., Fei, X., Wei, C., Ruina, M., Shiyin, C., and Pengcheng, C. MicroRNA-24 inhibits growth, induces apoptosis, and reverses radioresistance in laryngeal squamous cell carcinoma by targeting X-linked inhibitor of apoptosis protein. Cancer Cell Int, 2015, 15:61, doi: 10.1186/s12935-015-0217-x
66. Chang, Y., Chia-Ing, J., Chih-Yu, P., Yu-Chi, L., Fang-Wei, H., and Cheng-Chia, Y. Activation of microRNA-494-targeting Bmi1 and ADAM10 by silibinin ablates cancer stemness and predicts favourable prognostic value in head and neck squamous cell carcinomas. Oncotarget , 2015
67. Coutinho-Camillo, C.M., Lourenço, S.V., de Araújo Lima, L., Kowalski, L.P., and Soares, F.A. Expression of apoptosis-regulating miRNAs and target mRNAs in oral squamous cell carcinoma. Cancer Genet, 2015, 208:382-9, doi: 10.1016/j.cancergen.2015.04.004
68. Cheng, Y., Yang, L., Yuanyuan, N., Dong, L., Fei D., and Jun, Z. STAT3 is involved in miR-124-mediated suppressive effects on esophageal cancer cells. BMC cancer, 2015, 15:306
69. Ratovitski, E.A. Phospho-ΔNp63α-responsive microRNAs contribute to the regulation of necroptosis in squamous cell carcinoma upon cisplatin exposure. FEBS lett, 589:1352-1358, doi: 10.1016/j.febslet.2015.04.020
70. Kalfert, D., Pesta, M., Kulda, V., Topolcan, O., Ryska, A., Celakovsky, P., Laco, J., and Ludvikova, M. MicroRNA Profile in Site-specific Head and Neck Squamous Cell Cancer. Anticancer Res, 2015, 35: 2455-2463
71. Darda, L., Hakami, F., Morgan, R., Murdoch, C., Lambert, D. W., and Hunter, K.D. The role of HOXB9 and miR-196a in head and neck squamous cell carcinoma. PloS One, 2015, 10:e0122285, doi: 10.1371/journal.pone.0122285
72. Fan, S., Chen, W.X., Lv, X.B., Tang, Q.L., Sun, L.J., Liu, B.D., Zhong, J.L., Lin, Z.Y., Wang, Y.Y., Li, Q.X., Yu, X., Zhang, H.Q., Li, Y.L., Wen, B., Zhang, Z., Chen, W.L., and Li, J.S. miR-483-5p determines mitochondrial fission and cisplatin sensitivity in tongue squamous cell carcinoma by targeting FIS1. Cancer lett, 2015, 362: 183-191, doi: 10.1016/j.canlet.2015.03.045
73. Xu, Y., He, J., Wang, Y., Zhu, X., Pan, Q., Xie, Q., and Sun, F. miR-889 promotes proliferation of esophageal squamous cell carcinomas through DAB2IP. FEBS lett, 2015, 589:1127-1135, doi: 10.1016/j.febslet.2015.03.027
74. Wang, R., Fang, J., Ma, H., Feng, L., Lian, M., Yang, F., Wang, H., Wang, Q., and Chen, X. Effect of microRNA-203 on tumor growth in human hypopharyngeal squamous cell carcinoma. Mol Cell Biochem, 2015, 405:97-104, doi: 10.1007/s11010-015-2401-7
75. Hauser, B., Zhao, Y., Pang, X., Ling, Z., Myers, E., Wang, P., Califano, J., and Gu, X. Functions of MiRNA-128 on the Regulation of Head and Neck Squamous Cell Carcinoma Growth and Apoptosis. PloS One, 2015, 10:e0116321, doi: 10.1371/journal.pone.0116321
76. Peng, X., Cao, P., Li, J., He, D., Han, S., Zhou, J., Tan, G., Li, W., Yu, F., Yu, J., Li, Z., and Cao, K. MiR-1204 sensitizes nasopharyngeal carcinoma cells to paclitaxel both in vitro and in vivo. Cancer Biol Ther, 2015, 16:261-267, doi: 10.1080/15384047.2014.1001287
77. Ide, S., Toiyama, Y., Shimura, T., Kawamura, M., Yasuda, H., Saigusa, S., Ohi, M., Tanaka, K., Mohri, Y., and Kusunoki, M. MicroRNA-503 Promotes Tumor Progression and Acts as a Novel Biomarker for Prognosis in Oesophageal Cancer. Anticancer Res, 2015, 35:1447-1451.
78. Veit, J.A., Scheckenbach, K., Schuler, P.J., Laban, S., Wiggenhauser, S.P., Thierauf, J,. Klussmann J.P., and Hoffmann, T.K. MicroRNA Expression in Differentially Metastasizing Tumors of the Head and Neck: Adenoid Cystic Versus Squamous Cell Carcinoma. Anticancer Res, 2015, 35:1271-1277
79. Xu, Y.F., Li, Y.Q., Guo, R., He, Q.M., Ren, X.Y., Tang, X.R., Jia, W.H., Kang, T.B., Zeng, M.S., Sun, Y., Ma, J., and Liu, N. Identification of miR-143 as a tumour suppressor in nasopharyngeal carcinoma based on microRNA expression profiling. Int J Biochem Cell Biol, 2015, 61:120-128, doi: 10.1016/j.biocel.2015.02.006
80. Fukumoto, I., Hanazawa, T., Kinoshita, T., Kikkawa, N., Koshizuka, K., Goto, Y., Nishikawa, R., Chiyomaru, T., Enokida, H., Nakagawa, M., Okamoto, Y., and Seki, N. MicroRNA expression signature of oral squamous cell carcinoma: functional role of microRNA-26a/b in the modulation of novel cancer pathways. Br J Cancer, 2015, 112:891-900, doi: 10.1038/bjc.2015.19
81. Stanitz, E., Juhasz, K., Gombos, K., Gocze, K., Toth, C., and Kiss, I. Alteration of miRNA Expression Correlates with Lifestyle, Social and Environmental Determinants in Esophageal Carcinoma. Anticancer Res, 2015, 35:1091-1097
82. Li, G., Ren, S., Su, Z., Liu, C., Deng, T., Huang, D., Tian, Y., Qiu, Y., and Liu, Y. Increased expression of miR-93 is associated with poor prognosis in head and neck squamous cell carcinoma. Tumor Biol, 2015, 36:3949-3956, doi: 10.1007/s13277-015-3038-6
83. Wang, X., Li, M., Wang, Z., Han, S., Tang, X., Ge, Y., Zhou, L., Zhou, C., Yuan, Q., and Yang, M. Silencing of long noncoding rna malat1 by mir-101 and mir-217 inhibits proliferation, migration, and invasion of esophageal squamous cell carcinoma cells. J Biol Chem, 2015, 290:3925-3935, doi: 10.1074/jbc.M114.596866
84. Suh, Y.E., Raulf, N., Gäken, J., Lawler, K., Urbano, T.G., Bullenkamp, J., Gobeil, S., Huot, J., Odell, E., and Tavassoli, M. MicroRNA-196a promotes an oncogenic effect in head and neck cancer cells by suppressing annexin A1 and enhancing radioresistance. Int J Cancer, 2015, doi: 10.1002/ijc.29397
85. Boufraqech, M., Nilubol, N., Zhang, L., Gara, S.K., Sadowski, S.M., Mehta, A., He, M., Davis, S., Dreiling, J., Copland, J.A., Smallridge, R.C., Quezado, M.M., and Kebebew, E. miR30a Inhibits LOX Expression and Anaplastic Thyroid Cancer Progression. Cancer Res, 2015, 75:367-377, doi: 10.1158/0008-5472.CAN-14-2304
86. Zhang, R., Chen, X., Zhang, S., Zhang, X., Li, T., Liu, Z., Wang, J., Zang, W., Wang, Y., Du, Y., and Zhao, G. Upregulation of miR-494 Inhibits Cell Growth and Invasion and Induces Cell Apoptosis by Targeting Cleft Lip and Palate Transmembrane 1-Like in Esopha-

geal Squamous Cell Carcinoma. Dig Dis Sci, 2015, 60:1247-1255, doi: 10.1007/s10620-014-3433-7

87. Li, Y., Ahmad, A., Sarkar and F. H., ASPP and iASPP: Implication in cancer development and progression. *Cell. Mol. Biol.* 2015, **61(6)**: 2-8.

88. Amirkhah, R., Farazmand, A., Irfan-Maqsood, M., Wolkenhauerand, O. and Schmitz, U., The role of microRNAs in the resistance to colorectal cancer treatments. *Cell. Mol. Biol.* 2015, **61(6)**: 17-23.

89. Wang, Z., Chen, J. and Capobianco, A. J., The Notch signaling pathway in esophageal adenocarcinoma. *Cell. Mol. Biol.* 2015, **61(6)**: 24-32.

90. Limami, Y., Pinon, A., Riaz, A. and Simon, A., TRAIL and targeting cancer cells: between promises and obstacles. *Cell. Mol. Biol.* 2015, **61(6)**: 33-38.

91. Silva Galbiatti-Dias, A. L., Pavarino, É. C., Kawasaki-Oyama, R. S., Maniglia, J. V., Maniglia, E. J. V. and Goloni Bertollo, E. M., Cancer stem cells in head and neck cancer: A Mini Review. *Cell. Mol. Biol.* 2015, **61(6)**: 39-43.

92. Musella, A., Marchetti, C., Gasparri, M. L., Salerno, L., Casorelli, A., Domenici, L., Imperiale, L., Ruscito, I., Abdul Halim, T., Palaia, I., Di Donato, V., Pecorini, F., Monti, M., Muzii, L. and Panici, P. B., PARP inhibition: A promising therapeutic target in ovarian cancer. *Cell. Mol. Biol.* 2015, **61(6)**: 44-61.

93. Attar, R., Tabassum, S., Fayyaz, S., Ahmad, M. S., Nogueira, D. R., Yaylim, I., Timirci-Kahraman, O., Kucukhuseyin, O., Cacina, C., Farooqi, A. A. and Ismail, M., Natural products are the future of anticancer therapy: Preclinical and clinical advancements of *Viscum album* phytometabolites. *Cell. Mol. Biol.* 2015, **61(6)**: 62-68.

94. Hsu, Y-C., Hsieh, Y-H., Liao, C-C., Chong, L-W., Lee, C-Y., Yu, Y-L. and Chou, R-H., Targeting post-translational modifications of histones for cancer therapy. *Cell. Mol. Biol.* 2015, **61(6)**: 69-84.

95. Chong, L-W., Chou, R-H., Liao, C-C., Lee, T-F., Lin, Y., Yang, K-C. and Hsu, Y-C. Saturated fatty acid induces cancer stem cell-like properties in human hepatoma cells. *Cell. Mol. Biol.* 2015, **61(6)**: 85-91.

96. Smina, T. P., Mohan, A., Ayyappa, K. A., Sethuraman, S. and Krishnan, U. M., Hesperetin exerts apoptotic effect on A431 skin carcinoma cells by regulating mitogen activated protein kinases and cyclins. *Cell. Mol. Biol.* 2015, **61(6)**: 92-99.

97. Ahmadi, M., Jafari, R., Marashi, S. A. and Farazmand, A., Indirect role of microRNAs and transcription factors in the regulation of important cancer genes: A network biology approach. *Cell. Mol. Biol.* 2015, **61(6)**: 100-107.

98. Zahoor, A., Mansoor, Q., Farooqi, A. A., Fayyaz, S., Naz, G. and Ismail, M., Genetic variants in the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and death receptor (DR4) genes contribute to susceptibility to colorectal cancer in pakistani population. *Cell. Mol. Biol.* 2015, **61(6)**: 108-112.