|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author/year** | **Type of Cancer** | **Epigenetic alteration** | **Results** | **Mechanisms** | **comments** |
| Liu C-C et al. , 2015 | Lung Cancer | IL-6 increased DNMT1🡪methylation of cancer suppressor gene p53 and p21 in A549 cancer cells | Cancer up-regulated | inflammatory cytokines in microenviroment🡪 cancer progress | 1. In vitro study:lung cancer stem cells vs. IL-6 enrichment 2. IL-6 is also expressed in metabolic inflammation. |
| Yu Z et al. , 2015 | Breast cancer (BrCa) | DNMT1 expression higher in BrCa than fibroadenoma | Increase lymph node metastasis; shorter disease-free survival | DNMT1 🡪 promoter hypermethylation | 1. Human, longitudinal study 2. Potential causal |
| Zheng Y et al., 2015 | Hepatocellular carcinoma (HCC) | Histone de-Acetylation in cancer vs adjacent tissues | Hepatocellular Cancer down regulated | histone deacetylase (HDAC) increased the level of miR-376a (cancer suppressor) | 1. In vitro study 2. No causal inference |
| Karczmarski J et al., 2014 | Colorectal Cancer (CRC) | Histone acetylation  in CRC tissues and healthy mucosa samples | Histone (H3) acetylation is upregulated in CRC, | Proteomic approach for the detection of histone modifications at a global scale. | 1. In vitro study 2. No causal inference |

Supplemental Table1a. Selected examples of epigenetic modification and cancer

References:

Karczmarski J, Rubel T, Paziewska A, Mikula M, Bujko M, Kober P, Dadlez M, Ostrowski J. 2014. Histone H3 lysine 27 acetylation is altered in colon cancer. Clin Proteomics 11(1):24.24994966

Liu CC, Lin JH, Hsu TW, Su K, Li AF, Hsu HS, Hung SC. 2015. IL-6 enriched lung cancer stem-like cell population by inhibition of cell cycle regulators via DNMT1 upregulation. Int J Cancer 136(3):547-559.24947242

Yu Z, Xiao Q, Zhao L, Ren J, Bai X, Sun M, Wu H, Liu X, Song Z, Yan Y et al. . 2015. DNA methyltransferase 1/3a overexpression in sporadic breast cancer is associated with reduced expression of estrogen receptor-alpha/breast cancer susceptibility gene 1 and poor prognosis. Mol Carcinog 54(9):707-719.24464625

Zheng Y, Chen H, Yin M, Ye X, Chen G, Zhou X, Yin L, Zhang C, Ding B. 2015. MiR-376a and histone deacetylation 9 form a regulatory circuitry in hepatocellular carcinoma. Cell Physiol Biochem 35(2):729-739.25613642

Table 2a. (Supplemental) The role of microRNAs and cancer relationship

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author/year** | **Type of Cancer** | **miRNAs involved** | **Methods** | **Results** | **comments** |
| Kent OA et al. 2016 | Pancreatic and colorectal Cancer | miR-31 plus KRAS mutations | In patient derived xenografts and a panel of pancreatic and colorectal cancer cells, miR-31 promoter in a MAPK-dependent manner | Invasion and migration of multiple pancreatic cancer cells | 1. *In vitro* study 2. Mechanism study without comparison |
| Hung KF et al 2016 | Oral potential malignancies ( OPMD) | miR-31  upregulation | Saliva samples and tissue samples from OPMD patients followed 820days | Malignant transformation 🡪 increased expression of miR-31 | 1. Human, longitudinal study 2. Potential causal 3. miR-31 is the cause or just a mechanism? |
| Sun Y et al. 2015 | Esophageal Cancer | miR-204 | Expression level of miR-204 in primary EC cases and cell lines by quantitative Real-Time PCR | miR-204 inhibited epithelial-mesenchymal transition🡪cancer down regulation | 1. *In vitro* study 2. No causal inference |
| Shi W et al 2015 | Oral squamous cell carcinoma | miR-375 | MicroRNA and mRNA profiling in oral lichen planus (OLP), oral squamous cell carcinoma (OSCC), and normal tissue from the same patients. | 1. miR-375 decreased in tissues with malignant transformation 2. miR-375 may be oncosuppressors. | 1. *In vitro* study 2. No causal inference |
| Lerner et al 2015 | Head and neck squamous cell carcinoma | miR-146a & miR-155 | HNSCC patients (N=12) and sex- and age-matched controls (N=12) | 1. No diff at baseline miR profile 2. In patients: down-regulation of miR-146a and miR-155 🡪 distant metastasis | 1. Human, longitudinal study 2. Potentially causal 3. miR-146a and miR-155 may be oncosuppressors. |
| Shi XM et al 2015 | hepatocellular carcinoma | lncRNA Sox2ot | Tumor and adjacent non-tumor tissues | High lncRNA Sox2ot expression🡪 shorter survival | 1. Human, longitudinal study 2. lncRNA Sox2ot expression may be oncogenic |
| Chen X et al 2015 | Uterine Cervix squamous cell cancer | lncRNA CCAT2 | Cancer to the adjacent non-tumor tissues | High expression of lncRNA CCAT2 correlated with invasiveness of tumor and poor survival | 1. Human, longitudinal study 2. lncRNA CCAT2 may be onco-enhancer. |
| Zhang S et al 2015 | Oral squamous cell carcinoma | lncRNA profile | Samples from OSCC 57 patient vs normal gene from data base (N=22) | FTH1P3, PDIA3F and GTF2IRD2P1 targeted MMP1, MMP3, MMP9, PLAU (plasminogen activator, urokinase) and IL8. | 1. Cross-sectional in vitro study 2. lncRNA , the cause or just a mechanism? |
| Wu J et al 2015 | Oral squamous cell carcinoma (OSCC) | RNA-HOX transcript antisense intergenic RNA (HOTAIR) | surgically resected tumor tissue (N= 50) vs. paracancerous tissues | HOTAIR was highly expressed in OSCC tissues and facilitated the growth of OSCC cells. | 1. Blocking HOTAIR expression 🡪decelerated cell growth suggests potential causality. |
| Wu Y et al 2015 | Oral squamous cell carcinoma (OSCC) | lncRNA HOTAIR | OSCC vs. non-tumor tissue | 1. HOTAIR expression increased in OSCC. 2. HOTAIR🡪 poor survival | 1. Negative correlation HOTAIR and E-cadherin levels. |

References:

Chen X, Liu L, Zhu W. 2015. Up-regulation of long non-coding RNA CCAT2 correlates with tumor metastasis and poor prognosis in cervical squamous cell cancer patients. Int J Clin Exp Pathol 8(10):13261-13266.26722527

Hung KF, Liu CJ, Chiu PC, Lin JS, Chang KW, Shih WY, Kao SY, Tu HF. 2016. MicroRNA-31 upregulation predicts increased risk of progression of oral potentially malignant disorder. Oral Oncol 53:42-47.26675284

Kent OA, Mendell JT, Rottapel R. 2016. Transcriptional regulation of miR-31 by oncogenic KRAS mediates metastatic phenotypes by repressing RASA1. Mol Cancer Res.26747707

Lerner C, Wemmert S, Bochen F, Kulas P, Linxweiler M, Hasenfus A, Heinzelmann J, Leidinger P, Backes C, Meese E et al. . 2015. Characterization of miR-146a and miR-155 in blood, tissue and cell lines of head and neck squamous cell carcinoma patients and their impact on cell proliferation and migration. J Cancer Res Clin Oncol.26621153

Shi W, Yang J, Li S, Shan X, Liu X, Hua H, Zhao C, Feng Z, Cai Z, Zhang L et al. . 2015. Potential involvement of miR-375 in the premalignant progression of oral squamous cell carcinoma mediated via transcription factor KLF5. Oncotarget 6(37):40172-40185.26474386

Shi XM, Teng F. 2015. Up-regulation of long non-coding RNA Sox2ot promotes hepatocellular carcinoma cell metastasis and correlates with poor prognosis. Int J Clin Exp Pathol 8(4):4008-4014.26097588

Sun Y, Yu X, Bai Q. 2015. miR-204 inhibits invasion and epithelial-mesenchymal transition by targeting FOXM1 in esophageal cancer. Int J Clin Exp Pathol 8(10):12775-12783.26722467

Wu J, Xie H. 2015. Expression of long noncoding RNA-HOX transcript antisense intergenic RNA in oral squamous cell carcinoma and effect on cell growth. Tumour Biol 36(11):8573-8578.26036760

Wu Y, Zhang L, Zhang L, Wang Y, Li H, Ren X, Wei F, Yu W, Liu T, Wang X et al. . 2015. Long non-coding RNA HOTAIR promotes tumor cell invasion and metastasis by recruiting EZH2 and repressing E-cadherin in oral squamous cell carcinoma. Int J Oncol 46(6):2586-2594.25901533

Zhang S, Tian L, Ma P, Sun Q, Zhang K, GuanchaoWang, Liu H, Xu B. 2015. Potential role of differentially expressed lncRNAs in the pathogenesis of oral squamous cell carcinoma. Arch Oral Biol 60(10):1581-1587.26276270