

Mesenchymal Conversion

Subjects: Oncology

Contributor: Rogelio González-González

Mesenchymal conversion occurring in malignant epithelial neoplasms is undesirable in tumors since it promotes more aggressive tumor behavior. This phenomenon is not exclusive to head and neck carcinomas, and it is likely to be found in most neoplasms, as carcinomas are frequently aggressive. Mesenchymal conversion depends on different molecular interactions, signaling pathways, and tumor microenvironments that are related to the activation of several growth factors and diverse matrix metalloproteinases that promote ideal environments for the progression of tumor cells that are primarily associated with metastasis.

Keywords: epithelial–mesenchymal transition ; head and neck squamous cell carcinoma ; EMT transcription factors ; viral infections ; inhibition

1. Introduction

Head and neck squamous cell carcinomas (HNSCCs) are particularly aggressive neoplasms with a poor prognosis due to their high rates of local recurrence and metastasis. Approximately 850,000–900,000 cases of this epithelial neoplasm are diagnosed worldwide each year, causing an average of 450,000 deaths per year ^[1]. The most strongly associated risk factors are alcohol and tobacco intake, viral infections (human papillomavirus and Epstein–Barr virus), and diverse genetic factors ^{[2][3][4]}.

The EMT phenomenon describes the development of nonmobile polarized epithelial cells into fibroblast-like mesenchymal cells with a great migratory ability, in which several molecular complexes and reversible processes are involved. EMT is defined as cell regulatory events that are related to a phenotypic transformation of epithelial cells into mesenchymal cells, characterized by changes in apicobasal polarity, mobility, and cell adhesion, which provide the modified cell with a greater ability for migration, invasion, and distant colonization. It is also characterized by the alteration of epithelium-specific adhesion proteins and the induction of mesenchymal proteins, as well as the overexpression of matrix metalloproteinases (MMPs) in the tumor microenvironment ^{[5][6]}. Several oncogenic pathways, the induction of hypoxia, and viral infection play significant roles in EMT progression through the activation of several transcription factors (EMT-TFs), such as Snail, Slug, Twist, and other molecules related to EMT-TFs ^[7]. The plasticity phenomena, inflammatory response, and epigenetic regulation in EMT have also been described, which have an important role in the development of this phenomenon.

2. Inhibition of EMT Is Important in the Treatment of HNSCC

As described above, EMT-TFs and mesenchymal markers can interact with several signaling pathways associated with EMT that are related to the MMP stimulus, tumor budding, invasion, metastasis, and resistance to treatment. Different therapies have been studied for inhibiting EMT by focusing on the inhibition of signaling pathways and EMT-TFs. MicroRNAs (miRNAs) were identified in 1993 as a class of endogenous small non-coding RNAs related to the regulation of several roles through the union to mRNAs for cleavage or translational repression and with a potential function as oncogenes or tumor-suppressive genes in cancer ^{[8][9][10]}. Novel therapies with microRNAs have been proposed that are capable of inducing negative or positive interactions with EMT. In this regard, the miR-200 family acts as a tumor suppressor ^[11]. This family has properties related to epithelial and mesenchymal phenotypes and is closely related to EMT phenomena. In HNSCCs, miR-200a/b/c can inhibit EMT by the repression of ZEB1 and ZEB2 (transcription factors that repress E-cadherin and promote EMT in HNSCCs). The most important feature of the relationship between miR-200 and ZEB is that ZEB1 can repress the transcription of miR-200 by inducing a double-negative feedback loop, promoting EMT in HNSCCs ^{[12][13]}. A study by Kim et al. evaluated the relationship of an RNA-binding protein called quaking (QKI) related to miR-200a/b and found that the knockdown of QKI in CAL27 (tongue squamous cell carcinoma, cultured cells) promoted cancer cell growth and EMT in relation to an increase in ZEB1, vimentin, and N-cadherin. Moreover, they observed that the overexpression of miR-200 in cells induces the migratory ability induced by ZEB1, while the overexpression of QKI impairs this ^[13].

Therefore, the overexpression of QKI and miR-200 is capable of inhibiting EMT in HNSCCs, despite the migratory capacity induced in miR-200 by ZEB1. Another important miRNA related to the tumor microenvironment is miR-149-3p, whose overexpression has been associated with a reduction in tumor neovascularization and a decrease in fibroblast growth factor-2 (FGF-2) signaling, playing an important role in the tumor microenvironment and the reduction in hypoxia, inhibiting the proliferation of OSCC cells, inducing apoptosis via the activation of caspase 3 ^{[14][15][16]}, and possibly acting against EMT. Li et al. observed that the overexpression of miR-625 is capable of inducing the inhibition of EMT by the increase in the expression of E-cadherin and the decrease in the levels of N-cadherin and Vimentin. It is also capable of blocking the sex-determining region Y-box 4 (SOX4) in HNSCC ^[17]. SOX4 is considered as the main regulator of EMT, which is related to the induction of tumorigenesis and metastasis ^{[18][19]}. The presence of CSCs in HNSCC has been reported in several studies that are related to tumor progression, metastasis, and treatment resistance. The presence of CSCs and Wnt/ β -catenin signaling is related to the resistance to treatment due to the receptors of Wnt (frizzled related proteins) that promote resistance in several tumors ^{[20][21]}. Secreted frizzled-related protein-4 (sFRP4) is involved in the regulation of apoptosis, proliferation, and tumor growth ^{[22][23][24][25]}. As previously described, the loss of E-cadherin releases β -catenin into the cytosol and activates the Wnt signaling pathway to promote nuclear translocation. Warriar et al. evaluated an increase in the expression of E-cadherin following sFRP4 treatment associated with the induction of MET and observed the downregulation of Twist and Snail. They observed that sFRP4, an endogenously expressed Wnt antagonist, is capable of inhibiting CSC growth ^[26].

Hyperthermia is a modality of treatment related to an increase in the efficacy of conventional treatment approaches, which has been adopted as a minimally invasive treatment of some metastatic tumors in different organs ^{[27][28]}. Hyperthermia is related to the inhibition of tumor growth and contributes to the enhancement of therapy against cancer. It is also related to tumor cell killing and the sensitization of these cells to radio and chemotherapy ^{[29][30]}. Tang et al. studied the effect of hyperthermia on EMT, especially with Twist2, which is associated with EMT and metastases in HNSCC. They found that hyperthermia can reduce the expression of Twist2 by decreasing the capability of cell migration and increasing the levels of mRNA of E-cadherin expression in tongue squamous cell carcinoma cells ^[31].

The use of isothiocyanates (ITCs), which are natural compounds found in crucifer vegetables, has been proposed. These ITCs are related to anti-proliferative and apoptotic activity, as they are capable of destabilizing the mitochondrial membrane and inducing apoptosis by the increase in Bax and the inhibition of Bcl-2 and Bcl-XL ^{[32][33]}. Ma et al. evaluated the activity of Benzyl isothiocyanate and found that this ITC is capable of promoting apoptosis by the induction of caspase-3 and inhibiting the expression of MMP9, which is related to the induction of EMT ^[33].

The use of propofol has been proposed, although its use is still controversial. Propofol is an intravenous short-action anesthetic in which anti-neoplastic properties have been described, associated with the inhibition of cell proliferation, invasion, and angiogenesis, and is related to the inhibition of MMPs 2 and 9 in esophagus carcinoma cells ^[34]. Studies conducted by Li et al. established the association of the use of propofol with the increase in Snail and the promotion of EMT in tongue squamous cell carcinoma cells ^[35].

3. Conclusions

EMT is an important phenomenon capable of inducing aggressiveness, invasion, metastasis, proliferation, recurrence, and resistance to treatment via the interaction of several molecules and tumor microenvironments. The papers analyzed in the current review provide evidence that EMT can induce several interactions between cells and stromal tumors at the intracellular and extracellular levels. These interactions provide cells with greater capabilities for mesenchymal transformation, proliferation, invasion, angiogenesis, and metastasis, and they can be enhanced by inflammation and hypoxia, conferring resistance to conventional treatment. Head and neck tumors associated with EBV and HPV may show greater potential for EMT, aggression, and resistance to treatment. In tumors infected with HPV, it is important to detect homogeneity through molecular techniques in HNSCCs to establish therapeutic strategies focused on this phenomenon. Studies have recently been conducted regarding miRNA, QKI, hyperthermia, and the use of ITC as therapeutics to inhibit EMT to reduce tumor aggressiveness and improve treatment responses. However, the use of hyperthermia, ITC requires further studies to evaluate its capacity to inhibit EMT, and the use of propofol requires further studies focusing on HNSCCs with EMT phenotypes to evaluate their efficacy in these tumors.

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2018, 68, 394–424.

2. Leemans, C.R.; Snijders, P.J.F.; Brakenhoff, R.H. The molecular landscape of head and neck cancer. *Nat. Rev. Cancer* 2018, 18, 269–282.
3. Cardin, G.B.; Bernard, M.; Bahig, H.; Nguyen-Tan, P.F.; Ballivy, O.; Fillion, E.; Soulieres, D.; Philouze, P.; Ayad, T.; Guertin, L.; et al. Single nucleotide polymorphism rs6942067 is a risk factor in young and in non-smoking patients with HPV negative head and neck squamous cell carcinoma. *Cancers* 2019, 12, 55.
4. Domingo-Vidal, M.; Whitaker-Menezes, D.; Martos-Rus, C.; Tassone, P.; Snyder, C.M.; Tuluc, M.; Philp, N.; Curry, J.; Martinez-Outschoorn, U. Cigarette smoke induces metabolic reprogramming of the tumor stroma in head and neck squamous cell carcinoma. *Mol. Cancer Res.* 2019, 17, 1893.
5. Pastushenko, I.; Blanpain, C. EMT transition states during tumor progression and metastasis. *Trends Cell Biol.* 2019, 29, 212–226.
6. Umbreit, C.; Flanjak, J.; Weiss, C.; Erben, P.; Aderhold, C.; Faber, A.; Stern-Straeter, J.; Hoermann, K.; Schultz, J.D. Incomplete epithelial-mesenchymal transition in p16-positive squamous cell carcinoma cells correlates with β -catenin expression. *Anticancer Res.* 2014, 34, 7061–7069.
7. Bommi, P.V.; Ravindran, S.; Raychaudhuri, P.; Bagchi, S. DDB2 regulates Epithelial-to-Mesenchymal Transition (EMT) in Oral/head and neck squamous cell carcinoma. *Oncotarget* 2018, 9, 34708–34718.
8. Lee, R.C.; Feinbaum, R.L.; Ambros, V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 1993, 75, 843–854.
9. Bartel, D.P. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell* 2004, 116, 281–297.
10. Iorio, M.V.; Croce, C.M. MicroRNAs in cancer: Small molecules with a huge impact. *J. Clin. Oncol.* 2009, 27, 5848–5856.
11. Cho, E.S.; Kang, H.E.; Kim, N.H.; Yook, J.I. Therapeutic implications of cancer epithelial-mesenchymal transition (EMT). *Arch. Pharmacol. Res.* 2019, 42, 14–24.
12. Liu, Y.N.; Yin, J.J.; Abou-Kheir, W.; Hynes, P.G.; Casey, O.M.; Fang, L.; Yi, M.; Stephens, R.M.; Seng, V.; Sheppard-Tillman, H.; et al. miR-1 and miR-200 inhibit EMT via Slug-dependent and tumorigenesis via Slug-independent mechanisms. *Oncogene* 2013, 32, 296–306.
13. Kim, E.J.; Kim, J.S.; Lee, S.; Lee, H.; Yoon, J.S.; Hong, J.H.; Chun, S.H.; Sun, S.; Won, H.S.; Hong, S.A.; et al. QKI, a miR-200 target gene, suppresses epithelial-to-mesenchymal transition and tumor growth. *Int. J. Cancer* 2019, 145, 1585–1595.
14. Shen, Q.; Zhu, H.; Lei, Q.; Chen, L.; Yang, D.; Sui, W. MicroRNA-149-3p inhibits cell proliferation by targeting AKT2 in oral squamous cell carcinoma. *Mol. Med. Rep.* 2021, 23.
15. Dou, C.; Liu, Z.; Xu, M.; Jia, Y.; Wang, Y.; Li, Q.; Yang, W.; Zheng, X.; Tu, K.; Liu, Q. miR-187-3p inhibits the metastasis and epithelial-mesenchymal transition of hepatocellular carcinoma by targeting S100A4. *Cancer Lett.* 2016, 381, 380–390.
16. He, Y.; Yu, D.; Zhu, L.; Zhong, S.; Zhao, J.; Tang, J. miR-149 in human cancer: A systemic review. *J. Cancer* 2018, 9, 375–388.
17. Li, Y.; Tao, C.; Dai, L.; Cui, C.; Chen, C.; Wu, H.; Wei, Q.; Zhou, X. MicroRNA-625 inhibits cell invasion and epithelial-mesenchymal transition by targeting SOX4 in laryngeal squamous cell carcinoma. *Biosci. Rep.* 2019, 39.
18. Tiwari, N.; Tiwari, V.K.; Waldmeier, L.; Balwierz, P.J.; Arnold, P.; Pachkov, M.; Meyer-Schaller, N.; Schübeler, D.; van Nimwegen, E.; Christofori, G. Sox4 is a master regulator of epithelial-mesenchymal transition by controlling Ezh2 expression and epigenetic reprogramming. *Cancer Cell* 2013, 23, 768–783.
19. Vervoort, S.J.; van Boxtel, R.; Coffey, P.J. The role of SRY-related HMG box transcription factor 4 (SOX4) in tumorigenesis and metastasis: Friend or foe? *Oncogene* 2013, 32, 3397–3409.
20. Noda, T.; Nagano, H.; Takemasa, I.; Yoshioka, S.; Murakami, M.; Wada, H.; Kobayashi, S.; Marubashi, S.; Takeda, Y.; Dono, K.; et al. Activation of Wnt/ β -catenin signalling pathway induces chemoresistance to interferon- α /5-fluorouracil combination therapy for hepatocellular carcinoma. *Br. J. Cancer* 2009, 100, 1647–1658.
21. Flahaut, M.; Meier, R.; Coulon, A.; Nardou, K.A.; Niggli, F.K.; Martinet, D.; Beckmann, J.S.; Joseph, J.M.; Mühlethaler-Mottet, A.; Gross, N. The Wnt receptor FZD1 mediates chemoresistance in neuroblastoma through activation of the Wnt/ β -catenin pathway. *Oncogene* 2009, 28, 2245–2256.
22. Guo, K.; Wolf, V.; Dharmarajan, A.M.; Feng, Z.; Bielke, W.; Saurer, S.; Friis, R. Apoptosis-associated gene expression in the corpus luteum of the rat. *Biol. Reprod.* 1998, 58, 739–746.
23. Lacher, M.D.; Siegenthaler, A.; Jäger, R.; Yan, X.; Hett, S.; Xuan, L.; Saurer, S.; Lareu, R.R.; Dharmarajan, A.M.; Friis, R. Role of DDC-4/sFRP-4, a secreted frizzled-related protein, at the onset of apoptosis in mammary involution. *Cell Dev.*

24. Han, Q.F.; Zhao, W.; Bentel, J.; Shearwood, A.M.; Zeps, N.; Joseph, D.; Iacopetta, B.; Dharmarajan, A. Expression of sFRP-4 and beta-catenin in human colorectal carcinoma. *Cancer Lett.* 2006, 231, 129–137.
25. Hewitt, D.P.; Mark, P.J.; Dharmarajan, A.M.; Waddell, B.J. Placental expression of secreted frizzled related protein-4 in the rat and the impact of glucocorticoid-induced fetal and placental growth restriction. *Biol. Reprod.* 2006, 75, 75–81.
26. Warriar, S.; Bhuvanlakshmi, G.; Arfuso, F.; Rajan, G.; Millward, M.; Dharmarajan, A. Cancer stem-like cells from head and neck cancers are chemosensitized by the Wnt antagonist, sFRP4, by inducing apoptosis, decreasing stemness, drug resistance and epithelial to mesenchymal transition. *Cancer Gene Ther.* 2014, 21, 381–388.
27. Palazzi, M.; Maluta, S.; Dall'Oglio, S.; Romano, M. The role of hyperthermia in the battle against cancer. *Tumori* 2010, 96, 902–910.
28. Yu, J.; Liang, P.; Yu, X.; Wang, Y.; Gao, Y. Ultrasound-guided percutaneous microwave ablation of splenic metastasis: Report of four cases and literature review. *Int. J. Hypertherm.* 2011, 27, 517–522.
29. Lui, P.C.; Fan, Y.S.; Xu, G.; Ngai, C.Y.; Fung, K.P.; Tse, G.M.; Yu, A.M.; Li, J.Y. Apoptotic and necrotic effects of tumour necrosis factor-alpha potentiated with hyperthermia on L929 and tumour necrosis factor-alpha-resistant L929. *Int. J. Hypertherm.* 2010, 26, 556–564.
30. Alcala, M.A., Jr.; Park, K.; Yoo, J.; Lee, D.H.; Park, B.H.; Lee, B.C.; Bartlett, D.L.; Lee, Y.J. Effect of hyperthermia in combination with TRAIL on the JNK-Bim signal transduction pathway and growth of xenograft tumors. *J. Cell Biochem.* 2010, 110, 1073–1081.
31. Tang, Y.L.; Jiang, J.; Liu, J.; Zheng, M.; He, Y.W.; Chen, W.; Fan, Y.L.; Chen, Q.M.; Liao, C.H.; Liang, X.H. Hyperthermia inhibited the migration of tongue squamous cell carcinoma through TWIST2. *J. Oral Pathol. Med.* 2015, 44, 337–344.
32. Fowke, J.H. Head and neck cancer: A case for inhibition by isothiocyanates and indoles from cruciferous vegetables. *Eur J. Cancer Prev.* 2007, 16, 348–356.
33. Ma, L.; Chen, Y.; Han, R.; Wang, S. Benzyl isothiocyanate inhibits invasion and induces apoptosis via reducing S100A4 expression and increases PUMA expression in oral squamous cell carcinoma cells. *Braz. J. Med. Biol. Res.* 2019, 52, e8409.
34. Guo, X.G.; Wang, S.; Xu, Y.B.; Zhuang, J. Propofol suppresses invasion, angiogenesis and survival of EC-1 cells in vitro by regulation of S100A4 expression. *Eur Rev. Med. Pharmacol. Sci.* 2015, 19, 4858–4865.
35. Li, C.; Xia, M.; Wang, H.; Li, W.; Peng, J.; Jiang, H. Propofol facilitates migration and invasion of oral squamous cell carcinoma cells by upregulating SNAIL expression. *Life Sci.* 2020, 241, 117143.