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Mini Review

Epithelial Mesenchymal Transition in Non-Small Cell Lung Cancer (NSCLC)-Derived Cancer Stem Cells (Stem-Like NSCLC Cells)

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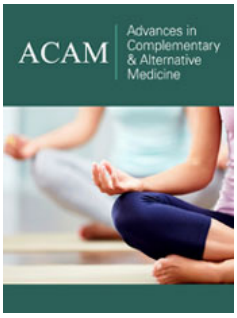

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Abstract

Cancer Stem Cells (CSCs) that are responsible for the onset and continuation of the tumour, they have an effective DNA repairing mechanisms, highly Multidrug Resistance/MDR transporters and also, they are silent cells protected in a hypoxic niche and are resistant to radiotherapy and chemotherapy. This small cell group, which is also highly resistant to apoptosis, is known to form other cancer cells once it has formed in the tissue. It is known that, after surgical removal of tumour tissue and/or after chemotherapy and radiotherapy applications, fewer cancer stem cells that remain in the region can re-establish tumour tissue and are responsible for recurrence of the disease. Cancer stem cells are also held responsible for metastasis seen after many years in many cancer cases that are thought to be treated. It is seen that CSCs show Epithelial Mesenchymal Transition (EMT) during metastasis and invasion. Recent studies also show that EMT stimulating factors simultaneously elicit CSC-like features in cancer cells. In summary, EMT is necessary for the acquisition and continuity of CSC characteristics and is therefore directly related to the recurrence and metastatic processes of NSCLC. However, the mechanisms that regulate these processes are still unknown.

Introduction

Lung cancer is a common health problem both in the world [1]. According to the 2012 records of the World Health Organization (WHO), an average of 8.2 million people dies each year due to cancer and this corresponds to 13% of all deaths in the world. The International Cancer Agency (IARC) report in 2012 states that 1.8 million people in the underdeveloped countries are expected to experience lung cancer in the future. Non-Small Cell Lung Cancer (NSCLC) accounts for 85% of all lung cancer cases. The prognosis in these cases is quite poor. The 5-year survival rate in these patients is less than 15% [2]. Treatment is decided according to the course of the disease, but current treatment approaches are insufficient in the later stages of the disease [3]. Some cells in the tumour show similar properties to stem cells. These cells have the ability to self-renew and reproducibly reproduce the same tumour phenotype. These cells are characterized by expression of distinct cell surface receptors.

The first Tumour Initiating Cells (TIC) in solid tumours were isolated from breast cancer. In addition to breast cancer, TICs have been identified in brain [4], liver [5], stomach [6], endometrium [7], ovary [8], lung [9] cancers. When the concept of Cancer Stem Cell (CSC) was first proposed, it was reported that only a small percentage (1-4%) of cancer cells proliferated extensively and formed colony. The CSC hypothesis claims that only a small subset of cells within a tumours are capable of both tumours initiation and maintenance of tumours growth. There is still increasing evidence; It supports the view that CSCs in solid and These cells may form spheres in serum-free medium and expresses stem cell markers that a property associated with stem cells and may differentiate into an abnormal cell phenotype that constitutes tumours heterogeneity. Hematopoietic tumours, including brain, breast, head and neck, colon, prostate, ovarian and lung cancers, are caused by a self-renewing subpopulation [10].

Simply, the process of epithelial cells forming mesenchymal cells is defined as “Epithelial Mesenchymal Transition” (EMT). EMT is physiologically important in embryonic development and tissue repair processes. However, it is also effective in pathological processes such as organ fibrosis, cancer progression and metastasis. EMT starts with the release of the apicolateral

connections of the epithelium, changes in the underlying basement membrane structure and the migration of the cells there from. These processes are induced by heterotypic signals secreted by mesenchymal cells in normal or neoplastic tissues. EMT now has three main stages of cancer development; invasion, migration and metastasis. When migrating cells reach their targets, they are thought to promote metastatic progression.

During the EMT process, cells lose their epithelial cell-cell connections and apical-basal polarity and gain the ability to migrate with spindle-shaped cells [11]. Various markers have been identified to represent the EMT in NSCLC. E-cadherin, integrin and cytokeratin are epithelial markers; N-cadherin, vimentin and fibronectin are widely used as mesenchymal markers. In recent years, E-cadherin and N-cadherin have been investigated to observe EMT in lung cancer development [12]. However, cells do not acquire mesenchymal properties in partial EMT. Early EMT; It involves loss of E-cadherin, not N-cadherin. It is important to consider not only epithelial or mesenchymal qualities during EMT, but also other processes related to EMT invasion, such as improving survival or decreasing proliferation [13].

During cancer progression, some cancer cells originating from the primary tumour may reactivate a latent embryonic program known as EMT, which is considered to be a necessary step in tumour invasion and metastasis. Through EMT, transformed epithelial cells are able to obtain mesenchymal properties that contribute to metastasis. The cancer cell with mesenchymal phenotype has the ability to overcome endothelial barriers and enter the blood and lymphatic circulation. When cancer cells reach other tissues, they no longer interfere with the signals they encounter in the primary tumour and become an epithelial phenotype through mesenchymal epithelial transition (EMT). Zinc-finger transcriptional factors such as SNAIL, SLUG, TWIST, ZEB1, SIP1 and E47 play a critical role in stimulating EMT by inhibition of E-cadherin [14]. Numerous signalling pathways such as TGFβ, Wnt, NF-κB, Notch, integrins and tyrosine kinase receptors (EGF, FGF, HGF, PDGF, IGF) have been shown to be very important in the pathway to EMT. Functional interaction between these pathways may result in signal amplification and may induce EMT and metastasis. The members of the transforming growth factor-β (TGF-β) family; embryonic development, wound healing, fibrotic diseases and cancer are known to induce EMT. Recent studies have shown that TGFβ plays an important role in regulating the phenotype of lung cancer stem cells and maintaining pluripotency [15].

TGF-β can induce EMT with different signalling pathways. In particular, it performs phosphorylation of ligand-activated receptors and cell-polarizing proteins of transcription factors called SMAD. TGFβ type II receptor in mammalian epithelial cells can directly phosphorylate SMAD2, SMAD 3 and cell polar protein pAr6A. Phosphorylation of pAr6A leads to loss of apical-basal polarization and disruption of tight connections between adjacent epithelial cells. TGFβ also affects the activity of Notch, Wnt and Integrin signalling pathways that induce EMT. While EMT plays a role in normal embryonic development, it also plays an active role in tissue fibrosis and cancer metastasis [16].

Despite many years of basic and clinical research aimed at preventing NSCLC, metastasis is still a difficult issue and remains the leading cause of cancer-related deaths worldwide. CSCs and EMT are known to play an important role in NSCLC cancer metastasis. In the prevention of lung tumours metastasis; to clarify the molecular mechanisms behind cancer invasion and metastasis, changes in cancer cells from EMT to acquisition of CHD characteristics and genomic structure in these changes need to be communicated. Despite cellular, clinical and epidemiological studies to date, biological mechanisms in NSCLC carcinogenesis have not yet been fully understood. Since there are few studies on this subject, future studies are needed to better clarify its role.

References

1. Yadav VR, Prasad S, Sung B, Aggarwal BB (2011) The role of chalcones in suppression of NF-κB-mediated inflammation and cancer. International Immunopharmacology 11(3): 295-309.
2. http://www.who.int/cancer/en/
3. Brundage MD, Davies D, Mackillop WJ (2002) Prognostic factors in non-small cell lung cancer: A decade of progress. Chest 122(3): 1037-1057.
4. Metellus P, Nanni MI, Delfino C, Colin C, Tchogandjian A, et al. (2011) Prognostic impact of CD133 mRNA expression in 48 glioblastoma patients treated with concomitant radiochemotherapy: A prospective patient cohort at a single institution. Ann Surg Oncol 18(10): 2937-2945.
5. Sasaki A, Kamiyama T, Yokoo H, Nakanishi K, Kubota K, et al. (2010) Cytoplasmic expression of CD133 is an important risk factor for overall survival in hepatocellular carcinoma. Oncol Rep 24(2): 537-546.
6. Ishigami S, Ueno S, Arigami T, Uchikado Y, Setoyama T, et al. (2010) Prognostic impact of CD133 expression in gastric carcinoma. Anticancer Res 30(6): 2453-2457.
7. Nakamura M, Kyo S, Zhang B, Zhang X, Mizumoto Y, et al. (2010) Prognostic impact of CD133 expression as a tumour-initiating cell marker in endometrial cancer. Hum Pathol 41(11): 1516-1529.
8. Silva IA, Bai S, Lean K, Yang K, Griffith K, et al. (2011) Aldehyde dehydrogenase in combination with CD133 defines angiogenic ovarian cancer stem cells that portend poor patient survival. Cancer Res 71(11): 3991-4001.
9. Woo T, Okudela K, Mitsui H, Yazawa T, Ogawa N, et al. (2010) Prognostic value of CD133 expression in stage I lung adenocarcinomas. Int J Clin Exp Pathol 4(1): 32-42.
10. Battula VL, Evans KW, Hollier BG, Shi Y, Marini FC, et al. (2010) Epithelial-mesenchymal transition-derived cells exhibit multilineage differentiation potential similar to mesenchymal stem cells. Stem Cells 28(8): 1435-1445.
11. Pirozzi G, Tirino V, Camerlingo R, Rocca A, Martucci N, et al. (2013) Prognostic value of cancer stem cells, epithelial-mesenchymal transition and circulating tumour cells in lung cancer. Oncology Reports 29(5): 1763-1768.
12. Mittal V (2016) Epithelial mesenchymal transition in aggressive lung cancers. Adv Exp Med Biol 890: 37-56.
13. Xiao D, He J (2010) Epithelial mesenchymal transition and lung cancer. Journal of Thoracic Disease 2(3): 154-159.

14. Garg M (2017) Epithelial plasticity and cancer stem cells: Major mechanisms of cancer pathogenesis and therapy resistance. World J Stem Cells 9(8): 118-126.

15. Sung WJ, Kim H, Park KK (2016) The biological role of epithelial-mesenchymal transition in lung cancer. Oncology Reports 36(3): 1199-1206.

16. Zeisberg M, Neilson G (2009) Biomarkers for epithelial-mesenchymal transitions. J Clin Invest 119(6): 1429-1437.