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Editorial

Addressing Epigenetic Changes Associated With Fibroblast Phenotypes Associated With Cancer In Lung Cancer.

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INTRODUCTION

Tumor microenvironment (TME) emphasis has lately replaced tumor-centricity as the primary focus of cancer research and treatment [1]. Malignant cells, immune cells, stromal cells, blood and lymph vessels, neuron fibers, extracellular matrix (ECM), and other acellular components make up the TME, which is a dynamic ecosystem [1]. Among these, fibroblasts that proliferate in the tumor microenvironment (TME)—now known as cancer-associated fibroblasts, or CAFs—have become important participants in tumor biology [2].In fact, CAFs are a very diverse cell population, with differences in their origins, molecular characteristics, and unique epigenetic profiles [3–4]. Epigenetic changes have recently been identified as key regulators of CAF heterogeneity and activation [4]. Surprisingly, Hanahan unveiled the revised hallmarks of cancer in 2022, highlighting the crucial part epigenetic modifications play in obtaining hallmark characteristics throughout tumor growth and progression [5]. Although CAFs have been found to contain genetic changes, this kind of fibroblast is often more genetically stable than tumor cells [6]. Nonetheless, the tumor-promoting characteristics of CAFs are significantly altered by epigenetic changes. Three primary categories of epigenetic regulatory mechanisms impact CAFs: non-coding RNAs (ncRNAs), DNA methylation, and histone modification (i.e., post-translational covalent modifications to histone tails that alter the structural state of chromatin, thereby the transcriptional status of genes within specific locations) [7].More precisely, lung cancer CAFs seem to have both targeted hypermethylation of important transcription factors such as SMAD3 and general hypomethylation [7]. Furthermore, a poor prognosis for individuals with non-small-cell lung cancer (NSCLC) is linked to overexpression of N-methyltransferases, metabolic enzymes that control cell metabolism and cause epigenetic changes [7, 8]. Regarding ncRNA changes in CAFs, it has been determined that a variety of microRNAs (miRNAs) are either increased or downregulated in lung cancer, which causes CAFs to have a phenotype that promotes tumor growth [7]. Notably, transforming growth factor beta (TGF-β) and other cytokines have been identified as important mediators of the aforementioned epigenetic modifications [7].Because epigenetic alterations may be reversible, therapies that target them hold greater promise than those that only focus on finding novel treatment approaches that target genome mutations [9]. The antitumor potential of HDAC inhibitors has long been known, and deregulated histone deacetylases (HDACs)—enzymes that remove an acetyl group from histone lysine residues, typically resulting in transcriptional inactivation of the involved DNA due to chromatin condensation—have been strongly linked to aberrant gene silencing and carcinogenesis [10]. Since HDACs play an abnormal role in the development of NSCLC [11], inhibiting these enzymes offers a viable treatment approach against CAFs in solid tumors. Notably, preclinical therapeutic benefits against activated CAFs in breast cancer and melanoma have been demonstrated by the HDAC inhibitor scriptaid (6-(1,3-dioxo-1H-benzo[de]isoquinolin-2-yl)N-hydroxyhexanamide) [12]. Suberoylanilide hydroxamic acid (SAHA), also marketed as Vorinostat, is a derivative of scriptaid that has not yet entered clinical trials; however, it has been tested in NSCLC clinical trials in conjunction with other chemotherapeutic agents [13] and the inhibitor of programmed cell death protein 1 (PD-1) pembrolizumab [14]. These trials have demonstrated that adding vorinostat to combination regimens improves treatment efficacy and increases patient survival.Similarly, fimepinostat (CUDC-907),

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a tiny chemical that may be taken orally and functions as a dual inhibitor of HDAC and phosphoinositide 3-kinase (PI3K) class I isoforms,has proven to be effective in inhibiting the growth of cancer cells, decreasing the synthesis of collagen and extracellular matrix, and limiting the migration and invasion potential of CAFs in vivo in models of non-small cell lung cancer [15]. Clinical trials are now being conducted to evaluate the effectiveness of HDAC inhibitors in action. In patients with metastatic non-small cell lung cancer (NSCLC), NCT01928576 is a phase-II research of epigenetic therapy that includes azacytidine, a cytotoxic nucleoside analog, and entinostat, a synthetic benzamide-derivative HDAC inhibitor, together with concurrent administration of the PD-1 inhibitor nivolumab. For advanced or metastatic non-small cell lung cancer, the oral bioavailable class-I selective HDAC inhibitor tucidinostat (HBI-8000) is being evaluated in conjunction with nivolumab in another phase-II trial, NCT05141357.In terms of miRNAs, LINC01614, a CAF-specific long noncoding RNA (lncRNA), improves the glutamine absorption of CAFs in the TME and is linked to a bad prognosis for patients with lung cancer [16]. The ability for lung cancer to spread in vivo was greatly decreased by the deletion of LINC01614, indicating new avenues for epigenetic therapy that targets miRNAs [16]. Additionally, because SMAD3 plays a significant role in determining the epigenetic profile of lung cancer CAFs, preclinical models have shown promising therapeutic outcomes in lung cancer using the SMAD3 inhibitor SIS3, a pyrrolopyridine that specifically inhibits TGF-β1-dependent SMAD3 phosphorylation [17]. Targeting this paracrine signaling component could be the focus of efforts because TGF-β is important in shaping the epigenetic landscape of CAFs. When galunisertib was used in conjunction with nivolumab, no patients were discovered to have anti-nivolumab antibodies, which is encouraging for the best possible use of immunotherapy in NSCLC [19]. It has been studied in phase-I and -II trials that enrolled patients with NSCLC with positive results. Furthermore, Shi et al. found that the growth of CAFs linked to squamous cell carcinoma (SCC) was inhibited in vivo by LY2109761, a strong and oral TGFβR1 inhibitor [20]. Finally, hydroxychloroquine-induced autophagy suppression prevented TGF-β synthesis and CAF activation, which hindered the growth of lung adenocarcinoma [21].In summary, Stephen Paget's timeless "seed and soil" hypothesis of cancer, which highlights the critical function of the TME, particularly CAFs, in tumor growth and progression, is still incredibly relevant today [22].We must develop and improve our therapeutic approaches if we are to successfully fight cancer and reduce the mortality that comes with it. In this continuous battle, focusing on the reversible epigenetic landscape of CAFs is a promising strategy. Luo et al. recently showed that the expression of the leucine rich repeat containing 3B (LRRC3B) gene, a tumor suppressor gene involved in the antitumor immune microenvironment, and the related DNA methylation at the LRRC3B promoter region may function as a useful predictive biomarker for anti-PD-1 therapy in NSCLC patients [23]. This suggests that the epigenetic profile of CAFs has even more potential value. I hope that future research will clarify the revolutionary potential of addressing epigenetic modifications in different TME components, particularly CAFs, opening the door to innovations in reducing lung cancer.

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REFERENCES

1. Jin, M.-Z.; Jin, W.-L. The Updated Landscape of Tumor Microenvironment and Drug Repurposing. Signal Transduct.Target.Ther.2020,5, 166. [CrossRef] [PubMed]

2. Wright, K.; Ly, T.; Kriet, M.; Czirok, A.; Thomas, S.M. Cancer-Associated Fibroblasts: Master Tumor Microenvironment Modifiers.Cancers 2023, 15, 1899. [CrossRef] [PubMed]

3. Wong, K.Y.; Cheung, A.H.; Chen, B.; Chan, W.N.; Yu, J.; Lo, K.W.; Kang, W.; To, K.F. Cancer-associated Fibroblasts in Nonsmall Cell Lung Cancer: From Molecular Mechanisms to Clinical Implications. Int. J. Cancer 2022, 151, 1195–1215. [CrossRef] [PubMed]

4. Kehrberg, R.J.; Bhyravbhatla, N.; Batra, S.K.; Kumar, S. Epigenetic Regulation of Cancer-Associated Fibroblast Heterogeneity.Biochim. Biophys. Acta Rev. Cancer 2023, 1878, 188901. [CrossRef]

5. Hanahan, D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022, 12, 31–46. [CrossRef]

6. Hosein, A.N.; Wu, M.; Arcand, S.L.; Lavallée, S.; Hébert, J.; Tonin, P.N.; Basik, M. Breast Carcinoma-Associated Fibroblasts Rarely Contain P53 Mutations or Chromosomal Aberrations. Cancer Res. 2010, 70, 5770–5777. [CrossRef]

7. Alcaraz, J.; Ikemori, R.; Llorente, A.; Díaz-Valdivia, N.; Reguart, N.; Vizoso, M. Epigenetic Reprogramming of Tumor-Associated Fibroblasts in Lung Cancer: Therapeutic Opportunities. Cancers 2021, 13, 3782. [CrossRef]

8. Sartini, D.; Seta, R.; Pozzi, V.; Morganti, S.; Rubini, C.; Zizzi, A.; Tomasetti, M.; Santarelli, L.; Emanuelli, M. Role of Nicotinamide N-Methyltransferase in Non-Small Cell Lung Cancer: In Vitro Effect of shRNA-Mediated Gene Silencing on Tumourigenicity.Biol.Chem.2015, 396, 225–234. [CrossRef]

9. Wright, J. Epigenetics: Reversible Tags. Nature 2013, 498, S10–S11. [CrossRef]

10. Konstantinopoulos, P.A.; Vandoros, G.P.; Papavassiliou, A.G. FK228 (Depsipeptide): A HDAC Inhibitor with Pleiotropic Antitumor Activities. Cancer Chemother. Pharmacol. 2006, 58, 711–715. [CrossRef]

11. Mamdani, H.; Jalal, S.I. Histone Deacetylase Inhibition in Non-Small Cell Lung Cancer: Hype or Hope? Front. Cell Dev. Biol. 2020,8, 582370. [CrossRef] [PubMed]

12. Kim, D.J.; Dunleavey, J.M.; Xiao, L.; Ollila, D.W.; Troester, M.A.; Otey, C.A.; Li, W.; Barker, T.H.; Dudley, A.C. Suppression of TGFβ-Mediated Conversion of Endothelial Cells and Fibroblasts into Cancer Associated (Myo)Fibroblasts via HDAC Inhibition.Br. J. Cancer 2018, 118, 1359–1368. [CrossRef] [PubMed]

13. Ramalingam, S.S.; Maitland, M.L.; Frankel, P.; Argiris, A.E.; Koczywas, M.; Gitlitz, B.; Thomas, S.; Espinoza-Delgado, I.; Vokes,E.E.; Gandara, D.R.; et al. Carboplatin and Paclitaxel in Combination with Either Vorinostat or Placebo for First-Line Therapy of Advanced Non–Small-Cell Lung Cancer. J. Clin. Oncol. 2010, 28, 56–62. [CrossRef] [PubMed]

14. Gray, J.E.; Saltos, A.; Tanvetyanon, T.; Haura, E.B.; Creelan, B.; Antonia, S.J.; Shafique, M.; Zheng, H.; Dai, W.; Saller, J.J.; et al.Phase I/Ib Study of Pembrolizumab Plus Vorinostat in Advanced/Metastatic Non–Small Cell Lung Cancer. Clin. Cancer Res.2019, 25, 6623–6632. [CrossRef]

15. Zhang, W.; Zhang, Y.; Tu, T.; Schmull, S.; Han, Y.; Wang, W.; Li, H. Dual Inhibition of HDAC and Tyrosine Kinase Signaling Pathways with CUDC-907 Attenuates TGFβ1 Induced Lung and Tumor Fibrosis. Cell Death Dis. 2020, 11, 765. [CrossRef]

16. Liu, T.; Han, C.; Fang, P.; Ma, Z.; Wang, X.; Chen, H.; Wang, S.; Meng, F.; Wang, C.; Zhang, E.; et al. Cancer-Associated Fibroblast-Specific lncRNA LINC01614 Enhances Glutamine Uptake in Lung Adenocarcinoma. J. Hematol. Oncol. J. Hematol.Oncol. 2022, 15, 141. [CrossRef]

17. Lian, G.-Y.; Wan, Y.; Mak, T.S.-K.; Wang, Q.-M.; Zhang, J.; Chen, J.; Wang, Z.-Y.; Li, M.; Tang, P.M.-K.; Huang, X.-R.; et al.Self-Carried Nanodrug (SCND-SIS3): A Targeted Therapy for Lung Cancer with Superior Biocompatibility and Immune Boosting Effects. Biomaterials 2022, 288, 121730. [CrossRef]

18. Melisi, D.; Garcia-Carbonero, R.; Macarulla, T.; Pezet, D.; Deplanque, G.; Fuchs, M.; Trojan, J.; Kozloff, M.; Simionato, F.; Cleverly,A.; et al. TGFβ Receptor Inhibitor Galunisertib Is Linked to Inflammation- and Remodeling-Related Proteins in Patients with Pancreatic Cancer. Cancer Chemother. Pharmacol. 2019, 83, 975–991. [CrossRef]

19. Zhang, H.; Yue, X.; Chen, Z.; Liu, C.; Wu, W.; Zhang, N.; Liu, Z.; Yang, L.; Jiang, Q.; Cheng, Q.; et al. Define Cancer-Associated Fibroblasts (CAFs) in the Tumor Microenvironment: New Opportunities in Cancer Immunotherapy and Advances in Clinical Trials. Mol. Cancer 2023, 22, 159. [CrossRef]

20. Shi, X.; Luo, J.; Weigel, K.J.; Hall, S.C.; Du, D.; Wu, F.; Rudolph, M.C.; Zhou, H.; Young, C.D.; Wang, X.-J. Cancer-Associated Fibroblasts Facilitate Squamous Cell Carcinoma Lung Metastasis in Mice by Providing TGFβ-Mediated Cancer Stem Cell Niche.Front. Cell Dev. Biol. 2021, 9, 668164. [CrossRef]