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Review Article

Combined small cell lung cancer: current progress and unmet needs

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Abstract: Combined small cell lung cancer (CSCLC) is a specific subtype of lung cancer characterized by a pathological mixture of small cell lung cancer and any subtype of non-small cell lung cancer components. Currently, our understanding of the clinicopathological features, origin, molecular characterization, treatment, and prognosis of CSCLC remains limited. CSCLCs represent examples of intratumor heterogeneity and pose challenges for accurate diagnosis. Are there any distinct clinicopathologic and molecular differences between pure SCLC and CSCLC? Furthermore, the prognostic outcomes and optimal treatments for CSCLC are urgently needed. This article aims to summarize the current biological features and clinical management of CSCLC, providing a reference for further understanding of this heterogeneous form of small cell lung cancer.

Keywords: Combined small cell lung cancer, pathological features, molecular features, diagnosis, treatment, prognosis

Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide [1, 2]. Small cell lung cancer (SCLC) is among the most lethal forms, characterized by high invasiveness, early metastasis, and a poor prognosis [3]. Combined small cell lung cancer (CSCLC) was first identified as a subtype of SCLC by the World Health Organization in 1981 and was formally categorized into pure small cell lung cancer (PSCLC) and CSCLC in 1999 [4, 5]. CSCLC can be diagnosed when coexisting with non-small cell lung cancer (NSCLC) subtypes such as adenocarcinoma (ADC), squamous carcinoma (SCC), or sarcomatous carcinoma, irrespective of the number of cells [6]. In CSCLC, more than two components can co-exist [7]. However, the updated edition of the NCCN Clinical Practice Guidelines for Small Cell Lung Cancer has redefined CSCLC to include tumour forms with a mixed component of SCLC containing at least 10% of large cell neuroendocrine carcinoma of the lung (LCNEC), which can be classified as CSCLC [8]. This redefinition is mainly due to the histological continuity between SCLC and LCNEC, making clinical distinction challenging [9, 10]. The prevalence of CSCLC has been reported to be much lower than that of PSCLC, with variations ranging from 5% to 28%, primarily attributed to differences in sample sources used in studies [11, 12]. Mutations in the driver gene EGFR have been detected in rare cases of primary SCLC, providing new insights into the treatment of SCLC and the origin of CSCLC. Despite advancements in diagnostic techniques leading to increased detection of CSCLC, the clinicopathological features, optimal treatment, and prognosis of CSCLC are still inconclusive. Several retrospective studies have previously reported specific clinical features of CSCLC, including a higher prevalence in male patients and an approximately equal distribution of tumour locations, either centrally

or peripherally, with the majority of patients presenting at an advanced stage [12]. In this review, we summarize the current advances and unmet needs in understanding the epidemiology, pathogenesis, tissue origin, biological features, and clinical management of CSCLC.

Clinicopathological characteristics

The utilization of diverse screening tools and diagnostic techniques has led to a significant increase in the diagnostic rate of CSCLC. Histological components in smaller biopsies or cytological specimens, such as bronchial biopsies and needle aspirations, are more diagnostically informative in surgically resected specimens. However, the reported incidence of CSCLC varies widely, ranging from 5% to 28%, mainly due to inconsistencies in the types of specimens used in different study centers [11-13]. In reality, the actual incidence of CSCLC would likely be considerably higher if CSCLC patients were diagnosed through postoperative pathology in this manner [14]. Accurate diagnosis of CSCLC through small sample biopsies is challenging due to an increase in extrusion artefacts, making it necessary to rely on bronchoscopy and needle aspiration biopsy [6, 15]. Studies have indicated that the most common histological components in CSCLC are predominantly SCC and to a lesser extent ADC [16]. However, other studies have shown that the most common pathology is SCLC combined with large cell carcinoma (LCC), followed by SCLC mixed with SCC [17]. Some studies have also suggested that the majority of combined cases are ADC [18]. Such discrepancies may be attributed to various uncontrollable factors, such as the gender ratio of patients, living environment, and individual genetics.

Regarding clinical characteristics, no differences were found between CSCLC and SCLC concerning age and lung metastases. However, significant differences were observed in race, gender, T-stage, N-stage, surgery, bone metastases, brain metastases, and liver metastases. According to Babakoohi et al. [11], the incidence of early-stage CSCLC (stage I and II) is much higher than that of PSCLC, with 29% of CSCLC patients diagnosed at stage I-II, as opposed to only 10% of SCLC cases [19]. Previous studies have reported that the median age of CSCLC patients is 59-64 years [11, 13], and the majority of CSCLC patients are male, accounting for 43% to 82.5% of cases [12, 20]. This gender imbalance may be closely associated with smoking, as almost all CSCLC patients have a history of heavy smoking. In the CSCLC group reported by Luo et al. [21], a history of smoking was a prominent characteristic, with 71 out of 88 evaluated CSCLC cases (more than 400 packs/year) having a clear smoking history. Additionally, the site of CSCLC development varies considerably. While most authors propose that CSCLC predominantly occurs in the central region, with a central mass observed in imaging in 86.4% of cases, including enlarged mediastinal lymph nodes [21], other studies have reported that 92 out of 114 patients with CSCLC had tumors located in the central region [22]. Nonetheless, Mangum et al. [23] found that 56% of CSCLC occurred in the peripheral region.

Molecular features

A comprehensive genetic analysis of patients with CSCLC is still lacking. To date, numerous articles have evaluated epidermal growth factor receptor (EGFR) mutations, which have been found to show identical mutations in different histological components of CSCLC [18, 24, 25]. For instance, a Japanese study reported a patient with SCLC mixed with ADC, where both components had identical mutations in exon 21 (L858R) of EGFR [24]. Similarly, Lu et al. [18] reported the same finding of the same EGFR mutation in the SCLC mixed with ADC component. However, some studies have reported that EGFR mutations were only present in the NSCLC component [26]. These discrepancies may be attributed to inadequate extraction of puncture biopsy specimens and differences in the sensitivity of genetic analysis methods. Further research using next-generation sequencing and immunohistochemical analysis of surgically resected tumour specimens has shown a high degree of concordance between tumour components, not only in the EGFR driver mutation but also in tumour protein P53 (TP53) and retinoblastoma 1 (RB1) mutations and p53 and Rb expression patterns [27]. This suggests that activation of the PI3K/AKT1 signalling pathway may play a crucial role in the development of concurrent or diachronic SCLC combined with NSCLC [28]. Additionally, the same KLC1-ALK fusion has

been identified in both histological components of primary SCLC combined with ADC [29]. The current study revealed the highest frequency of TP53 mutations in CSCLC and PSCLC, followed by RB1, as a major cause of SCLC tumorigenesis [30]. Moreover, abnormalities in Notch family genes (Notch1, Notch3), CREBBP, CDKN2A, and MYC are also key to the development of SCLC [31]. One investigation analyzed 223 CSCLC patients and found that CSCLC was more likely to be accompanied by EGFR mutations, anaplastic lymphoma kinase (ALK) rearrangements, and high levels of CEA, SCCA, and CYFRA21-1 expression [32]. Studies have shown that major somatic mutations are present in different histological components of CSCLC, but that achaet-scute homolog-1 (ASCL1) expression is higher in the SCLC component than in the NSCLC component, suggesting that each histological component of CSCLC undergoes morphological evolution due to differences in ASCL1 expression, independent of differences in acquired somatic mutations [33]. In genetically engineered mouse models (GEMM) with dual Trp53/p16 mutations, it was observed that Trp53/p16-deficient mice eventually developed CSCLC, indicating that the different components of CSCLC may be derived from the same pluripotent monoclonal cell [34]. Nevertheless, there is limited understanding of the cellular and molecular abnormalities underlying the development, progression, and treatment resistance of CSCLC. Further investigations are required to address these aspects.

Pathogenesis

Understanding the cellular origins of different lung cancer tissue types can help identify molecular differences in various cancers and facilitate the development of specific targeted drugs [35-37]. The origin of CSCLC involves two main mechanisms: heterogeneity and transdifferentiation [38] (**Figure 1**). Heterogeneity in SCLC tumorigenesis has been observed in genetically engineered mouse models (GEMM) [38], which produce mixed tumours to varying degrees when combined with different genes in RB1 or p53 knockout models. These mixed tumours consist of a variable mixture of SCLC with LCNEC or NSCLC. On the other hand, transdifferentiation refers to the transformation of cells from one type to another [39], which has been reported as a mechanism of acquired drug resistance in lung ADCs [40, 41]. Moreover, subcomponents of CSCLC are believed to originate from the collision of a common precursor tumour cell or multiple primordial cells growing at the same site, indicating that intra-tumour metastatic collisions are an alternative mechanism of SCLC co-evolution [42]. Genomic aberrations, including TP53, RB1 mutations, and MYC proto-oncogene protein (c-Myc) amplification, are closely associated with the tumorigenic and aggressive features of SCLC [40, 41, 43]. Studies have shown that CSCLC patients exhibit the same TP53 mutations and chromosomal abnormalities in all components of SCLC mixed with SCC, suggesting a possible common clonal origin [44]. Zhao et al. [7] also found a large number of common mutations in the mixed components of CSCLC patients, supporting the idea of a shared clonal origin. Notch mutation inactivation, ASCL1 (achaet-scute complex homologue 1) expression, and double allelic deletion of TP53 and RB1 have been proposed as factors linking SCLC to NSCLC [45, 46]. The restoration of Notch 1 expression in SCLC, along with downregulation of histone deacetylation near the Notch 1 promoter, has been linked to the co-emergence of epithelial-like regions in SCLC, providing a potential mechanism for the histogenesis of CSCLC [31]. Furthermore, it has been suggested that various components of CSCLC may grow independently in adjacent regions and then accumulate in the primary tumour [47, 48]. In conclusion, TP53 and RB1 are the most commonly mutated genes in CSCLC. Less than 10% of common mutations were identified in CSCLC, whereas more than 50% of common mutations were found in mixed components, which may explain the tumour heterogeneity and common progenitor cells. Studies have proposed that individual pluripotent clones may give rise to distinct components during CSCLC genesis and grow and proliferate following mutations [44, 49, 50]. For instance, a report describes a young female patient who developed resistance after 18 months of treatment with osimertinib and was diagnosed with a change from adenocarcinoma of the lung to mixed small cell lung cancer in her pleural effusion [51]. However, there is still no consensus on the origin of CSCLC. Further research is needed to fully understand the underlying mechanisms of CSCLC development.

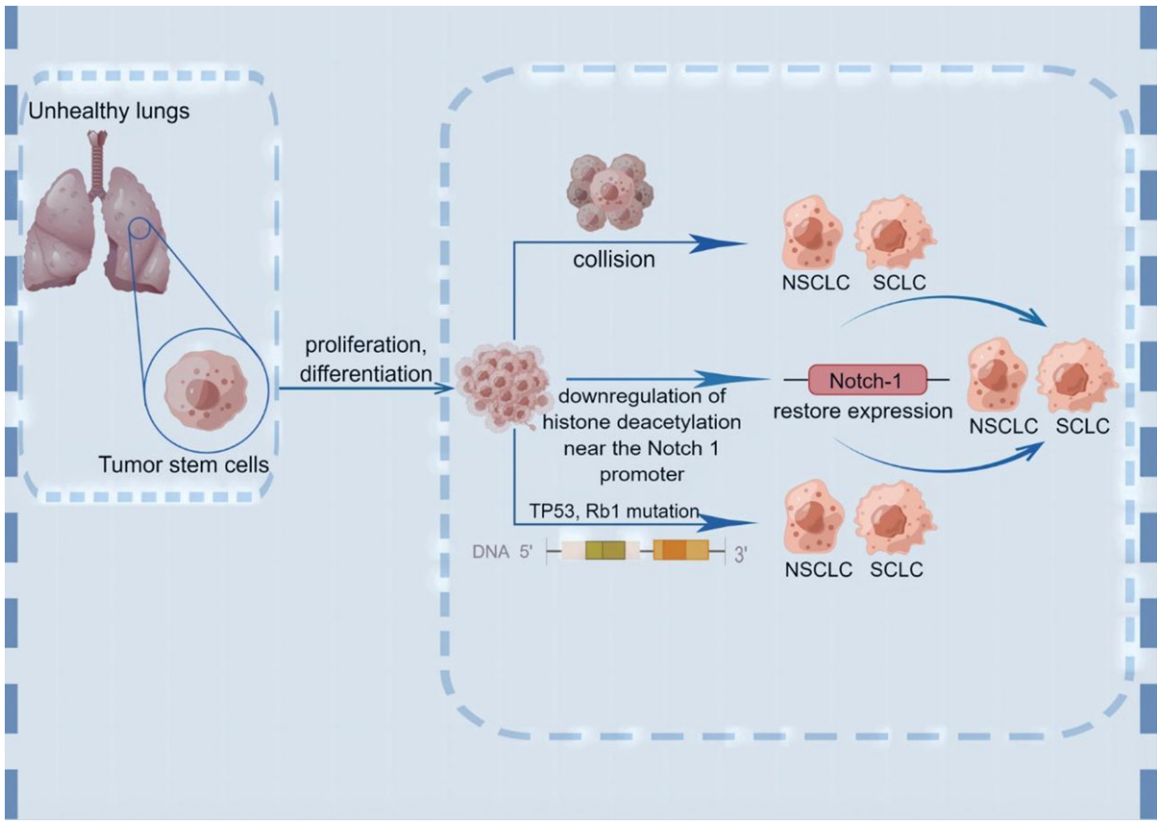

Figure 1. Relevant mechanisms of compound small cell lung cancer (CSCLC). Firstly, the subcomponents of CSCLC may arise from collisions between common precursor tumor cells or multiple progenitor cells growing at the same location. Secondly, the downregulation of histone deacetylation near the Notch 1 promoter in SCLC leads to the restoration of Notch 1 expression, promoting the coexistence of epithelial-like regions in SCLC. This offers a potential mechanism for the histogenesis of CSCLC. Moreover, in CSCLC patients, the components of mixed SCLC and SCC demonstrate identical TP53 mutations and chromosomal abnormalities, suggesting that they may originate from the same clone before the onset of TP53 mutations and chromosomal abnormalities.

Treatment strategies

CSCLC represents a rare and specific subtype of SCLC, and its complex composition poses challenges in treatment. Surgical intervention may be crucial for patients in stages IA-IB, while for stages IIA-IIIA, a combination of surgery, chemotherapy, and radiotherapy can be effective in improving prognosis. For patients with advanced disease, chemotherapy-based treatment should be considered. However, there is currently no universally recommended treatment regimen for CSCLC. Based on current evidence, the treatment of CSCLC should follow conventional SCLC guidelines, and a multidisciplinary and comprehensive treatment approach should be adopted.

Surgery

The role of surgery in the early stages of CSCLC remains uncertain. However, the majority of studies have demonstrated that surgical treatment is highly beneficial for patients with early-stage CSCLC. Hage et al. [52] evaluated 26 postoperative patients and found that surgery led to long-term disease-free survival (DFS) or even cure for stage I CSCLC patients. Babakoohi et al. [11] compared 22 CSCLC patients with 406 PSCLC patients and observed that surgical treatment was more frequently utilized in the CSCLC group. Men et al. [22] reported the outcome of 114 CSCLC patients from one institution, of whom 70.2% received two or more treatment modalities, and the 5-year overall survival (OS) was better in the surgical group than the non-surgical group (48.9% and 36.6%, respectively). Another study reported a patient with CSCLC who presented with an isolated polypoid tipped endotracheal lesion, and after rigid bronchoscopic R0 resection, the patient experienced immediate symptomatic relief and was discharged on the first postop-

erative day [53]. These findings underscore the importance of surgical treatment in CSCLC patients. However, the inclusion of radiotherapy and its timing and sequence still require further investigation.

Radiotherapy

Limited data are available on radiotherapy for CSCLC patients, but one study reported a case of a CSCLC patient who achieved clinical complete remission after receiving immunotherapy combined with radiotherapy, suggesting a potential new treatment option [54]. In another case study, a patient with a long history of smoking and a mixture of tissue types, experiencing persistent cough due to endotracheal metastases, underwent radiotherapy in combination with carboplatin and etoposide, resulting in significant improvement as the lesion shrank and the cough subsided [55]. Individual studies have demonstrated that postoperative radiotherapy (PORT) can significantly improve overall survival (OS) in patients with CSCLC resected at the pathological pN2 stage and also enhance OS in patients with a high rate of lymph node metastases [56]. Patients with CSCLC are known to have a relatively high risk of developing brain metastases. Data suggest that prophylactic brain irradiation (PCI) may improve OS and disease-free survival in patients with surgically resected CSCLC and help reduce the incidence of brain metastases [57]. The earlier NCCN guidelines state that PCI reduces the incidence of brain metastases and improves OS in patients with limited-stage SCLC who respond well to initial treatment, and it is recommended as a class I application. PCI also reduces the incidence of brain metastases in patients with extensive-stage SCLC who have responded effectively to systemic therapy [10]. To address the possible side effects of PCI, it has been suggested that memantine can be added during and after radiotherapy to reduce the neurocognitive impairment associated with whole-brain radiotherapy for brain metastases. The old NCCN guidelines recommended "considering PCI using intraoperative magnetic resonance imaging (IMRI) to preserve the hippocampus". The new NCCN guidelines propose that IMRI for prophylactic intracranial irradiation and avoidance of the hippocampal area (HA) could be considered as a potential strategy to improve cognitive preservation [58]. However, whether PCI can be integrated into a comprehensive treatment model for CSCLC requires further evaluation.

Pharmacotherapy

Most patients diagnosed with Combined Small Cell Lung Cancer (CSCLC) typically undergo a combination of treatments, including chemotherapy, surgery, and radiotherapy. Chemotherapy involves a platinum-based combination regimen that includes platinum agents along with paclitaxel, irinotecan, pemetrexed, or other suitable regimens. However, a retrospective study by Li et al. [59] revealed that the paclitaxel-etoposide-carboplatin/cisplatin (TEP/TCE) regimen may not be the preferred choice for treating CSCLC. Currently, the etoposide-carboplatin/cisplatin (EP/CE) regimen remains the primary treatment option for CSCLC patients. For those with extensive stage Small Cell Lung Cancer (SCLC), the preferred approach mostly involves a combination of etoposide-carboplatin/cisplatin along with immunotherapeutic agents. The new NCCN guidelines have introduced a new category, along with the previous three preferred regimens, known as "carboplatin AUC5 1st d - etoposide 100 mg/m^2 1st, 2nd, 3rd d - atezumab 1200 mg 1st d (repeated every 21 d times 4 cycles), followed by sequential atezumab maintenance therapy 1680 mg (repeated every 28 d, i.e. Q4w)" [58].

A retrospective analysis provided compelling evidence for the efficacy and safety of anlotinib in treating elderly patients with Combined Small Cell Lung Cancer (CSCLC) [60]. Moreover, anlotinib-induced hypertension during treatment was associated with a better prognosis [61]. Notably, patients undergoing anlotinib treatment experienced tumour cavitation, where intense expansion and contraction movements of the bubble mechanically destroyed tumour cells, serving as an independent predictor of improved progression-free survival (PFS) [62]. However, the effective predictive biomarkers for anlotinib are currently unknown and require further investigation. One study reported on a young female patient with ALK-positive CSCLC who successfully responded to alectinib treatment after failing immunochemotherapy for Small Cell Lung Cancer (SCLC) and cytotoxic chemotherapy for adenocarcinoma [63]. Additionally, the study suggested that ALK

testing could be reasonable for SCLC patients with an adenocarcinoma component. Another case report presented a unique scenario of coexisting Small Cell Lung Cancer (SCLC) and enteric adenocarcinoma. The patient, who had an epidermal growth factor receptor (EGFR) p.L861Q mutation, showed significant benefit from gefitinib treatment in combination with EP chemotherapy [64]. In a pioneering study on SCLC combined with Lung Squamous Cell Carcinoma (LUSC), the clinical benefit of PD-1 alone as a third-line treatment for Combined Small Cell Lung Cancer (CSCLC) was sustained and demonstrated a better prognosis than conventional standard chemotherapy (median PFS: 0.7 months) and anlotinib (median PFS: 4.1 months) [65]. Another study reported a case of a patient with CSCLC who presented early with adrenal, rib, and mediastinal lymph node metastases and underwent treatment with carboplatin, etoposide, and envelceptimab. After six cycles of chemotherapy, the lung lesions were significantly reduced, and a comprehensive efficacy assessment showed beneficial results [66]. Immunotherapy is now being used as a third-line treatment for SCLC, and it is theoretically expected to be more sensitive for Combined Small Cell Lung Cancer (CSCLC) due to the highly unstable genome and chromosomes in SCLC. One study reported a case of a middle-aged female patient with a primary diagnosis of SCLC who exhibited stable lung lesions during pablizumab treatment combined with radiotherapy, suggesting a potential benefit of immunotherapy [67]. However, it should be noted that PD-L1 and tumour mutation burden (TMB) do not adequately predict the response to immunotherapy in SCLC. Therefore, genotyping may offer new perspectives for future drug selection. The subdivision of SCLC into four subtypes based on key transcriptional regulators has shown that different genotypes have varying sensitivities to drug therapy. Consequently, testing different genotypes becomes essential for screening immunotherapy populations. For instance, in immunoreactive mouse models of the SCLC-A subtype, there is a clear synergistic effect between the inhibition of PARP (a DNA repair enzyme playing a crucial role in DNA damage repair and apoptosis) or CHK1 (cell cycle detection site kinase 1) and the inhibition of PD-1 [68]. Interestingly, the gene expression profile of CSCLC appears to be different from that of SCLC, and current next-generation sequencing technology fails to match it to any existing subtype [69]. As a result, further classification of CSCLC into specific types is necessary. Nevertheless, reports on immune checkpoint inhibitor (ICI) therapy are still limited, and the efficacy of immunotherapy in CSCLC warrants further in-depth exploration. Due to the uncertain status of drug combinations for the treatment of CSCLC, these results require confirmation through large prospective clinical trials.

Prognosis

The prognosis of patients with Combined Small Cell Lung Cancer (CSCLC) can be influenced by various factors, and the findings from different studies tend to vary. In a study utilizing the SEER database, 400 CSCLC patients were analyzed, revealing that age, race, gender, T-stage, N-stage, surgery, and the presence of bone, brain, liver, and lung metastases significantly affected CSCLC prognosis ($P < 0.05$) [70]. In an article, a rare case of an elderly patient with CSCLC was reported, presenting a tumour consisting of three distinct components (SCLC, adenocarcinoma, and spindle cell tumour). Remarkably, the tumour size increased by 2.59-fold in just 20 days. The authors concluded that the coexistence of CSCLC and spindle cell tumour contributed to the rapid disease progression and poor prognosis [71]. Another investigator conducted a retrospective analysis of 31 CSCLC patients and found that sequential radiotherapy, staging, and chemotherapy significantly influenced survival according to multivariate analysis ($P=0.015$, $P=0.022$, $P=0.049$) [72]. These findings highlight the complexity of determining prognostic factors in CSCLC and underscore the importance of further research and larger studies to gain a more comprehensive understanding of the disease's clinical course.

Conclusions

With advancements in medical technology, the diagnosis of CSCLC is steadily increasing, creating a pressing demand for more extensive research and improved treatment approaches for this patient group. However, the understanding of CSCLC at the fundamental level is still in its infancy, and the precise mechanisms and histogenesis of the disease remain speculative. Investigating the cellular origins of differ-

ent lung cancer tissue types can aid in identifying molecular distinctions among various cancers, thereby facilitating the development of targeted therapeutic interventions. Specifically, it is crucial to determine whether the distinct NSCLC components within CSCLC exhibit diverse biological properties and differ in terms of treatment and diagnosis. Simultaneously, there has been a growing body of recent studies on transformed SCLC, but the similarities and differences with CSCLC are still not fully elucidated. Furthermore, patients with this subtype have limited survival time, underscoring the importance of providing precise and personalized treatment. While most studies have shown that adjuvant therapy can confer survival benefits to these patients, the data originate from diverse patient characteristics and various study centres. Moreover, despite some studies attempting to predict factors affecting the prognosis of CSCLC patients, the findings have been inconsistent and often based on small samples from single cohorts. Consequently, there is an urgent need for comprehensive research based on clinical samples and animal models, utilizing innovative histological techniques, and exploring novel treatment strategies through multicentre clinical studies. This concerted effort is essential to enhance our comprehension of CSCLC and to advance more effective and tailored therapeutic interventions for patients suffering from this challenging disease.

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Disclosure of conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be perceived as a potential conflict of interest.

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