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Commentary

Gene Expression Signatures Predicting Survival and Chemotherapy Benefit in Patients with Resected Non-small-Cell Lung Cancer

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Adjuvant cisplatin-based chemotherapy is standard use in adenocarcinomas and squamous cell lung cancer patients with stage IIA, IIB or IIIA disease who have undergone complete surgical resection [1]. Adjuvant chemotherapy has proven to be efficacious in a total of 12,473 patients (median age, 64 (57–70) years) when started up to 4 months postoperatively in patients who recovered slowly from surgery. A Cox model identified the lowest mortality risk when chemotherapy was started 50 days postoperatively [2].

Guo et al., in the current EbioMedicine issue, have reported a 7-gene signature predicting survival in NSCLC patients. In the Case Western Reserve University (CWRU) patient cohort, the 30 month survival rate was less than 40% in the high-risk patients who did not receive chemotherapy, while the 30 months survival rate was 100% in patients receiving adjuvant chemotherapy [3]. In a validation set, the 5-year survival rate was 70.9% in high-risk patients who received adjuvant chemotherapy, whereas it was only 45.8% in high-risk patients who did not receive adjuvant chemotherapy. Conversely, no benefit of chemotherapy was obtained in patients deemed low-risk. The 7-gene signature of Guo et al. is akin to the 14-gene signature developed by David Jablons in resected lung adenocarcinomas [4]. In the Jablons study, the 5-year disease-free survival rate was 91.7% in high-risk patients who received adjuvant chemotherapy, whereas it was only 48.9% in high-risk patients who did not receive adjuvant chemotherapy. Untreated molecular low-risk patients had a 5-year disease-free survival rate of 93.8% [4].

Intriguingly, another study reported that for low-risk patients, adjuvant chemotherapy could be detrimental for survival [5]. This finding posit that chemotherapy can be nefarious for resected NSCLC patients and, furthermore, experiments support that chemotherapy induces tumor cells expressing the actin protein, mammalian-enabled (MENA), to migrate and, despite decreasing tumor size, it increases the risk of metastatic dissemination [6] (Fig. 1). Moreover, chemotherapy can induce hypoxia, causing enhanced expression of tumor cell surface markers, such as CD47, that functions as a ligand for signal regulatory protein-α (SIRPα), a protein expressed on macrophage and dendritic cells, and CD73, causing immune evasion [7] (Fig. 1). Guo et al. highlight that CD27, as part of the 7-gene signature, induces NF-kB activation and could be a potential target for immunotherapy [3]. The findings are of interest and can pave the way to develop new theranostic models for PD-1 blockade in early resected NSCLC [8]. The 5-year survival rates range from 67% for patients with T1 N0 disease to 23% for T1-3 N2 disease [1]. Gene expression signatures for predicting metastasis and survival in early NSCLC has been numerously reported in adenocarcinoma, and, to a lesser extent, in squamous cell carcinoma of the lung. Despite a lack of commonality of many genes identified between the published prognostic signatures, numerous gene expression signatures occupy overlapping prognostic space and were able to predict outcome in early NSCLC [9]. The Guo et al. predictive assay based on mRNA expression should be pondered and adapted to the evolving concepts in NSCLC, taking into account the crossover in sex incidences, the accumulation of somatic mutations, known as drivers, and, possibly, other genomic alterations [3]. Adenosine deaminases acting on RNA (ADARs) can induce A-to-I RNA editing where genomically encoded adenosines are transformed and recognized as guanosines in the RNA sequence, creating an inner transcriptome diversity that, unlike DNA mutations, does not leave traces on the genome [10]. Further clarification on the potentially harmful effect of chemotherapy in promoting metastasis via blood vessel tumor cell migration warrants investigation, as it has been shown that MENA is differentially spliced in streaming

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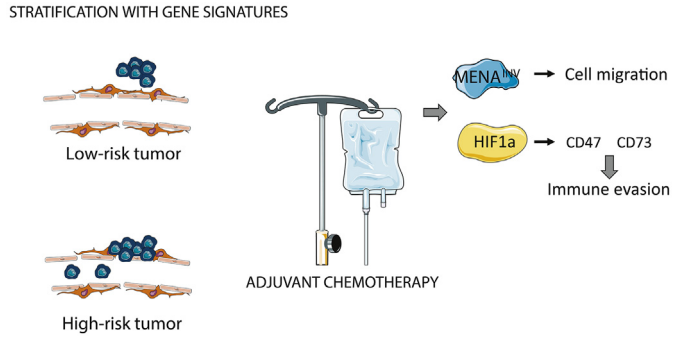

Fig. 1. Gene signatures for prediction of benefit to adjuvant chemotherapy in surgically resected NSCLC. Adjuvant chemotherapy is of benefit for NSCLC patients that are stratified as high risk. Caution should be taken for the nefarious effect of chemotherapy due to the activation of MENA and HIF1a. HIF1a, Hypoxia-inducible factor 1-alpha; MENA, mammalian enabled.

disseminating tumor cells, showing the splicing pattern of $MENA^{INV}$-high and $MENA^{11a}$-low [6] (Fig. 1). In short, somatic mutations, RNA editing and the role of macrophages should be kept in mind, in addition to gene transcription, for further optimization of adjuvant and neoadjuvant therapies, including anti-PD-1 and anti-PD-L1 blockade.

Disclosure

The authors declare no conflict of interest.

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