MUTATIONAL LANDSCAPE INFORMS THE TREATMENT OF

Non-Small Cell Lung Cancer

INTRODUCTION

Lung cancers are the leading cause of cancer deaths worldwide, with non-small cell lung cancers (NSCLC) accounting for approximately 85% of all lung cancers.[1,2] Although they vary in clinical presentations, NSCLCs are best characterized as a group of cancers that share cellular and molecular origins.[3] Importantly, NSCLCs differ histologically from small cell lung cancers (SCLCs) and are relatively insensitive to chemotherapy.[4,5] Approximately 40% of patients with NSCLC present with advanced-stage cancer, for which the five-year survival rate is approximately 2%.[6] Recent advances have begun to unravel the biology of NSCLCs. This has led to the development of novel targeted agents that exhibit greater efficacy, compared to chemotherapy alone, in patients with certain genetic mutations.[2,3,7-9]

ETIOLOGY AND CLASSIFICATION

Smoking is by far the leading risk factor for lung cancer, and accounts for more than 85% of all lung cancer related deaths.[10] Cigarette smoke contains more than 6,000 components, many of which lead to DNA damage.[11] Though most DNA damage is repairable, leftover unrepaired DNA due to epigenetic silencing of repair genes are hypothesized to lead to the development of NSCLC. To date, nine DNA repair genes have been found to be repressed by promoter hypermethylation, which has found to be increased in NSCLCs.[12-15]

The two predominant NSCLC histological phenotypes are adenocarcinoma (ADC; ~50%) and squamous cell carcinoma (SCC; ~40%). In general, ADCs develop in the distal airways, whereas SCCs develop in the proximal airway structures.[3] ADC is the most common type of lung cancer in the United States and is the most frequently occurring type of lung cancer in nonsmokers.[16-18] SCC is one of the few types of lung cancer more common in men than in women, and is more closely correlated with a history of tobacco use than other lung cancers.[18,19]

Regardless of histological phenotype, there are two genetic markers that are routinely profiled in NSCLC tumours to guide treatment decision making: mutations within the epidermal growth factor receptor *(EGFR)* and anaplastic lymphoma kinase *(ALK)* genes.[20] *EGFR* and *ALK* mutations, which lead to the constitutive expression and overproduction of their encoded proteins, are mutually exclusive and are observed in about 15% and 7% of all NSCLC tumours, respectively. Despite these low frequencies, research suggests that these mutations are predictive of responses to targeted therapeutics.[22]

THERAPEUTIC ADVANCES

The discovery of *EGFR* and its ligand won the 1986 Nobel Prize in Medicine.[22] Overexpression of *EGFR* and other receptor tyrosine kinases is associated with the development of tumours.[4] Expressed in >60% of NSCLCs, *EGFR* is a gatekeeper to several downstream signalling molecules which play a crucial role in anti-apoptotic functions that promote cell survival.[4,22,23] In 2004, two groups led by led by Lynch and Paez revolutionized the field of lung cancer research through reporting the discovery of important mutations in the tyrosine kinase (TK) domain of the *EGFR* gene in NSCLCs.[4,24-27] They found that NSCLC cells harbouring select mutations on exons 18 and 21 of *EGFR* display constitutive receptor activation and dependency on the *EGFR* signalling pathway for survival.[4,26,27] This discovery allowed scientists to postulate that antagonizing the receptor could reduce the rates of tumour progression.[3,9,26] This hypothesis was confirmed after the administration of tyrosine kinase inhibitors (TKIs) was found to be effective in treating patients whose tumours had sensitizing mutations.[9,28,29] Two TKIs, erlotinib and gefitinib, are currently approved for the treatment of NSCLC in Canada.[30] With the development of these inhibitors, patients with these specific mutations can now live up to 3-4 years compared to 1 year for those without targetable mutations.[31]

The remarkable success of *EGFR* TKIs has highlighted the importance of identifying genotype-specific subsets of patients so that NSCLC treatment may be tailored to them.[3,4,25,26] The recent identification of the fusion gene between echinoderm microtubule-associated protein-like 4

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Pathoprofile

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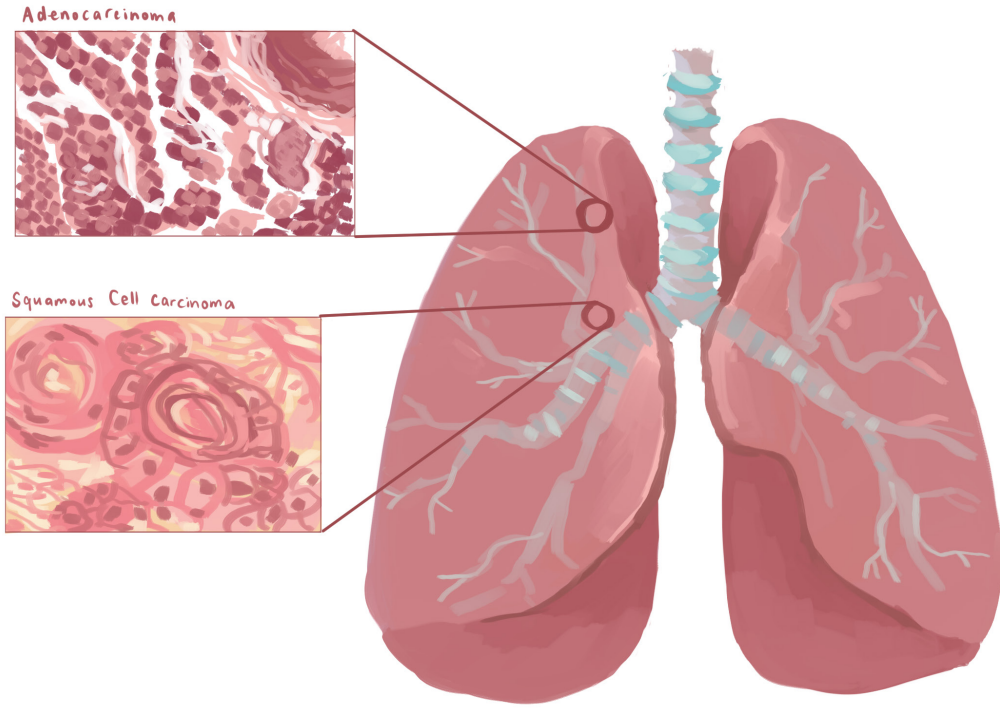
(EML4) and *ALK* genes has expanded the list of targetable mutations in lung cancer.[21,26,32] The *EML4-ALK* fusion gene is a result of a translocation mutation that occurs in a subset of ADCs which, similar to the *EGFR* mutation, causes constitutive activation of ALK kinase and aberrant downstream signalling.[4,21,28] Though clinical trials are ongoing, two ALK inhibitors, ceritinib and crizotinib, have been approved for the treatment of ALK-positive NSCLC in Canada.[33]

FUTURE PERSPECTIVES

Although these discoveries have altered the public perception that little or no progress has been made in lung cancer research, many challenges lie ahead.[4] One major challenge is the management of patients who acquire resistance to EGFR or ALK inhibitors after months or years of treatment.[34,35] Epithelial-to-mesenchymal transition (EMT) is a process that commonly occurs in cancer whereby epithelial cells acquire stem cell-like properties.[34,35] In NSCLCs, drug-tolerant persister cells may undergo EMT, allowing them to develop greater resistance to TKIs and become more metastatic.[27,34,36] The efficacy of combination drug therapies that also target the EMT is currently being investigated.[34,36] Another challenge is the feasibility of testing the genetics of all patients with NSCLC for *EGFR* and *ALK* mutations to determine their course of treatment, especially given the low frequency of the alleles.[9,28] Placing NSCLC patients on standard of care platinum-based chemotherapy without genetic testing is straightforward.[9,29] However, facilitating broad, rapid, and high-quality diagnostic testing that is affordable for all patients with NSCLC is difficult without access to highly specialized cancer centres.[4] Despite the new challenges, these landmark discoveries have given hope that more effective ways of managing NSCLCs are on the horizon.



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