Basic science of lung cancer

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The molecular success story in non-small-cell lung cancer (NSCLC) has not been fast developing. Despite the discovery of an oncogenic *KRAS* mutation in NSCLC in 1984 [1], it was not until 2004 that *epidermal growth factor receptor* (*EGFR*) mutations were found to predict response to gefitinib [2] and erlotinib [3]. Since then, lung cancer has evolved from a disease classified by its appearance under the light microscope to one that is characterised at a molecular level by an increasing number of driving mutations. This abstract will focus on recent molecular developments in NSCLC and their potential therapeutic implications. Subsequent to the identification of *EGFR* mutation numerous genes involved in the signalling cascade from receptor tyrosine kinases on the cell surface to the nucleus have been implicated in the pathogenesis of NSCLC (reviewed in Pao and Gerard [4]). To date, the *mitogen activated kinase P* (*MAPK*) pathway containing *RAS*, *RAF*, *MEK* and *ERK* as well as the *PI3K/Akt/mTOR* pathway are best understood. Both amplify growth factor signalling from cell surface receptors, regulate cell growth and proliferation and are central to the survival of many cancers.

EGFR

In-frame deletions of exon 19 of the *EGFR* gene and the point mutation L858R are the most prevalent and associated with adenocarcinomas, female sex, never-smokers and south-east Asian ethnicity. In *EGFR*-mutant lung cancer treatment with gefitinib or erlotinib results in dramatic and fast responses in a high proportion of patients initially, but resistance usually occurs. A further point mutation in the *EGFR* gene, T790M, has been identified as the predominant cause for acquired resistance [5]. Preclinical experiments suggest that this resistance may be difficult to overome even with the second generation TKIs that are currently in development. Combinations of a second generation TKI with mTOR inhibitor or the EGFR antibody cetuximab may be a successful strategy as is the third generation inhibitor WZ4002, which has been specifically designed to overcome the T790M resistance mutation [5].

ERBB2

Deregulation of the Human Epidermal growth factor Receptor 2 (HER2) protein, a member of the ErbB family, plays an important role in the development and progression of many cancers. Mutations in the kinase domain of the *ERBB2* gene, which encodes for HER2, are also present in a small proportion (3%) of lung adenocarcinomas most of which are in-frame duplications or insertions affecting exon 20 and lead to constitutive activation of the receptor tyrosine kinase [6]. Characteristics of patients with *ERBB2* mutant tumours are similar to those with *EGFR* mutations, with higher rates in females, never-smokers, adenocarcinomas and Asian ethnicity [4]. *ERBB2* mutant lung cancers seem resistant to EGFR TKIs and pre-clinical data suggest sensitivity to lapatinib or afatinib [4].

c-MET

The Hepatocyte Growth Factor Receptor (HGFR), encoded by the gene *c-MET*, has been implicated in secondary resistance to EGFR targeting TKIs in up to 20% of cases. It is thought that the tumour overcomes targeting of the *EGFR* oncogene by amplification of *c-MET* and overexpression of an alternative cell surface receptor. This process, termed kinase switch, results in HGFR instead of EGFR driving downstream pathways and maintaining oncogene addiction [5]. *c-MET* amplification and activating point mutations are also seen independently of EGFR targeting in both squamous-cell carcinoma and adenocarcinoma. Multiple small molecule inhibitors of HGFR are currently in development [4].

MAPK pathway

One of the signalling cascades downstream of receptor tyrosine kinases is the *MAPK* pathway. It transmits growth signals from the cell surface via *RAS*, *RAF*, *MEK* and *ERK* to the nucleus and promotes proliferation and cell division. Mutations in *KRAS*, a GTPase downstream of *EGFR,* are seen in ~17% of NSCLC, are more common in smokers and confer a poor prognosis. *KRAS* mutations predict for primary resistance to EGFR targeting TKIs [5] as well as lack of benefit from adjuvant chemotherapy [7]. As oncogenic *KRAS* mutations confer loss of function (impaired GTPase activity) and result in constitutive activation of the protein they have proven a difficult therapeutic target as the defect could not be overcome by small molecule inhibition [7]. Mutations in the downstream *B-RAF* are found in ~3% of NSCLC and several B-RAF inhibitors are currently in clinical development. The downstream *MEK* is activated by mutation in 1% of cases, but MEK inhibitors, which are currently undergoing clinical trials may also be of benefit if the upstream pathway is activated. Interestingly, *HER2*, *EGFR*, *KRAS*, *B-RAF* and *MEK* mutations are primarily seen in adenocarcinomas and seem mutually exclusive, possibly because they share the same signalling pathway [4].

PI3K pathway

Parallel to the MAPK pathway is the PI3K pathway. P*hosphatidylinositol-3-kinase* (*PI3K*) is thought to contribute to lung cancer development through amplification or activating mutation and is more often found in men, smokers and in 8–10% of squamous-cell carcinomas. Unlike mutations in the MAPK pathway mutations in *PI3K* can exist alongside *EGFR* and *KRAS* mutations [4]. Inhibitors of PI3K may also be indicated following loss of the tumour suppressor gene *PTEN* as the latter has inhibitory activity on the PI3K pathway [8]. Mutated protein kinase B, which is downstream of PI3K and encoded by *Akt,* can lead to PI3K independent activation of the pathway and is found in ~1% of NSCLC, mainly squamous cell carcinomas [4].

The mammalian Target Of Rapamycin (mTOR) is a central kinase in the PI3K pathway, interacting with and regulating numerous cellular processes. Mutations in *FRAP1*, which encodes for mTOR in humans, are infrequent in NSCLC, but hyperactivation of the pathway is often observed, explaining the universal interest in mTOR as a therapeutic target. Unlike many of the investigational compounds above, the mTOR inhibitors rapamycin, temsirolimus and everolimus have regulatory approval for various indications including cancer [9]. Single agent activity of these drugs in unselected NSCLC have been disappointing, but recent pre-clinical experiments show promising data in combination with afatinib and early clinical trials in combination with gefitinib yielded positive results [4,5,9].

EML4-ALK

The *EML4-ALK* oncogene is caused by small inversions within the short arm of chromosome 2. These fusions are generally found in tumours with wild-type *EGFR* and *KRAS* and the mutation frequency is increased in young adults, adenocarcinomas and in never- or light smokers [4]. Tumours harbouring this translocation have shown promising response rates when treated with the ALK inhibitor crizotinib, which is currently in phase III development. Acquired resistance through secondary mutations (C1156Y and L1196M) in the kinase domain of *EML4-ALK* have already been described [10].

Since 2004 our understanding of the molecular pathogenesis of lung cancer has made significant and rapid advances. Molecular testing already informs treatment in a proportion of lung cancer patients and will be applicable, if the pace of target identification and drug development is maintained, to most patients within our working lives. This will lead to personalised medicine and ultimately benefit our patients in what was deemed an untreatable disease not long ago.

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