# Immune Resistance in Lung Adenocarcinoma

Subjects: Immunology

Contributor: Georgios Stathopoulos

Lung adenocarcinoma (LUAD) is the major subtype of lung cancer and represents the deadliest human cancer, affecting current-, ex-, and even non-smokers. LUAD is driven by the accumulation of mutations in several different genes, which results in uncontrolled proliferation of the lung cells and the formation of tumors.

Keywords: non-small cell lung cancer ; lung adenocarcinoma ; immune resistance ; targeted therapies ; immunotherapy

## 1. Introduction

Lung cancer represents one of the most challenging health problems, claiming each year more lives than breast, prostate and pancreatic cancer combined[1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer incidence, and lung adenocarcinoma (LUAD), NSCLC's most prevalent subtype, is still increasing in current-, ex-, and even non-smokers[2]. Patients with localized and early stage disease receive standard surgery, but the vast majority of patients are usually diagnosed with advanced disease, receive conventional therapies such as combination chemotherapy and radiation, and face a high mortality rate.

In the classical sense, cancer is driven by genetic and epigenetic aberrations and the complicated cross-talk between many different pathways, involving mainly mutations activating proto-oncogenes and/or suppressing tumor suppressors and resulting in uncontrolled cell proliferation. Targeted therapies have been developed for some of these genetic aberrations, rendering the molecular characterization of a patient's tumor an imperative prerequisite for the successful design of the most efficient targeted treatment strategy. Among the most commonly found mutations in LUAD, caused spontaneously, by genetic predisposition, or by cigarette smoking and other noxious inhaled agents, are activating mutations in epidermal growth factor receptor (*EGFR*, 14%), Kirsten rat sarcoma virus (*KRAS*, 33%), mesenchymal epithelial transition factor proto-oncogene (*MET*, 7%), B-Raf proto-oncogene (*BRAF*, 10%), and Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (*PIK3CA*, 7%), mutations in tumor suppressor genes like tumor protein p53 (*TP53*, 46%) and serine/threonine kinase 11 (*STK11*, 17%), and translocations in anaplastic lymphoma kinase (*ALK*, 3–7%), ROS proto-oncogene 1(*ROS1*, 2%), or Ret proto-oncogene (*RET*, 1–2%)[3]. In the case of *EGFR* activating mutations, first-line treatment includes EGFR tyrosine kinase inhibitors (EGFR-TKI, like gefitinib, erlotinib, afatinib, and osimertinib), whereas *BRAF*-mutant tumors can be treated with dabrafenib and trametinib[4][5][6]. Encouraging results have also been demonstrated for patients harboring *ALK* (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib), *ROS1* (crizotinib, ceritinib, and lorlatinib) or *RET* translocations (cabozantinib)[5][6][7][8]. Crizotinib can be also effective against *MET*-mutant cancers[5]. The inhibitors of PIK3CA signaling pathway, temsirolimus and everolimus, are currently under clinical trials[6]. Unfortunately, these treatments benefit only a small subset of LUAD patients, not only because all other mutated genes are not yet effectively clinically targeted, but also due to the development of primary and secondary resistance [9]. *KRAS*, the most commonly mutated driver oncogene in LUAD, remains notoriously untargeted. What is more, its mutations are mutually exclusive with *EGFR* mutations, so patients with *KRAS* mutations are resistant to *EGFR* targeted treatment and are faced with no efficient treatment options and a poor prognosis[10][11]. Encouragingly, the $KRAS^{G12C}$ inhibitor sotorasib can potentially be the first approved targeted therapy for patients with $KRAS^{G12C}$-mutant NSCLC[12].

The emergence of deregulated host inflammatory pathways as an important hallmark of cancer development[13] has added great complexity to the above classical sense of cancer pathogenesis, but has also provided an alternative approach for novel therapeutic strategies. Chronic lung inflammation associated with tobacco smoking is strongly implicated in LUAD development, highlighting the dynamic communication of lung tumors with the surrounding tumor microenvironment (TME), consisting of the interface of the bronchoalveolar compartment with host immune cells, cytokines, chemokines, and other components[13]. Developing tumors can hijack and evade host immune surveillance mechanisms[13], and immunotherapies aim to stimulate the patient's immune system to elicit a competent anti-tumor immune response. Several such approaches have been developed, including vaccine therapy [14], chimeric antigen receptor (CAR) T cells[15], and immune checkpoint inhibitors (ICI) like antibodies against cytotoxic T-lymphocyte-

associated antigen 4 (CTLA-4)[16], programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1)[17][18][19], and are currently used in clinical practice for the treatment of several cancers, including lung cancer[20]. Despite these encouraging results, increased immune tolerance is often documented in many cancers[21], implying that there is more to learn about the cross-talk between the developing tumors and the immune cells within the TME. Interestingly, *KRAS* mutations are increasingly shown to affect tumor interactions with the surrounding TME[11][22][23][24][25].

## 2. Adaptive Immune Resistance

Tumors are rich sources of neoantigens, formed as a sequence of their somatic mutations, which are foreign to the immune system and therefore capable of eliciting a robust antitumor immune response[26]. This indicates that tumors can progressively foster their growth by adopting mechanisms permitting tumor neoantigens to go unnoticed by the host immune defenses. The term adaptive immune resistance describes the process in which tumor cells change their phenotype, in a dynamic and reactive fashion, in order to avoid a host immune attack orchestrated by tumor neoantigen-specific cytotoxic T cells[27]. The adaptive immune resistance is the product of the cross-talk between tumor and host immune cells within the TME. Normally, T cell activation requires the interaction of antigen-specific T cells with the cognate tumor antigen. After T cell activation, signaling through the T-cell receptor (TCR) induces a robust immune response, triggered by secretion of interferon, and the expression of regulatory receptors (such as PD-1 and CTLA-4), which will act as a negative feedback mechanism. For this to happen, interferon also induces the expression of PD-L1, and the molecular interaction between the receptor and the ligand limits the inflammatory response[19]. This adaptive process is used by the tumor, which expresses PD-L1 and thereby turns off PD-1-positive T cells[28]. Usually PD-L1 expression is restricted at the invasive margin of the tumor, an area with abundant T cells, suggesting that PD-L1 expression is a counteracting mechanism adopted by tumor cells as a consequence of the presence of tumor antigen-specific T cells[29][30]. Interestingly, PD-L1 expression is not only triggered in cancer cells but also on the surface of dendritic cells, macrophages, myeloid-derived cells, TME stromal cells, and even tumor infiltrating T cells[31][29][32][33]. Another alternative is that PD-L1 overexpression is the result of gene amplification events of chromosome 9[34]. Disruption of this negative feedback using anti-PD-1, anti-PD-L1, or anti-CTLA4 antibodies reactivates T-cell cytotoxic properties which effectively lead to tumor antigen-specific immune responses and tumor killing[16][17][18][19].

The production of proinflammatory cytokines within the TME may also result in tumor adaptive changes and immune evasion. It has been shown that tumor necrosis factor-a (TNF-α) production by infiltrating T cells promoted a dedifferentiating process in melanoma cancer cells, thereby leading to tumor antigen loss and an adaptive immune escape mechanism[35]. This process resembles the epithelial-to-mesenchymal transition (EMT), and in fact many aspects of EMT are related to inflammatory cytokines like IL6, TNFα and tumor growth factor-β TGFβ[35][36][37]. In this way, an adaptive immune resistance mechanism can even be a tumor promoting mechanism.

## 3. Acquired Immune Resistance

Blocking the PD-1 and CTL-4 axes with specific antibodies (like the anti-PD-1 molecules nivolumab, pembrolizumab and the emerging cemiplimab, the anti-PD-L1 antibodies atezolizumab and durvalumab, and the anti-CTL-4 antibody ipilimumab) exhibits durable beneficial effects for patients with NSCLC, with or without *KRAS* mutations [38][39][40][41][42][43].

Unfortunately, not all patients with LUAD can benefit from blockade of immune checkpoints, and many of the initial responders will eventually develop resistance to the therapy[44], while the mechanisms behind this phenomenon are currently under intense scrutiny.

For patients who are refractory to immune checkpoint blockade, one possible explanation is that their tumors contain low mutational load and they lack immunogenic tumor antigens, such as nonsmoker LUAD[45][46]. In conjunction with low mutation burden, the activation of MAPK in *EGFR*-mutant LUAD contributed in the establishment of highly immunosuppressive conditions due to increased recruitment of Tregs and TAMs[47].

For patients with acquired resistance to immunotherapies, possible explanations are the upregulation of alternative immune checkpoints, mainly T-cell immunoglobulin mucin-3 (TIM-3)[48], loss of HLA haplotypes due to rearrangement of chromosome 6[49][50][51] and somatic mutations in interferon receptor-associated Janus kinase 1 (*JAK1*) or Janus kinase 2 (*JAK2*) and antigen-presenting protein beta-2-microglobulin [*B2M*, leading to loss of surface expression of major histocompatibility complex class I (MHC I)] [52][53]. Loss of tumor neoantigens through elimination of tumor subclones or chromosomal deletions has also been described as a mechanism of immune edited acquired resistance in lung cancer, in which tumors responded to the selective pressure of immune checkpoint blockade by eliminating mutations affecting MHC and TCR binding[54]. Similarly, immunoediting induced by immune checkpoint blockade transformed NSCLC to SCLC (small cell lung cancer) by selectively eliminating the treatment-sensitive tumor cells[55][56].

## 4. Drug Resistance

Cancer cells can become excessively dependent on specific driver mutations, a characteristic defined as “oncogene addiction”[57]. As a result, many targeted therapies have been developed aiming to inhibit these oncogenic driver mutations and genotype-directed therapy in advanced NSCLC has led to significant improvements in overall survival [58]. For patients with *EGFR* somatic mutations, administration of small molecule TKIs of EGFR (gefitinib, erlotinib, afatinib, and osimertinib) is the standard course of treatment, resulting in high response rates and prolonged progression-free survival[4]. Encouraging results have also been demonstrated for patients harboring *ALK* rearrangements, after receiving treatment with ALK-TKIs (crizotinib, ceritinib, and alectinib)[7]. The effectiveness of TKI therapy is however limited by the ability of cancer cells to evolve under the pressure of the therapy and to ultimately acquire resistance[9].

A total of 4–10% of newly diagnosed NSCLC patients will not respond to TKI therapy, exhibiting what is called primary (intrinsic) resistance[9]. One mechanism underlying intrinsic resistance could be the existence of activating yet non-sensitizing driver mutations, as has been described for the *EGFR*-T790M mutation with reported frequencies varying from <10% to 65%[59][60]. The combination of *EGFR* mutations with other genetic alterations has also been shown to contribute to intrinsic resistance to TKIs, like *MET* amplification and *BCL2L11* mutation [60][61]. Another potential modulator conferring intrinsic resistance to EGFR-TKIs is NF-κB. It has been reported that knocking down NF-κB in *EGFR*-mutant lung cancer cells enhanced erlotinib sensitivity, while patient response to erlotinib was associated with high expression of the NF-κB inhibitor IκBα[62], raising hope that a combinatorial treatment targeting both EGFR and NF-κB can have beneficial responses in the clinic.

Unfortunately, even patients who initially respond positively to TKIs administration, usually develop secondary or acquired resistance to the treatment followed by disease progression. Most commonly, this is attributed to secondary somatic mutations of the target gene which hinder the binding of the drug and confer in this way resistance to treatment. In *EGFR*-mutant NSCLC, the dominant cause of TKI acquired resistance is the *EGFR*-T790M mutation, accounting for more than half of the incidences of reported resistance[61][63]. The most common secondary mutations found in *ALK*-mutant NSCLC are the *ALK*-L1196M and *ALK*-G1269A mutations, causing resistance by interfering with TKI binding[64][65]. Another mechanism responsible for acquired resistance to TKI therapy is gene target amplification. This has been documented with both mutant *EGFR* and *ALK*, and gene amplification can occur alone or in combination with the secondary somatic resistance mutations[63][65]. LUAD can also adapt to the pressure of TKIs by activating bypass signaling pathways, which allow cancer cells to continue to grow despite the targeting of the driver gene mutations, like PI3K/AKT or RAF/MEK/ERK pathways[3][66], or by triggered mutations activating downstream effector molecules of the targeted cascade, like MAPK activation in both *EGFR*- and *ALK*-mutant NSCLC[67][68]. NSCLC has also been shown to phenotypically transform to SCLC in order to resist TKIs treatment, resulting in the formation of an *EGFR*- or *ALK*-mutant SCLC, which is insensitive to TKIs therapy [63][69]. Finally, the notion of “drug tolerant cells” has been also suggested to explain both intrinsic and acquired resistance, which dictates that small populations of cancer cells can tolerate the drug exposure, possibly due to epigenetic changes, persist under a quiescent state and propagate until a more permanent resistance mechanism is acquired [70].

Conceptually, all resistance mechanisms can be viewed as the dynamic manifestations of cancer evolution in order to overcome the selective pressure of targeted therapies.

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