Cancer Research and Medicine
DOI: https://doi.org/10.63626/f0w24507
ISSN Online: 3104-4131
ISSN Print: XXXX-XXXX

Review Article

PDL1 and KRAS: Immune system evasion and genetic aberrations in cancers

Iqra Shaukat, Talha Saleem
Department of Medical Laboratory Technology, Superior University, Lahore

ABSTRACT

Cancer is a leading global health challenge, representing a significant burden on healthcare systems because of its high fatality ratio. According to WHO, cancer is the second most frequent cause of mortality all around the world, accounting for millions of fatalities each year. The rising incidence of cancer cases necessitates ongoing research and the development of novel treatment strategies for optimizing patient health outcomes. Among the promising advancements in cancer therapy is immunotherapy, which aims to enhance the capability of the immune system to recognize and annihilate malignant cells. Immune checkpoint inhibitors, including interventions aimed at PD-1/PD-L1 pathway, have gained attention for their potential to reactivate T cells and bolster anti-tumor responses. This review counters around mechanisms regulating PD-L1 expression and the role of KRAS mutations in tumor progression and immune evasion. The role of PD-L1 in binding to PD-1 receptors on T cells is pivotal in masking immune response thereby allowing tumor cells to bypass immune surveillance and destruction. The review discusses various factors influencing PD-L1 expression, including transcriptional regulation by key signaling pathways and the impact of inflammatory cytokines within the tumor microenvironment (TME). Additionally, it highlights how genetic alterations, particularly KRAS mutations, can drive PD-L1 overexpression and contribute to tumor aggressiveness. In conclusion, understanding the sophisticated interplay between PD-L1 expression and KRAS mutations is essential for developing targeted immunotherapies and enhancing precision medicine approaches in oncology. By elucidating these mechanisms, researchers can identify new therapeutic targets and improve treatment strategies, ultimately aiming to enhance patient survival rates and health-related life quality in cancer care. This review underscores the importance of ongoing research in this area to address the challenges posed by cancer's heterogeneity and resistance to existing therapies.

Corresponding Author: Talha Saleem
Email: talha.saleem@superior.edu.pk

INTRODUCTION

Cancer is the most prevalent serious health problem; morbidity and mortality ranked cancer as the second leading contributor to deaths globally. In 2013, more than 8 million deaths occurred from this disease globally which ranked cancer as the third leading cause of death in 1990 to the second (1, 2). An increase in approximately 6 million new cases has been reported by the International Agency for Research on Cancer (IARC) from 2012 to 2022. Lung cancer has been recognized as the most frequently diagnosed cancer in 2022 with 273,904 new cases compared to 2020. The global rate of new cancer cases is anticipated to reach 35.3 million cases, including 2.5 million cases of lung cancer by the year 2050 (3, 4). High Incidence and mortality rate impose a significant impact on healthcare systems and demand further investigation to improve survival and treatment efficacy.

There are high chances of survival by immunotherapy with antibodies in lung cancer through inhibition of the reciprocation among PD-L1 and its binding protein, PD-1. (5, 6). The two dominant histological forms of lung cancer are SCLC and NSCLC. Depending on classification and severity of lung cancer surgery, radiation therapy, chemotherapy, and targeted therapy form the backbone of treatment therapies. Though there is better diagnosis and treatment therapy these days yet lifelong prospects and well-being for the patients of lung cancer are still suboptimal (7, 8). New advances in cancer immunotherapy have emerged as one of the leading fields of investigation in oncology because this improves the specificity of the immune mechanisms against cancer, including lung cancer. Immune checkpoints, including PD-1 and CTLA-4,

have been demonstrated in experimental studies that these proteins function as "brakes" on immune activity. This indicates that blocking these immune checkpoints could potentially reactivate T cells, thereby improving their capability to recognize, target and destroy cancer cells more effectively (9). Disruption/blockage of the PD-1/PD-L1 cascade has proved to improve clinical efficacy, especially linked to t-cell penetration, in various cancers. Interaction of PDL-1 and KRAS and their co-expression was observed in different studies with good outcomes where RAS/MEK/ERK signaling pathway regulated by this combination also recorded (10). So, the positive correlation of these molecules could be a better approach in the immunotherapeutic treatment of lung cancer.

Overview of PD-1/PDL-1 pathway

PDL-1, encoded by CD274 gene, present on tumor cells serves as a binding molecule for receptor (PD-1) located on T cells. The interaction of PD-1 with specific receptors is responsible for the T-cells activation, proliferation, and secretion of cytotoxic chemicals ultimately leading to degeneration of anti-cancer immune defense. Thus, apoptosis of activated T-cells resulting in a diminished capacity to identify tumor cells facilitating the proliferation of cancer metastases as shown in Figure 1 (5).

PD-1

PD-1, or alternatively termed as CD279, was first identified in 1992 through research conducted at Kyoto University. They discovered PD-1 while investigating genes associated with apoptosis using a subtractive hybridization technique. The protein was isolated from two specific murine cell lines: 2B4.11 and LyD9 (12). This immune checkpoint protein, entangled in regulating immune responses, weighing 55-kD, comprising 288 amino acids, featuring N-terminal and membrane-permeating domains, and a cytoplasmic tail containing tyrosine residues (13).

PD-L1

PD-1 ligand, identified as CD279 or B7-H1, is categorized as a member of the B7 family of proteins. It is a 33-kDa glycoprotein of type 1 transmembrane category, composed of 290 amino acids (14). It is predominantly expressed on several types of lymphocytes including macrophages, activated T cells, B cells in the context of inflammatory conditions, and also presents on tumor cells as an immunotherapeutic strategy that evades anti-tumor immune responses (15). PD-L1 actually appears as pro-tumorigenic characteristics within cancer cells by binding to its receptor, thus activating pathways that govern survival mechanisms and cellular growth (16). It was found from an experimental study that the PD-1 molecules were positive on the surface of Lewis lung cancer cells, T cells in spleens of C57BL/6 mice and circulating T lymphocytes in peripheral blood. In the comparison study, it was reported that a 10-μg dose of sPD-L1 administered caused significant tumor volume growth in the mice bearing Lewis lung cancer cell-derived tumors. Conversely, there was no significant alteration in tumor volume with lower doses of 2.5 μg and 5 μg. Therefore, a particular dosage of sPD-L1 seems to augment development of xenograft tumors arising from Lewis lung cancer cells in C57BL/6 mice (17).

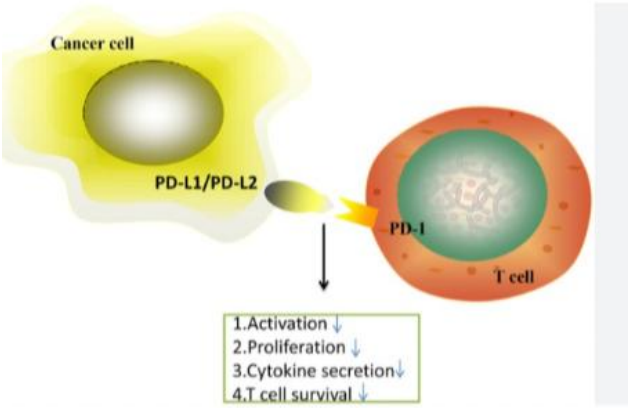

Figure 1.: Interaction of PD-1/PD-L1 of cancer cell with T cell resulting in activation and survival of T-cell (11)

Mechanisms Regulating PD-L1 Expression

Transcriptional Regulation of PD-L1 in Tumours

PD-L1 is among the significant immune checkpoint proteins involved in tumor immune evasion. Tumor expression of PD-L1 can be controlled at multiple levels, though mainly at the transcriptional level (Figure 2).

Activator Protein 1

AP-1, a transcriptional factor belonging to Jun and Fos protein families, is triggered and activated by different types of stress signals. AP-1 also upregulates PD-L1 for inflammatory stimuli or on signal oncogenic (18).

NF-κB

This transcription factor is induced by inflammatory cytokines and may induce PD-L1 in most cancers. NF-κB signaling is often activated by tumor-associated inflammation, and presence of PD-L1on cells can be a critical factor of immune evasion (19).

STAT3

This is another transcription factor typically implicated in the induction of PD-L1. It is triggered by cytokine activity such as IL-10 and IL-6, which are generally overexpressed in tumor cells. Activated STAT3 results in increased expression of PD-L1 and is generally associated with immune tolerance through its role in downregulating T-cell activation.

Interferon Signalling

Interferon Gamma (IFN-γ)

IFN-γ is powerful stimulator of PD-L1 expression, acting through JAK-STAT pathway, particularly the STAT1 component, to induce PD-L1 transcription. This is part of an immune response in the TME, where IFN-γ is secreted by immune cells, including T-cells and NK cells (19).

Type I Interferons (IFN-α/β)

These interferons also contribute to PD-L1 expression in tumors, especially in the context of viral infections or other forms of immune cell activation (19).

Epigenetic Regulation

DNA Methylation

Excessive methylation of the PD-L1 gene promoter region in some cancers also downregulates its expression. However, demethylation of PD-L1 gene's promotor area has been found to cause overexpression of PD-L1 in many cases, and it has been observed that PD-L1 is often induced by inflammatory signals (20).

Histone Modification

Histone alterations occurring after translation including acetylation and methylation also regulate PD-L1 expression. Inflammation and oncogenic mutations may also modify these events and cause changes in the accessibility of chromatin as well as in transcriptional upregulation of PD-L1 (20).

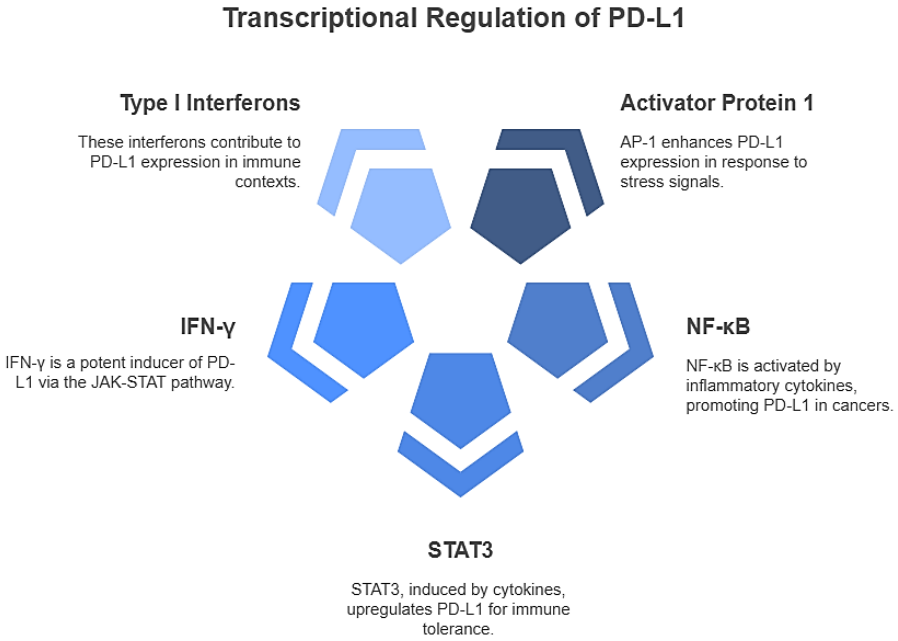

Figure 2: Mechanisms Regulating PD-L1 Expression (21)

The Role of Inflammatory Cytokines and Tumor Microenvironmental Factors

TME has been recognized as a crucial regulator of PD-L1 expression. Key mediators of inflammatory cytokines in this process are identified as IFN-γ, produced by immune cells within the TME, as an effective inducer of PD-L1; this overexpression of PD-L1 in tumor cells creates a feedback loop in which PD-L1 engagement with PD-1 on immune cells inhibits T-cell activation, thus aiding in immune evasion. In addition, IL-6 and IL-10, which are normally elevated in the TME because of inflammation, further support PD-L1 expression modulated by STAT3 signaling. IL-6 participates in the "JAK-STAT" signaling axis that upregulates expression of PD-L1, facilitating tumor cells in evading immune detection and response. TGF-β also acts as a PD-L1 key regulator within the TME, as it induces PD-L1 expression for immune suppression and allows tumors to evade immune detection. Besides this, hypoxia in tumors can activate HIFs, especially HIF-1α, which has been demonstrated to cause induction of PD-L1 due to low oxygen levels that further contribute to immune evasion during tumor progression. Collectively, these inflammatory factors create an immunosuppressive environment that fosters tumor growth and resistance to immune-mediated destruction (19, 22, 23).

Tumor-Intrinsic Factors Influencing PD-L1 Expression

Genetic Alterations and Mutations Driving PD-L1 Overexpression

Genetic abnormalities, such as mutations and CNVs, can drive PD-L1 overexpression in tumors. In some cancers, PD-L1 itself undergoes amplification. This is particularly seen in cancers such as NSCLC and HNSCC, where increased copy numbers of the PD-L1 gene directly translate into higher expression levels of PD-L1 on the surface of the tumor cell (24).

Oncogenic Mutations and Pathways:

KRAS Mutations

As noted in the previous sections, KRAS mutations in certain cancers are linked to increased PD-L1 expression in some malignancies. Mutant KRAS activates several key pathways such as MAPK and PI3K/AKT, potentially contributing to PD-L1 upregulation either directly or indirectly via intermediary transcription factors involving STAT3 and NF-κB (25).

EGFR Mutations

EGFR mutations, which are common in NSCLC, have also been associated with PD-L1 overexpression. EGFR signaling activates PI3K/AKT and STAT3 pathways, which promote PD-L1 transcription (25).

PIK3CA Mutations

Another mechanism through which immune escape is created in cancer is through PIK3CA mutations, an essential gene in the PI3K/AKT pathway, leading to the upregulation of PD-L1 expression. This is particularly evident in breast cancer and endometrial cancer (26).

Chromosomal Aberrations

The PD-L1 overexpression may also result from chromosomal instability that causes the disruption in the regulatory regions of the PD-L1 gene. For example, LOH or translocations at particular loci could induce upregulation of PD-L1 (26).

Relationship Between PD-L1 Expression and Tumor Development

Over-expression of PD-L1 has been correlated with aggressive behaviour of the tumor and worse prognosis in a variety of cancers. PD-L1 mediates tumor immune evasion through the inhibition of cytotoxic T-cells and NK cells function, allowing the tumor to grow unchecked, which contributes to metastasis and resistance to therapy. High PD-L1 expression typically suggests that TME is enhanced by increased inflammation and angiogenesis, since tumors having high PD-L1 are usually found in a pro-inflammatory environment that favors increased survival, angiogenesis, and evasion of the immune system. However, in some contexts, PD-L1 expression can be utilized as a predictive marker for the effectiveness of immune checkpoint inhibitors, thus highlighting its dual role in cancer biology as both a marker of poor prognosis and a potential target for therapeutic intervention (27-30).

Therapeutic implications of PD-L1 in cancer treatment

Role of PDL-1 in lung cancer treatment

NSCLC patients commonly diagnosed at advanced and unresectable stage leading to consistently poor outcomes and limited treatment options with low survival rate (31, 32). The clinical effectiveness of PD-1/PD-L1 blockade/inhibitors has been evaluated across various cancers, such as colorectal, gastric, bladder, ovarian and pancreatic cancers. In the case of NSCLC response rate ranging from 6% to 17% with an improved survival rate was observed in patients (33). A study on lung cancer examined the effects of combining two therapeutic approaches anti-C5a treatment using l-aptamer AON-D21 and the anti-PD-1 therapy employing monoclonal antibody RMP1-14. This dual targeting strategy showed that combinational treatment resulted in more potent tumor inhibition than the treatments given alone. It showed that in the subcutaneous 393P model, there was a synergistic effect, which resulted in the tumor growing less compared to the treatment with a single

agent (34). Another research has established the fact that modulation in PD-L1expression correlates with the following aspects: male sex, smoking history, advanced-staged cancer, vascular invasion, squamous cell malignancy, and presence of EGFR mutation and is in wild type. Survival analysis, whether it be univariate or multivariate, demonstrates that a worse prognosis occurs among patients with PD-L1 positive as opposed to negative tumors (35).

PDL-1 in lung cancer Prognosis

PD-L1 is an effective biomarker to predict the prognosis and therapeutic effectiveness, facilitating to opt a best treatment strategy as well as enhancing the effectiveness of precision medicine (36). For example, over-expression of PD-L1 in various cancers, including hepatocellular carcinoma, is linked to unfavorable clinical outcomes. Although PDL-1 value depends on various factors but an Increased expression of PD-L1 linked to poorer outcomes ($p = 0.0367$) (37).

Drugs or PD-1/PDL-1 inhibitors in lung cancer treatment

Different targeted drugs including Nivolumab (marketed as Opdivo), Pembrolizumab (marketed as Keytruda), and Cemiplimab (marketed as Libtayo) are engineered to target PD-1. PD-1 typically functions in maintaining immune by inhibiting overactive T cells from attacking healthy cells in the body. By inhibiting PD-1, these medications enhance the capability of immune system to detect and target cancerous cells, potentially leading to tumor shrinkage as shown in **Figure 3**. Atezolizumab (Tecentriq) and Durvalumab (Imfinzi) are immunotherapeutic agents that specifically target PD-L1, a protein associated with PD-1, present on certain tumor and immune cells. By targeting this protein, these therapies enhance ability of immune system to battle cancer. The administration of PD-1/PD-L1 inhibitors can vary based on lab test results and the stage of lung cancer. These treatments may be combined with chemotherapy or used alone, and they can also be paired with CTLA-4 inhibitors. Additionally, they may be administered either before or after surgical intervention for early-stage lung cancer, or continued for an extended duration in cases of advanced-stage lung cancer (38, 39). A meta-analysis carried out recently encompassing seven randomized controlled trials has showed that anti–PD-1/PD-L1 therapies significantly performed better compared to other treatments. The findings indicated a marked improvement in these clinical outcomes when using anti–PD-1/PD-L1 therapies compared to traditional chemotherapeutic approach (40).

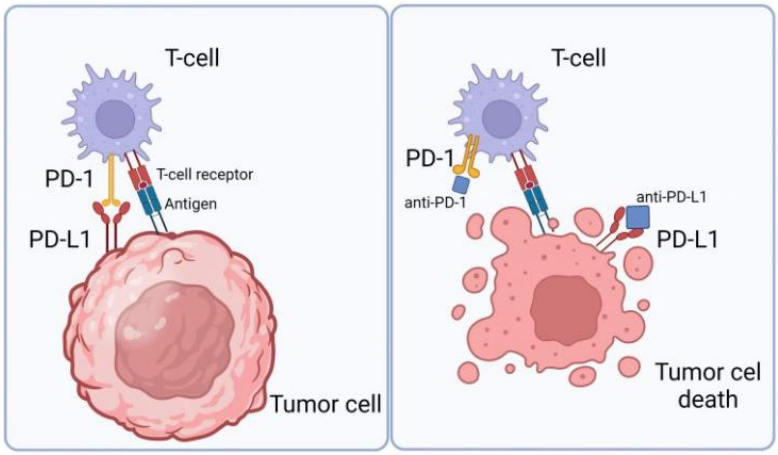

Figure 3: PD-1/PDL-1 interaction with T-cell with and without inhibitors (https://blogs.cuit.columbia.edu/postdocsociety/2023/08/)

Genetic and Molecular Features of KRAS Mutations

KRAS is a small GTPase involved in intracellular signaling pathways for cellular proliferation, survival, and differentiation. As a member of the RAS family, KRAS resides at 12p12.1 and serves as a molecular regulator, it modulates by switching between its active GTP-bound and inactive GDP-bound conformities. Mutations of KRAS take place predominantly at codons 12, 13, and 61, while codon 12 mutations make up almost 90% of the total number of KRAS mutations, the most prevalent variants being G12C, G12D, and G12V (41). These cause constitutive activation of the KRAS protein, activating oncogenic signaling through such pathways as MAPK/ERK and PI3K/AKT, among others, to promote proliferation, survival, angiogenesis, and invasion (42). Codon 13 mutations, such as G13D, also activate KRAS and are relatively less common. While less common, the codon 61 mutation is coupled with MAPK pathway activation and tumorigenesis.

KRAS mutations are ubiquitous among many solid tumors, making this an important aspect of cancer biology and its treatment outcome (42). In NSCLC, it is estimated that up to 25-30% of cases carry KRAS mutation, and G12C is the most prevalent among them; these often show association with smoking and predict for poor prognosis and drug resistance to EGFR inhibitors. In CRC, there is about 35-45% KRAS mutation predominantly at codon 12, which results in poor outcomes and a failure to the anti-EGFR therapies (41). Pancreatic cancer indicates the highest prevalence of the KRAS mutations with its over 90% prevalence being found in pancreatic ductal adenocarcinoma (PDAC); and these are early events that correlate with aggressive disease and also poor survival rates. 10-20 % of serous carcinomas of ovarian cancers carry KRAS mutations. These mutations are known to contribute to chemotherapy resistance. In the case of endometrial cancer, 20-30% of the patients have their KRAS mutations, a high frequency seen in serous types, which gives the tumor aggressive behaviors. In other cancers such as bladder, esophageal, biliary tract, and melanoma, KRAS mutations have lower frequencies but still are clinically relevant. Knowledge about the prevalence and impact of KRAS mutations across the different types of cancers can help in developing targeted therapies and improving patient management strategies (43, 44).

Mechanisms of KRAS-Mediated Tumorigenesis

Activation of MAPK/ERK pathway: KRAS mutations activate the MAPK/ERK signaling cascade, resulting in the phosphorylation and activation of transcriptional regulators like AP-1, c-Fos and c-Jun, which contribute to the upregulation of genes crucial for cellular proliferation and survival. This pathway is essential for proper regulation of cellular proliferation, notably during the critical G1 to S phase transition.

Activation of PI3K/AKT pathway

Another critical signaling cascade activated by mutant KRAS is the PI3K/AKT pathway, which supports cell survival by suppressing pro-apoptotic proteins (Bad & BAX) and activating pro-survival proteins, such as Bcl-2. The AKT pathway also controls metabolism and supports cell growth (45, 46).

Evasion of apoptosis

Mutant KRAS triggers resistance to cell death signals. For instance, cancers with the KRAS mutation cause anti-apoptotic proteins, such as Bcl-2, to upregulate so that under the conditions that would have otherwise made these cells to die (47).

TME remodelling

Mutant KRAS influences the TME, which promotes immune evasion and tumor-associated inflammation. The mutations in KRAS lead to the recruitment of immunosuppressive cellular population (MDSCs, Tregs and TAMs) thereby suppressing anti-tumor immune responses (47).

Angiogenesis

KRAS mutation also contributes to angiogenesis, as tumors stimulate the growth of new vessels to supply nutrients and oxygen towards growing tumor masses. They do this by upregulating factors that include vascular endothelial growth factor (VEGF) (**Figure 4**) (48).

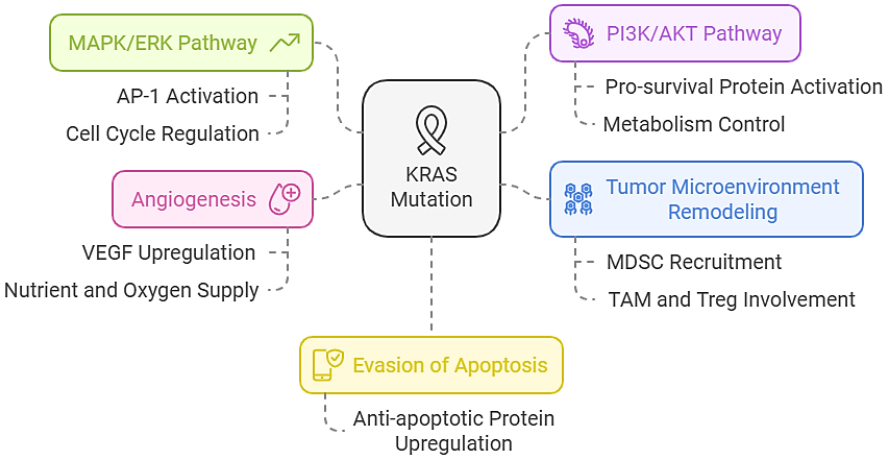

Figure 4: Mechanisms of KRAS-Mediated Tumerogenesis (49)

Interplay Between KRAS Mutations and PD-L1 Expression

The interplay between KRAS mutations and PD-L1 has recently attracted considerable attention through its implications in tumor immune evasion, immune checkpoint resistance, and cancer progression. KRAS mutations not only drive the oncogenic transformation of tumor cells but are also crucial for the modeling of the TME (50). The interplay between KRAS mutations and PD-L1 expression serves as major pathway of immune evasion in many KRAS-driven cancers, including NSCLC, pancreatic cancer, colorectal cancer, and others. KRAS mutations activate several critical signaling pathways, including PI3K-AKT and NF-κB, that lead to increased PD-L1 expression, creating an immunosuppressive TME that limits the effectiveness of immune-based therapies. Here's a detailed exploration of this interplay.

Impact of KRAS Mutations on TME

Alteration of Immune Cell Recruitment

KRAS mutations are involved in sculpting the TME made up of malignant, stromal and immune cells along with extracellular matrix elements. Oncogenesis by KRAS typically leads to TME that supports suppression of the immune environment while favouring tumor growth and progression. The mutation, in turn, influences many different types of immune recruitment and activation in TME such as MDSCs, TAMs, and Tregs. These cells function in immune tolerance and anti-killer cell immunity-related killing of tumor cells (51, 52).

Immune Suppression and PD-L1 Expression

KRAS mutations within tumor cells indirectly alter the expression of PD-L1 through altered infiltrative patterns of immune cells and cytokines production in the TME. For instance, both TAMs and MDSCs, which are often attracted to KRAS-driven tumors, can secrete IFN-γ, among other pro-inflammatory cytokines that activate PD-L1. The PD-1/PD-L1 pathway then inhibits the function of TILs, especially CTLs, thereby promoting immune escape. KRAS mutations also modulate release of pro-inflammatory cytokines, which may contribute to stimulation of the immune checkpoint pathways, such as PD-L1 (53, 54).

Fibroblast Activation and Tumor Stiffness

KRAS mutations affect the activation of fibroblasts and the remodeling of the extracellular matrix, which can both contribute to tumor stiffness and immune suppression.CAFs can also produce TGF-β, which further supports immune suppression and the expression of PD-L1 on tumor cells. KRAS mutations can also induce a pro-fibrotic TME, promoting immune cell exclusion, such as CTLs, and contributing to the overall immune evasion phenotype (55, 56).

Regulation of PD-L1 by KRAS-Driven Pathways

Several signaling pathways initiated by KRAS mutations are known to directly or indirectly regulate PD-L1 expression on tumor cells. These include key molecular players such as PI3K-AKT, MAPK/ERK, and NF-κB which drive immune evasion and tumor survival as shown in Figure 5.

MAPK/ERK Pathway

KRAS mutations most commonly activate the MAPK/ERK pathway, particularly in malignancies such as NSCLC and pancreatic cancer. This pathway is vital to promote proliferation and survival; however, it also seems to mediate immune escape. MAPK/ERK activation leads to upregulation of PD-L1 through transcription. For instance, AP-1, a transcription factor that is activated downstream of ERK signaling, has been shown to drive the expression of several immune checkpoint molecules, such as PD-L1. The upregulation of MAPK signaling can create an immune-surveillance-evading capability for tumor cells through T cell inhibition and exhaustion of cytotoxic T lymphocytes (57).

PI3K-AKT Pathway

Another key downstream signaling cascade triggered by mutations of KRAS is the PI3K-AKT pathway. AKT (Protein Kinase B) regulates various processes related to survival, metabolism, and immune evasion directly. Upon its activation, it promotes up-regulation of NF-κB, a transcription factor known for enhancing PD-L1. NF-κB, through its transcriptional activity, mediates an immunosuppressive TME by stimulating the expression of PD-L1 on malignant and immune cells. AKT also phosphorylates and thus activates mTOR, an established activator of signaling that leads to increased levels of PD-L1 in numerous cancers (45, 58).

NF-κB Pathway

NF-κB is an established mediator of inflammation and immune evasion in TME. KRAS mutation activation leads to NF-κB activation that facilitates a tolerance mechanism by transcriptionally upregulating many immune checkpoint molecules, of which PD-L1 is the most significant. These cytokines (IL-1 and TNF-α) may activate the NF-κB pathway in both tumor and immune cells, which in aggregate supports a chronic inflammatory status that fuels tumor growth while suppressing immunity (57).

JAK-STAT Pathway

Another important regulator for the expression of PD-L1 is the JAK-STAT signaling pathway. Mutations in KRAS trigger the activation of STAT3 within certain

cancers, such as pancreatic cancer, which induce upregulation of PD-L1 on tumor and diffusing immune cells. Upon activation, STAT3 upregulates the secretion of proinflammatory cytokines, particularly IL-6, thus inducing PD-L1 upon tumor cells through both JAK-STAT signaling pathway and MAPK pathway (19).

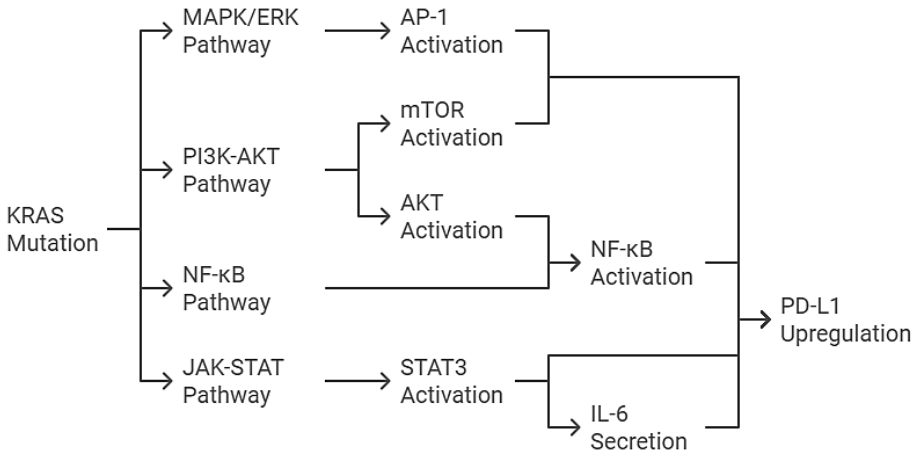

Figure 5: KRAS driven PDL-1 upregulation (59)

Preclinical and Clinical Evidence of KRAS Mutation and PD-L1 Expression Correlation

Preclinical Studies

Preclinical studies have greatly advanced our understanding of the relationship between KRAS mutations and PD-L1 expression, showing how KRAS-driven signaling pathways contribute to immune evasion and resistance to immune checkpoint inhibitors. These agents also decrease the PD-L1expression in models of NSCLC. Thus, KRAS mutations seem to induce PD-L1 among tumor cells, and it appears that targeting KRAS could indeed help to evade immune inhibition. Moreover, combination therapy with KRAS inhibitors along with PD-1 inhibitors has proven efficacious in preclinical studies, confirming the relationship between KRAS mutations and the regulation of PD-L1. In pancreatic cancer, studies using preclinical models have demonstrated that KRAS-mutant tumors exhibit increased PD-L1 expression due to the activation of the MAPK/ERK and PI3K-AKT pathways. The combination of PI3K inhibitors or immune checkpoint inhibitors with KRAS-targeting agents has been shown to enhance immunity. Likewise, in CRC models, increased expression of PD-L1 in tumors harboring KRAS mutation promotes immune escape, but a study suggests that therapy that targets KRAS coupled with anti-PD-1/PD-L1 inhibitor improves the competency of immunotherapy (50, 60-62).

Clinical Studies and Observations

Clinical studies further support the alliance between KRAS mutations and elevated PD-L1 expression across various cancers, indicating a potential link to immune evasion via the PD-1/PD-L1 pathway. NSCLC patients with KRAS mutations frequently exhibit elevated PD-L1 levels and reduced responsiveness to anti-PD-L1 treatment therapies; however, therapies targeting KRAS-G12C mutations have demonstrated substantial potential in reducing PD-L1 expression and improving outcomes with immune checkpoint blockade. In pancreatic cancer, elevated PD-L1 levels correlate with poor immunotherapy responses in patients with KRAS-driven tumors, while combination therapies targeting both KRAS and PD-1/PD-L1 have led to significant tumor regression in animal models. In CRC, higher PD-L1 expressions are observed in KRAS-mutant cases, particularly in microsatellite stable tumors, which typically exhibit resistance to immune checkpoint inhibitors; ongoing research is exploring combinations of KRAS-targeted therapies with these inhibitors to improve treatment outcomes. Additionally, in melanoma, KRAS mutations correspond with increased PD-L1 level and resistance to immunotherapy, prompting investigations into the proficiency of coupling KRAS inhibitors with PD-1 inhibitors in this patient population (61, 63-66).

Immune Evasion Mechanisms in KRAS-Mutant Cancers

KRAS mutations are critical oncogenic drivers of cancer development and significantly alter the TME, which promotes evasion of the immune system. These cancers harbor an altered immune landscape which impairs the immune system's capability to monitor such cancers and treat them. The TME becomes immunosuppressive in these cancers, promoting the evasion by the immune system and, consequently, destruction of such tumors (51). Here's

a detailed exploration of the immune evasion mechanisms in KRAS-mutant cancers.

Immunosuppressive TME in KRAS-Mutant Cancers

KRAS mutations have a substantial effect on the composition and functionality of the TME to establish an immunosuppressive environment that promotes immune evasion. Oncogenic KRAS stimulates important signaling pathways such as PI3K-AKT, MAPK, and JAK-STAT to activate pro-inflammatory signals paradoxically, which promote immune tolerance. This altered immune landscape is characterized by an increase in immune cell types that support tumor progression, such as MDSCs, Tregs and TAMs. MDSCs are expanded in KRAS-mutant tumors, releasing cytokines with immunosuppressive effects (TGF-β & IL-10) that block T cell activation. Tregs also proliferate in response to KRAS mutations, further mitigating anti-tumor immune responses through similar cytokine secretion (52, 67, 68). KRAS mutations also activate CAFs that secrete TGF-β and contribute to extracellular matrix remodeling, leading to tumor stiffness that hinders immune cell infiltration—a phenomenon known as immune exclusion. In addition, the mutations of KRAS alter the expression of cytokines and chemokines within the TME, causing upsurge in concentrations of pro-inflammatory mediators (IL-6 and TNF-α), recruiting immunosuppressive cells while also activating pathways that induce the expression of molecules associated with immune checkpoints such as PD-L1, thereby facilitating immune resistance (55). Strong clinical correlations exist between KRAS mutations and increased PD-L1 levels in most cancers, implicating these mutations in the immune evasion pathway through the PD-1/PD-L1 axis. KRAS mutations in NSCLC have been correlated with high levels of PD-L1, and responses to anti-PD-1 or anti-PD-L1 therapy are very poor. However, targeted KRAS G12C inhibitors have demonstrated the ability to decrease PD-L1 expression and enhanced responses to immune checkpoint inhibitors (61). In pancreatic cancer, patients with KRAS-driven tumors have higher levels of PD-L1, correlated with poor immunotherapy response; combination therapies targeting KRAS and PD-1/PD-L1 have demonstrated excellent tumor regression in preclinical models (69). In CRC, KRAS mutations are linked to increased PD-L1 expression, specifically in microsatellite stable tumors that are usually resistant to immune checkpoint inhibitors; ongoing research is focused on combining KRAS-targeted therapies with these inhibitors to improve the efficacy of treatment (70, 71). Moreover, in melanoma, KRAS mutations are associated with elevated PD-L1 expression and resistance to immunotherapy, hence clinical trials are conducted in evaluating the efficacy of combinational therapy between KRAS inhibitors and PD-1 inhibitors for enhanced outcomes in patients with KRAS-mutant melanoma (72).

Increased PD-L1 Expression and Resistance to Immunotherapy

Mechanisms of Resistance to PD-1/PD-L1 Inhibitors in KRAS-Mutant Tumors

PD-L1 Expression in KRAS-Mutant Tumors: KRAS mutations are often related to upregulation of PD-L1 in tumor cells. Increased PD-L1 in tumor cells assists in evasion of tumor from immune system by blocking activation of CTLs and other immune cells. Binding of PD-L1 with the PD-1 receptor on T cells leads to T cell exhaustion and further blocks their antitumor activity (50).

KRAS and PD-L1 Upregulation

KRAS mutations activate multiple signaling pathways, including the MAPK/ERK and PI3K-AKT pathways, which directly induce PD-L1 expression in tumor cells. These pathways induce activation of PD-L1 through transcriptional regulators such as NF-κB, AP-1 and STAT3. Therefore, KRAS-driven tumors express higher levels of PD-L1, contributing to their ability to evade immune surveillance (54).

TME and Immune Evasion

The immunosuppressive TME in KRAS-mutant tumors is typically dominated by high levels of TGF-β, IL-6, and TNF-α, which promote the expression of PD-L1 and induce immune tolerance. These cytokines and immune cells help create an environment where anti-PD-1/anti-PD-L1 inhibitors are less effective (51, 67).

Tumor Heterogeneity and Immune Evasion

Tumor Heterogeneity

Mutations of KRAS contribute to intratumoral heterogeneity that interferes with the success of immune checkpoint inhibitors. Different responses to therapy might arise in heterogeneous PD-L1 expression tumors or mutations within other immune-related genes. In certain areas of the tumor, PD-L1 expression may be low with T cell activation in contrast to the upregulation of PD-L1, in other regions, where this leads to immune escape (73).

Resistance Mechanisms

Even in the presence of PD-1/PD-L1 inhibitors, KRAS-mutant tumors can exhibit various resistance mechanisms that undermine the efficacy of these therapies. One significant mechanism is the modulation/activation of secondary immune checkpoints. As a reaction to PD-1/PD-L1 inhibition, tumors may increase the expression of other immune checkpoints (LAG-3/TIM-3). This upregulation can further inhibit T cell function and contribute to

immune evasion. Additionally, KRAS mutations can alter T cell infiltration patterns within the TME, affecting the assembly and activation of T cells. This alteration may lead to a reduced overall efficacy of checkpoint blockade therapies, as the presence of activated T cells is vital for orchestrating successful anti-tumor immune response (74, 75).

Potential Role of Other Immune Evasion Mechanisms in KRAS-Driven Cancers

Cytokine Dysregulation

KRAS mutations alter cytokine production considerably to establish a highly immunosuppressive TME. One of the central cytokines involved in such an immunosuppressive environment is IL-6. IL-6 can enable immune evasion in KRAS-mutant cancers through chronic inflammation and STAT3 pathway activation, eventually facilitating the expansion of MDSCs and Tregs. Moreover, IL-6 also promotes the stimulation of NF-κB; the latter in turn initiates the expression of PD-L1 on tumor cells. KRAS mutations similarly stimulate the release of more IL-10 and TGF-β, whose immune-suppressive activities are as effective as IL-10 to promote Treg cells' differentiation, inhibit cytotoxic functions of T cells and boost immune tolerance in TME. Together, altered production of cytokines stimulates the microenvironment that tolerates tumor growth while the anticancer immune responses will not be efficient (76, 77).

Tumor-Associated Macrophages (TAMs)

TAMs play a vital role in KRAS-mutant cancers by supporting immune suppression and promoting tumor progression, often polarizing to the M2 phenotype that supports tumor growth, angiogenesis, and immune tolerance. In KRAS-driven tumors, M2 macrophages produce cytokines that suppress immunity, such as IL-10 and TGF-β, which limit the activation of effector T cells and facilitate the recruitment of other cells like MDSCs and Tregs. This immunosuppressive environment not only aids tumor survival but also contributes to treatment resistance. This represents a promising therapeutic approach which targets TAMs to be repolarized from their M2 phenotype toward their M1 phenotype, more associated with increased anti-tumor immunity. Aiming for the shift of balance within the pro-inflammatory state of TAMs, this could lead to improvements in the treatment outcomes in patients with KRAS-mutant cancers (78, 79).

Exosome-Mediated Immune Suppression

KRAS-mutant tumor cells also secrete exosomes, small vesicles carrying immunosuppressive proteins, miRNAs, and cytokines. Immune suppression can be an effect of the exosomes through alteration of neighbouring immune cells. Immune evasion was enhanced, immune tolerance supported, and cytotoxic cell activity was inhibited by transfer of PD-L1, TGF-β, and miRNAs via exosomes (51, 80).

Immune Checkpoints Beyond PD-L1/PD-1

Apart from PD-1/PD-L1, other immune checkpoint molecules are upregulated in KRAS-mutant cancers, such as TIM-3, LAG-3, and CTLA-4, which contribute to T cell exhaustion and immune escape. Combination therapies directing towards PD-1/PD-L1 along with other immune checkpoints may be needed to overcome resistance and achieve improved therapeutic outcomes in KRAS-driven cancers (81).

Conclusion

The exploration of the PD-1/PD-L1 immune checkpoint pathway and KRAS mutations significantly implicates a potential new advance in strategies for cancer treatment. Being a critical mechanism of immune evasion, PD-L1 expression plays a critical role in allowing the tumor to escape immune surveillance, thus facilitating the progression of tumor and poor clinical outcomes. Deciphering the cellular and molecular mechanisms behind PD-L1 expression, influenced by transcriptional factors and TME, is crucial to developing effective immunotherapies. Additionally, the connection between KRAS mutations and increased PD-L1 expression further complicates the relationship between genetic alterations and dynamics of immune response. This relationship not only complicates treatment responses but also presents opportunities for targeted therapeutic interventions that can enhance the efficacy of existing treatments. As research continues to reveal the intricacies of these pathways, there is a potential for significant advancements in precision medicine. The identification of specific biomarkers and their roles in tumor biology allow clinicians to tailor treatment approaches according to the patient's profile, leading to better outcomes.

In summary, understanding the mechanisms that pose a challenge to PD-L1 and KRAS mutations will be essential for developing novel cancer therapies. Continued investigation in these areas will lead to new interventions to overcome resistance to current therapies and improve the overall efficacy of cancer treatment, ultimately enhancing survival and quality of life for patients. It is important that this field has ongoing research to transform the care given for cancer and to promote better health globally.

REFERENCES

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The global burden of cancer 2013. 2015;1(4):505-27.
2. Nagai H, Kim YHJJotd. Cancer prevention from the perspective of global cancer burden patterns. 2017;9(3):448.
3. Bizuayehu HM, Ahmed KY, Kibret GD, Dadi AF, Belachew SA, Bagade T, et al. Global disparities of cancer and its projected burden in 2050. 2024;7(11):e2443198-e.
4. J IAfRoCJSM. Global cancer burden growing, amidst mounting need for services. 2024;45(3):326-7.
5. Ai L, Xu A, Xu JJRoCICM, Mechanisms C, Therapy. Roles of PD-1/PD-L1 pathway: signaling, cancer, and beyond. 2020:33-59.
6. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. 2015;373(2):123-35.
7. Hammerschmidt S, Wirtz HJDÄI. Lung cancer: current diagnosis and treatment. 2009;106(49):809.
8. Lemjabbar-Alaoui H, Hassan OU, Yang Y-W, Buchanan PJBeBA-RoC. Lung cancer: Biology and treatment options. 2015;1856(2):189-210.
9. Ljunggren HG, Jonsson R, Höglund PJSjoi. Seminal immunologic discoveries with direct clinical implications: The 2018 Nobel Prize in Physiology or Medicine honours discoveries in cancer immunotherapy. Wiley Online Library; 2018. p. e12731.
10. Cao Y, Liang W, Fang L, Liu Mk, Zuo J, Peng Yl, et al. PD-L1/PD-L1 signalling promotes colorectal cancer cell migration ability through RAS/MEK/ERK. 2022;49(12):1281-93.
11. Han Y, Liu D, Li LJAjocr. PD-1/PD-L1 pathway: current researches in cancer. 2020;10(3):727.
12. Ishida Y, Agata Y, Shibahara K, Honjo TJTEj. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. 1992;11(11):3887-95.
13. Freeman GJJPotNAoS. Structures of PD-1 with its ligands: sideways and dancing cheek to cheek. 2008;105(30):10275-6.
14. Zak KM, Grudnik P, Magiera K, Dömling A, Dubin G, Holak TAJS. Structural biology of the immune checkpoint receptor PD-1 and its ligands PD-L1/PD-L2. 2017;25(8):1163-74.
15. Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang XJTimm. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. 2015;21(1):24-33.
16. Nunes-Xavier CE, Angulo JC, Pulido R, López JIJCur. A critical insight into the clinical translation of PD-1/PD-L1 blockade therapy in clear cell renal cell carcinoma. 2019;20:1-10.
17. Yang K, Han W, Qin Y, Chen LJJoBR, Agents H. Effects of different levels of soluble PD-L1 protein on the growth of Lewis lung cancer transplanted tumor. 2019;33(2):537-42.
18. Zhang S, You X, Xu T, Chen Q, Li H, Dou L, et al. PD-L1 induction via the MEK-JNK-AP1 axis by a neddylation inhibitor promotes cancer-associated immunosuppression. Cell Death & Disease. 2022;13(10):844.
19. Antonangeli F, Natalini A, Garassino M, Sica A, Santoni A, Di Rosa F. Regulation of PD-L1 expression by NF-κB in cancer. Front Immunol 11: 584626. 2020.
20. Asgarova A, Asgarov K, Godet Y, Peixoto P, Nadaradjane A, Boyer-Guittaut M, et al. PD-L1 expression is regulated by both DNA methylation and NF-kB during EMT signaling in non-small cell lung carcinoma. Oncoimmunology. 2018;7(5):e1423170.
21. Lin X, Kang K, Chen P, Zeng Z, Li G, Xiong W, et al. Regulatory mechanisms of PD-1/PD-L1 in cancers. Molecular Cancer. 2024;23(1):108.
22. Chen S, Crabill GA, Pritchard TS, McMiller TL, Wei P, Pardoll DM, et al. Mechanisms regulating PD-L1 expression on tumor and immune cells. Journal for immunotherapy of cancer. 2019;7:1-12.
23. Cha J-H, Chan L-C, Li C-W, Hsu JL, Hung M-C. Mechanisms controlling PD-L1 expression in cancer. Molecular cell. 2019;76(3):359-70.
24. Ma L-J, Feng F-L, Dong L-Q, Zhang Z, Duan M, Liu L-Z, et al. Clinical significance of PD-1/PD-Ls gene amplification and overexpression in patients with hepatocellular carcinoma. Theranostics. 2018;8(20):5690.
25. Ruiz G, Enrico D, Mahmoud YD, Ruiz A, Cantarella MF, Leguina L, et al. Association of PD-L1 expression with driver gene mutations and clinicopathological characteristics in non-small cell lung cancer: A real-world study of 10 441 patients. Thoracic Cancer. 2024;15(11):895-905.
26. Georgiou K, Chen L, Berglund M, Ren W, De Miranda NF, Lisboa S, et al. Genetic basis of PD-L1 overexpression in diffuse large B-cell lymphomas. Blood, The Journal of the American Society of Hematology. 2016;127(24):3026-34.
27. Wang Q, Liu F, Liu L. Prognostic significance of PD-L1 in solid tumor: an updated meta-analysis. Medicine. 2017;96(18):e6369.
28. Li H, Xu Y, Wan B, Song Y, Zhan P, Hu Y, et al. The clinicopathological and prognostic significance of PD-L1 expression assessed by immunohistochemistry in lung cancer: a meta-analysis of 50 studies with 11,383 patients. Translational lung cancer research. 2019;8(4):429.
29. Zhou Z-J, Zhan P, Song Y. PD-L1 over-expression and survival in patients with non-small cell lung cancer: a meta-analysis. Translational lung cancer research. 2015;4(2):203.
30. Zhang M, Sun H, Zhao S, Wang Y, Pu H, Zhang Q. Expression of PD-L1 and prognosis in breast

cancer: a meta-analysis. Oncotarget. 2017;8(19):31347.
31. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. 2018;36(17):1714-68.
32. Zago G, Muller M, van den Heuvel M, Baas PJBT, Therapy. New targeted treatments for non-small-cell lung cancer–role of nivolumab. 2016:103-17.
33. Salmaninejad A, Valilou SF, Shabgah AG, Aslani S, Alimardani M, Pasdar A, et al. PD-1/PD-L1 pathway: basic biology and role in cancer immunotherapy. 2019;234(10):16824-37.
34. Ajona D, Ortiz-Espinosa S, Moreno H, Lozano T, Pajares MJ, Agorreta J, et al. A combined PD-1/C5a blockade synergistically protects against lung cancer growth and metastasis. 2017;7(7):694-703.
35. Takada K, Toyokawa G, Okamoto T, Shimokawa M, Kozuma Y, Matsubara T, et al. A comprehensive analysis of programmed cell death ligand-1 expression with the clone SP142 antibody in non–small-cell lung cancer patients. 2017;18(5):572-82. e1.
36. Perrino M, De Vincenzo F, Cordua N, Borea F, Aliprandi M, Santoro A, et al. Immunotherapy with immune checkpoint inhibitors and predictive biomarkers in malignant mesothelioma: work still in progress. 2023;14:1121557.
37. Zhang Y, Wu J, Zhao C, Zhang S, Zhu JJJoC. Recent advancement of PD-L1 detection technologies and clinical applications in the era of precision cancer therapy. 2023;14(5):850.
38. Reck M, Remon J, Hellmann MDJJoCO. First-line immunotherapy for non–small-cell lung cancer. 2022;40(6):586-97.
39. Lim SM, Hong MH, Kim HRJIN. Immunotherapy for non-small cell lung cancer: current landscape and future perspectives. 2020;20(1).
40. Khan M, Lin J, Liao G, Tian Y, Liang Y, Li R, et al. Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials. 2018;97(33):e11936.
41. Lee JK, Sivakumar S, Schrock AB, Madison R, Fabrizio D, Gjoerup O, et al. Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. NPJ Precision Oncology. 2022;6(1):91.
42. Yang Y, Zhang H, Huang S, Chu Q. KRAS mutations in solid tumors: characteristics, current therapeutic strategy, and potential treatment exploration. Journal of Clinical Medicine. 2023;12(2):709.
43. Jacobsen IC, Spanggaard I, Højgaard M, Belcaid L, Qvortrup C, Yde CW, et al. Extensive genomic analysis in patients with KRAS-mutated solid tumors shows high frequencies of concurrent alterations and potential targets but has limited clinical impact. Acta Oncologica. 2022;61(12):1499-506.
44. Salem ME, El-Refai SM, Sha W, Puccini A, Grothey A, George TJ, et al. Landscape of KRAS G12C, associated genomic alterations, and interrelation with immuno-oncology biomarkers in KRAS-mutated cancers. JCO Precision Oncology. 2022;6:e2100245.
45. Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. Signal transduction and targeted therapy. 2021;6(1):386.
46. Hymowitz SG, Malek S. Targeting the MAPK pathway in RAS mutant cancers. Cold Spring Harbor perspectives in medicine. 2018;8(11):a031492.
47. Bahar ME, Kim HJ, Kim DR. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. Signal transduction and targeted therapy. 2023;8(1):455.
48. Gillies TE, Pargett M, Silva JM, Teragawa CK, McCormick F, Albeck JG. Oncogenic mutant RAS signaling activity is rescaled by the ERK/MAPK pathway. Molecular systems biology. 2020;16(10):e9518.
49. Ma Q, Zhang W, Wu K, Shi L. The roles of KRAS in cancer metabolism, tumor microenvironment and clinical therapy. Molecular Cancer. 2025;24(1):14.
50. Ji M, Liu Y, Li Q, Li X, Ning Z, Zhao W, et al. PD-1/PD-L1 expression in non-small-cell lung cancer and its correlation with EGFR/KRAS mutations. Cancer biology & therapy. 2016;17(4):407-13.
51. Hamarsheh Sa, Groß O, Brummer T, Zeiser R. Immune modulatory effects of oncogenic KRAS in cancer. Nature communications. 2020;11(1):5439.
52. Tanjak P, Chaiboonchoe A, Suwatthanarak T, Acharayothin O, Thanormjit K, Chanthercrob J, et al. KRAS mutations suppress the tumor immune microenvironment in colorectal cancer. Cancer research. 2023;83(7_Supplement):2242-.
53. Yang Y, Shen S, Sun Y, Husain H, Zhou H, Lu S, et al. The relationship between different subtypes of KRAS and PD-L1 & tumor mutation burden (TMB) based on next-generation sequencing (NGS) detection in Chinese lung cancer patients. Translational Lung Cancer Research. 2022;11(2):213.
54. Falk A, Yazbeck N, Thon L, Guibert N, Hofman V, Zahaf K, et al. Impact of Kras mutant subtypes on PD-L1 expression in lung adenocarcinoma. Annals of Oncology. 2016;27:vi28.
55. Dias Carvalho P, Mendonça S, Martins F, Oliveira MJ, Velho S. Modulation of fibroblast phenotype by colorectal cancer cell-secreted factors is mostly independent of oncogenic KRAS. Cells. 2022;11(16):2490.

56. Clevenger AJ, Collier CA, Gorley JPM, Colijn S, McFarlin MK, Solberg SC, et al. Oncogenic KRAS Mutations Confer a Unique Mechanotransduction Response to Peristalsis in Colorectal Cancer Cells. Molecular Cancer Research. 2024:OF1-OF15.
57. Drosten M, Barbacid M. Targeting the MAPK pathway in KRAS-driven tumors. Cancer cell. 2020;37(4):543-50.
58. Xu L, Ding R, Song S, Liu J, Li J, Ju X, et al. Single-cell RNA sequencing reveals the mechanism of PI3K/AKT/mTOR signaling pathway activation in lung adenocarcinoma by KRAS mutation. The Journal of Gene Medicine. 2024;26(1):e3658.
59. Watterson A, Coelho MA. Cancer immune evasion through KRAS and PD-L1 and potential therapeutic interventions. Cell Communication and Signaling. 2023;21(1):45.
60. Chen N, Fang W, Lin Z, Peng P, Wang J, Zhan J, et al. KRAS mutation-induced upregulation of PD-L1 mediates immune escape in human lung adenocarcinoma. Cancer Immunology, Immunotherapy. 2017;66:1175-87.
61. Cronin-Fenton D, Dalvi T, Movva N, Pedersen L, Hansen H, Fryzek J, et al. PD-L1 expression, EGFR and KRAS mutations and survival among stage III unresected non-small cell lung cancer patients: a Danish cohort study. Scientific Reports. 2021;11(1):16892.
62. Abounar SA, El-Nikhely NA, Turkowski K, Savai R, Saeed H. CRISPR/Cas-Mediated Knockdown of PD-L1 and KRAS in Lung Cancer Cells. International Journal of Molecular Sciences. 2024;25(16):9086.
63. Tsiouda T, Domvri K, Boutsikou E, Bikos V, Kyrka K, Papadaki K, et al. Prognostic Value of KRAS Mutations in Relation to PDL1 Expression and Immunotherapy Treatment in Adenocarcinoma and Squamous Cell Carcinoma Patients: A Greek Cohort Study. Journal of Personalized Medicine. 2024;14(5):457.
64. Christopoulos P, Blasi M, Eberhard D, Kazdal D, Romero Cruz T, Bozorgmehr F, et al. The impact of PD-L1 expression and co-mutations on outcome of KRAS-driven non-small-cell lung cancer. American Society of Clinical Oncology; 2023.
65. Erhart C-C, Cefalì M, Mangan D, Kasenda B, Wannesson L. Prognostic value of KRAS G12C in advanced non-small cell lung cancer with high PD-L1 expression treated with upfront immunotherapy: a systematic review and meta-analysis. Swiss Medical Weekly. 2024;154(7):3695-.
66. Calles A, Liao X, Sholl LM, Rodig SJ, Freeman GJ, Butaney M, et al. Expression of PD-1 and its ligands, PD-L1 and PD-L2, in smokers and never smokers with KRAS-mutant lung cancer. Journal of Thoracic Oncology. 2015;10(12):1726-35.
67. Ischenko I, D'Amico S, Rao M, Li J, Hayman MJ, Powers S, et al. KRAS drives immune evasion in a genetic model of pancreatic cancer. Nature communications. 2021;12(1):1482.
68. Xu M, Zhao X, Wen T, Qu X. Unveiling the role of KRAS in tumor immune microenvironment. Biomedicine & Pharmacotherapy. 2024;171:116058.
69. Zhang Z, Zhang H, Liao X, Tsai H-i. KRAS mutation: The booster of pancreatic ductal adenocarcinoma transformation and progression. Frontiers in Cell and Developmental Biology. 2023;11:1147676.
70. Guo L, Tang X, Wong SW, Guo A, Lin Y, Kwok HF. Regulation of IFN-γ-mediated PD-L1 expression by MYC in colorectal cancer with wild-type KRAS and TP53 and its clinical implications. Frontiers in Pharmacology. 2022;13:1022129.
71. Qiu Q, Tan D, Chen Q, Zhou R, Zhao X, Wen W, et al. Clinical implications of PD-L1 expression and pathway-related molecular subtypes in advanced Asian colorectal cancer patients. American Journal of Cancer Research. 2024;14(2):796.
72. Cicenas J, Tamosaitis L, Kvederaviciute K, Tarvydas R, Staniute G, Kalyan K, et al. KRAS, NRAS and BRAF mutations in colorectal cancer and melanoma. Medical oncology. 2017;34:1-11.
73. Blank A, Roberts DE, Dawson H, Zlobec I, Lugli A. Tumor heterogeneity in primary colorectal cancer and corresponding metastases. Does the apple fall far from the tree? Frontiers in medicine. 2018;5:234.
74. Lei Q, Wang D, Sun K, Wang L, Zhang Y. Resistance mechanisms of anti-PD1/PDL1 therapy in solid tumors. Frontiers in cell and developmental biology. 2020;8:672.
75. Skoulidis F, Goldberg ME, Greenawalt DM, Hellmann MD, Awad MM, Gainor JF, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. Cancer discovery. 2018;8(7):822-35.
76. Casacuberta-Serra S, González-Larreategui Í, Capitán-Leo D, Soucek L. MYC and KRAS cooperation: from historical challenges to therapeutic opportunities in cancer. Signal Transduction and Targeted Therapy. 2024;9(1):205.
77. Cullis J, Das S, Bar-Sagi D. Kras and tumor immunity: friend or foe? Cold Spring Harbor perspectives in medicine. 2018;8(9):a031849.
78. Liu H, Liang Z, Zhou C, Zeng Z, Wang F, Hu T, et al. Mutant KRAS triggers functional reprogramming of tumor-associated macrophages in colorectal cancer. Signal Transduction and Targeted Therapy. 2021;6(1):144.
79. Zhou Y, Kuang Y, Wang C, Yu Y, Pan L, Hu X. Impact of KRAS mutation on the tumor microenvironment in colorectal cancer. International Journal of Biological Sciences. 2024;20(5):1947.
80. Pathania AS, Prathipati P, Challagundla KB. New insights into exosome mediated tumor-immune escape: Clinical perspectives and therapeutic

strategies. Biochimica Et Biophysica Acta (BBA)-Reviews on Cancer. 2021;1876(2):188624.
81. Li Y, Hu L, Peng X, Xu H, Tang B, Xu C. Resistance to immune checkpoint inhibitors in KRAS-mutant non-small cell lung cancer. Cancer Drug Resistance. 2022;5(1):129.