REVIEW

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Oncogenic KRAS as an Architect of Mucinous Lineage Identity in Ovarian Carcinoma: Signaling Networks and Epithelial Reprogramming

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ABSTRACT

Primary mucinous ovarian carcinoma (MOC) represents a unique biological entity that frequently exhibits resistance to standard chemotherapy. A major clinical challenge in MOC management remains accurately distinguishing primary tumors from gastrointestinal metastases. This narrative review synthesizes current evidence on how oncogenic KRAS signaling functions as a "master architect" driving lineage plasticity and shaping cellular identity in MOC. The literature indicates that KRAS/MAPK hyperactivation extends beyond driving cellular proliferation to orchestrate massive epithelial reprogramming. It actively recruits key transcription factors (such as AP-1, FOXA, and CDX2) that physically remodel chromatin and establish super-enhancers to epigenetically "lock in" a mucinous and intestinal identity. Furthermore, this state is continuously reinforced by a pro-inflammatory tumor microenvironment (via the IL-6/STAT3 axis) and specific metabolic adaptations, including enhanced glycolysis and glutaminolysis, creating a robust feed-forward loop. This mechanistic integration establishes that mucinous differentiation is not a static morphological label, but rather an actively maintained transcriptional state. Consequently, the clinical paradigm for MOC must shift toward precision oncology. This demands rigorous primary diagnostic confirmation intrinsically coupled with comprehensive molecular stratification. Future therapeutic strategies must move beyond conventional chemotherapy to exploit specific vulnerabilities within epigenetic circuits, metabolic dependencies, and targetable molecular subgroups (such as ERBB2 amplification), ultimately dismantling the resilient cellular identity of this recalcitrant tumor.

Keywords: Mucinous Ovarian Carcinoma, KRAS, Epithelial Reprogramming, Epigenetics, Tumor Microenvironment, Precision Oncology.
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INTRODUCTION

Epithelial ovarian tumors comprise biologically heterogeneous entities characterized by distinct histotypes, varying genetic drivers, patterns of dissemination, and therapy responsiveness. High-grade serous carcinoma (HGSC) is the predominant subtype. In contrast, mucinous ovarian carcinoma (MOC) constitutes a smaller yet clinically significant subset with a unique clinicopathologic profile and outcomes heavily influenced by stage [1–3]. Clinically, localized MOC treated with optimal cytoreduction correlates with a favorable prognosis. However, advanced or recurrent disease often exhibits minimal benefit from standard platinum–taxane regimens primarily developed for HGSC. This disparity highlights the critical need for histotype-specific biological insights and therapeutic advancements [1–4].

In addition to clinical behavior, developments in molecular profiling indicate a consistent biological theme in mucinous ovarian tumors, characterized by the predominant activation of the RAS–MAPK pathway, especially by KRAS mutations. These mutations occur with significant frequency in invasive MOC and are even more prevalent in mucinous precursor lesions, establishing KRAS activation as an early event in mucinous tumorigenesis [4,5]. The persistence of a "gastrointestinal-like" phenotype suggests that KRAS-driven signaling interacts with specific transcriptional and epigenetic programs. These programs stabilize mucinous and intestinal differentiation states, effectively linking oncogenic signaling to the maintenance of lineage identity and potentially influencing therapeutic vulnerabilities [3,4]. Concurrently, mechanistic investigations into ovarian cancer chemoresistance demonstrate that signaling reconfiguration and downstream effectors dictate platinum sensitivity. This reinforces the overarching concept that pathway-level dependencies drive treatment failure in specific biological contexts [6].

A critical diagnostic requirement in this domain is the precise differentiation between primary ovarian mucinous tumors

and metastatic mucinous carcinomas to the ovary, which predominantly originate from gastrointestinal or pancreatobiliary sites. Numerous clinicopathologic series underscore that a significant proportion of tumors previously categorized as primary MOC are eventually reclassified as metastases. Distinguishing between the two is not merely a semantic exercise, but an absolute necessity for accurate prognosis and management [1,2,5,7]. Misclassification has significant clinical implications, as metastatic mucinous cancers require site-specific treatment strategies. Misattributing them to a main ovarian origin can result in unsuitable treatment and adverse patient outcomes [2,7]. Consequently, modern guidelines mandate an integrated workflow. This approach combines gross and microscopic evaluation with radiologic and clinical correlation, often including targeted assessment of the gastrointestinal tract, particularly when bilaterality, surface involvement, or extraovarian spread suggests metastatic disease [1].

Because morphology alone is frequently insufficient to determine the site of origin, immunohistochemistry (IHC) serves as a diagnostic cornerstone, with contemporary recommendations emphasizing multi-marker panels rather than reliance on any single stain [1,2,5,7]. In practice, CK7/CK20 remains a foundational first-line pairing and is most informative when interpreted in conjunction with staining distribution (diffuse vs. focal) and the broader clinicopathologic context. To strengthen discrimination toward a lower gastrointestinal primary, SATB2 is particularly valuable because it is highly specific for colorectal/appendiceal origin and is generally absent in primary ovarian mucinous neoplasms. However, its incomplete sensitivity means that SATB2 negativity cannot fully exclude a lower GI source [8,9]. Conversely, markers supporting a Müllerian/ovarian lineage such as PAX8 can be helpful in appropriate settings, although reported expression in selected non-ovarian malignancies requires cautious, context-dependent interpretation [8,9]. Given the residual overlap across profiles, adjunct markers including DPEP1 and CK17 may further refine classification in challenging cases, reinforcing the need for algorithmic and integrative IHC strategies within a layered diagnostic workflow [10].

Against this backdrop, subtype-specific translational strategies are increasingly framed around molecular stratification in MOC. These include targeting HER2/ERBB2 alterations, exploiting MAPK-pathway dependencies in KRAS-driven tumors, and exploring lineage-informed targets such as claudin-18.2 [3,4,11]. Therefore, a synthesis that integrates diagnostic imperatives with emerging KRAS-centered biology is highly timely. In this narrative review, we examine how oncogenic KRAS/MAPK signaling interfaces with epithelial reprogramming, transcriptional circuitry, and epigenetic regulation to shape and maintain histologic identity in mucinous ovarian carcinoma. Furthermore, we discuss how deciphering these lineage-linked networks may inform the next generation of diagnostic and therapeutic approaches.

METHOD

This narrative literature review synthesizes current evidence regarding oncogenic KRAS signaling, epithelial reprogramming, and lineage plasticity, alongside the epigenetic and microenvironmental mechanisms shaping mucinous and intestinal identity in primary mucinous ovarian carcinoma (MOC). A comprehensive literature search was conducted utilizing PubMed, ScienceDirect, and Google Scholar, supplemented by backward and forward citation chaining to ensure literature saturation. To capture the most contemporary molecular insights, the search prioritized literature published over the past decade (2016-2026), while older landmark studies were selectively included to provide foundational mechanistic context.

Search strategies iteratively utilized Boolean operators (AND/OR) across four conceptual domains: (i) primary MOC molecular profiling (e.g., KRAS, ERBB2/HER2, TP53, CDKN2A, RNF43/Wnt, sequencing, and copy-number alterations); (ii) KRAS signaling networks (MAPK/ERK/MEK, PI3K–AKT–mTOR, RalGDS, Hippo/YAP, Wnt/β-catenin, AP-1/ETS/MYC); (iii) lineage reprogramming and mucinous differentiation (CDX2, HNF4α, FOXA, GATA, MUC2/MUC5AC); and (iv) epigenetics, the tumor microenvironment, and metabolism (chromatin accessibility, histone marks, DNA methylation, super-enhancers, IL-6/STAT3, and glucose/glutamine metabolism).

Eligible sources included peer-reviewed original research, clinical and translational reports, and relevant systematic reviews with accessible full texts in English. Crucially, studies were explicitly excluded if they were restricted to abstracts, were non-peer-reviewed editorials, or if they failed to clearly distinguish primary ovarian MOC from metastatic gastrointestinal or pancreatobiliary tumors to the ovary. Extracted evidence was synthesized narratively using a thematic framework reflecting the biological hierarchy of the disease: progressing from genomic alterations and signaling networks to lineage reprogramming, epigenetic regulation, microenvironmental and metabolic interactions, and concluding with therapeutic implications.

RESULT AND DISCUSSION

Molecular Landscape of Mucinous Ovarian Carcinoma

The Diagnostic Prerequisite for Molecular Profiling

Primary MOC represents a molecularly distinct entity whose accurate interpretation is inextricably linked to strict case definition. Because a substantial proportion of mucinous tumors involving the ovary are metastatic from gastrointestinal or pancreatobiliary primaries, robust conclusions regarding mutation frequencies and driver hierarchies necessitate the strict separation of primary MOC from metastases. While this is achieved through integrated clinicopathologic workflows and multi-marker immunohistochemistry (e.g., CK7/CK20, CDX2, SATB2, PAX8), this rigorous diagnostic stratification is the fundamental prerequisite for understanding the true molecular landscape of primary ovarian mucinous disease.

Within rigorously defined primary MOC, the dominant activation of the RAS–MAPK pathway emerges as the central genomic axis spanning from mucinous precursor lesions to invasive

carcinomas . This activation occurs most commonly via KRAS alterations [12–15]. The recurrence of KRAS mutations across the mucinous continuum supports an early, initiating role for MAPK signaling in both mucinous lineage specification and tumor evolution. Notably, KRAS hotspot patterns in MOC are enriched for canonical exon 2 events (codon 12 and 13 variants), broadly paralleling GI-type mucinous tumors and reinforcing the biological overlap across mucinous phenotypes. Importantly, this persistent KRAS/MAPK activation suggests a broader function beyond mere proliferation; it likely sustains epithelial lineage programs through transcriptional and epigenetic circuitry to maintain stable mucinous/intestinal features [3,4,14].

Actionable Targets: ERBB2/HER2 Amplification

A clinically meaningful subset of MOC is characterized by ERBB2 (HER2) alterations, including amplifications and/or mutations, providing a receptor tyrosine kinase (RTK)-driven oncogenic input with significant therapeutic potential 13. While patterns of ERBB2 co-occurrence with KRAS vary across cohorts, the recurrent conclusion is that ERBB2 amplification defines a biologically distinct, targetable subgroup—particularly in tumors lacking BRCA-driven homologous recombination deficiency (HRD). Although MOC-specific prospective trial evidence remains limited, translational observations across ovarian tumors strongly support HER2-directed strategies in biomarker-selected settings, positioning ERBB2 as a pragmatic marker for clinical trial enrollment [16,17].

Secondary Alterations and Copy Number Architecture

Additional recurrent lesions help delineate the heterogeneity within MOC and sharpen its contrast with HGSC. TP53 disruption, which is ubiquitous in HGSC, is substantially less frequent in MOC. When present, it is typically enriched in more aggressive or transformed/high-grade mucinous tumors, consistent with a progression-associated role rather than an initiating event [13,14,18,19]. Cell-cycle dysregulation is also prominent, with CDKN2A loss repeatedly reported as a characteristic event in mucinous cohorts [13]. Furthermore, Wnt-pathway perturbations are observed in MOC. This includes RNF43 mutations, which are well recognized in GI-type mucinous cancers and suggest shared etiologic features with GI biology. Copy-number architecture similarly reflects a non-HGSC biology: MOC often exhibits focal events, such as ERBB2 amplification, alongside broader copy number alterations (CNAs) like recurrent CDKN2A loss. This sharply contrasts with the extensive chromosomal instability and HRD-associated signatures defining HGSC [13,15].

Ultimately, comparative frameworks position MOC squarely between ovarian and GI mucinous biology. Primary MOC and GI-type mucinous tumors share core drivers (KRAS/MAPK), creating genuine molecular overlap that complicates origin inference. Conversely, MOC fundamentally diverges from HGSC, lacking the uniform TP53 involvement and HRD signatures that confer platinum and PARP-inhibitor sensitivity [13,14,19,20]. It is crucial to note that the interpretation of reported mutation frequencies must account for methodological variability, including shifting diagnostic criteria, cohort composition (borderline vs. invasive), sequencing platforms, and copy-number variant (CNV) calling pipelines. With these caveats acknowledged, convergent evidence establishes MOC as a KRAS/MAPK-dominant disease with recurrent cooperative lesions (ERBB2, CDKN2A, RNF43). This distinct genomic architecture provides the necessary foundation for the mechanistic exploration of KRAS signaling, epithelial reprogramming, and downstream therapeutic implications discussed in the subsequent sections.

Mechanistic Wiring of MOC: KRAS as the Master Scaffolding Driver

Building upon the genomic foundation that establishes KRAS as the central driver of primary MOC, it is essential to dissect its functional outputs. In MOC, KRAS functions as a molecular switch cycling between active (GTP-bound) and inactive (GDP-bound) states. However, its continuous oncogenic activation is not merely a mitogenic trigger; rather, it coordinates a complex hub of canonical and non-canonical signaling pathways that reconfigure transcriptional programs and stabilize a mucinous/intestinal lineage identity. This paradigm positions KRAS-driven signaling as the master scaffolding axis shaping MOC biology. Across the mucinous continuum, from benign and borderline lesions to invasive carcinoma, KRAS hotspot mutations (particularly at codons 12 and 13) can bias downstream signaling in ways that shape histologic features and clinical behavior. This mechanistic wiring provides the foundation for contrasting MOC with high-grade serous carcinoma (HGSC) and underscores its biological overlap with gastrointestinal (GI) mucinous tumors [13,16,21].

The RAF–MEK–ERK (MAPK) Cascade

The canonical RAF–MEK–ERK cascade is repeatedly identified as the principal effector axis in MOC and related GI-type mucinous tumors. Upon activation, KRAS-GTP engages RAF kinases, which phosphorylate MEK1/2, subsequently activating ERK1/2. Activated ERK translocates to the nucleus to drive robust transcriptional and cellular responses. Beyond driving cell-cycle entry, MAPK outputs include anti-apoptotic and stress-adaptive programs that enable tumor survival under oncogenic and microenvironmental pressures. Crucially, ERK signaling modulates epithelial lineage programs via transcription factors, driving the mucinous and intestinal differentiation outputs characteristic of MOC. However, translating this knowledge into clinical practice presents challenges. While robust MAPK activation correlates with KRAS-driven lineage programs and rationalizes targeted therapies, the RAF–MEK–ERK axis is tightly regulated by negative feedback loops (e.g., DUSP phosphatases, SPRY family members). Consequently, adaptive resistance to MEK/ERK monotherapy is common and often arises through rebound receptor tyrosine kinase (RTK) signaling or activation of compensatory pathways. These patterns support combination strategies, such as RTK co-inhibition or modulation of the YAP/Hippo axis, to mitigate resistance in KRAS-driven mucinous tumors [4,13,16,17,22,23].

The PI3K–AKT–mTOR Intersection

Operating in tandem with the MAPK cascade is the PI3K–AKT–mTOR pathway, activated either directly by KRAS or via upstream RTKs (such as ERBB2). This axis culminates in the generation of PIP3, AKT activation, and mTORC1/2 activity, ultimately coordinating cellular survival, protein synthesis, and metabolic reprogramming (e.g., enhanced glucose uptake and lipid biosynthesis). In MOC, these metabolic adaptations reinforce the mucinous tumor phenotype. Importantly, the MAPK and PI3K–AKT–mTOR pathways exhibit significant cross-talk; the inhibition of one axis can unleash the compensatory activity of the other. This redundancy further explains the limited efficacy of single-agent therapies and underscores the translational relevance of combining MAPK inhibitors with PI3K/AKT/mTOR modulators, or exploiting context-specific vulnerabilities like ERBB2 amplifications [4,13,16,17].

Non-Canonical Signaling and Lineage Plasticity

Beyond canonical growth cascades, KRAS coordinates morphological and lineage-specific changes through non-canonical effectors. The Ral-GDS pathway serves as a prime example. KRAS signaling through RalGDS activates RalA and RalB GTPases, which regulate exocyst-mediated vesicle trafficking and epithelial polarity. These outputs directly influence invasion, glandular architecture, and mucin secretion, providing a mechanistic rationale for how KRAS drives the unique "GI-like" morphologic phenotypes observed in MOC [13,15]. Furthermore, KRAS networks cooperate with Wnt/β-catenin and Hippo/YAP signaling to sustain intestinal differentiation and lineage plasticity. The Wnt-driven state supports stem-like plasticity, reinforcing the mucinous programs shared between MOC and GI tumors. Concurrently, YAP/TAZ, the downstream effectors of the Hippo pathway, can become hyperactivated as an adaptive resistance response to MAPK inhibition. By sustaining transcriptional programs that promote survival and lineage plasticity, YAP/TAZ signaling represents a rational co-target for dual-inhibition strategies in resistant MOC [13,16,17,24].

KRAS and Transcriptional Rewiring

Ultimately, various signaling pathways converge to restructure the chromatin architecture and induce transcriptional reconfiguration. This is mainly facilitated by various essential transcription factor networks. The initial process is AP-1 activation, wherein MAPK signaling activates AP-1 components (FOS/JUN), serving as a pivotal chromatin-remodeling hub. AP-1 regulates genes associated with extracellular matrix interactions, inflammatory reactions, and differentiation, which aligns seamlessly with the secretory and glandular characteristics of MOC. Secondly, ETS factors are phosphorylated by ERK activation, affecting ETS family members such as ELK1 and ETS1. In collaboration with AP-1, ETS factors modulate enhancer activity to reinforce mucinous/intestinal identity and augment invasive potential. The third aspect is MYC Regulation, wherein the interaction between MAPK and PI3K pathways amplifies MYC activity. MYC functions as a universal transcriptional amplifier, enhancing ribosome biogenesis and metabolic productivity, hence fortifying the lineage programs and aggressive phenotypes associated with advanced KRAS-driven MOC [13,14,21].

Epithelial Reprogramming and Mucinous Differentiation

Lineage Plasticity as a Framework for Mucinous Identity

Oncogenic KRAS signaling in MOC is not confined to mitogenic output but reshapes nuclear gene-expression programs through MAPK-centered signaling and transcriptional rewiring. Within a lineage-plasticity framework, the mucinous or intestinal-like phenotype of MOC can be understood as an acquired epithelial identity that is actively instructed and stabilized by oncogenic signaling and chromatin remodeling, rather than a fixed morphologic label determined by a single cell of origin. A practical view considers two plausible epithelial substrates: ovarian surface epithelium (OSE), a mesothelial-like lining capable of metaplastic change, and Müllerian epithelium, which is predisposed to glandular differentiation programs. Because the cell-of-origin for MOC remains debated, this framework does not require an exclusive origin; instead, it emphasizes that ovarian epithelia can access alternative lineage programs under oncogenic pressure, consistent with intestinal-like features observed in mucinous ovarian tumors despite an ovarian milieu [25,26].

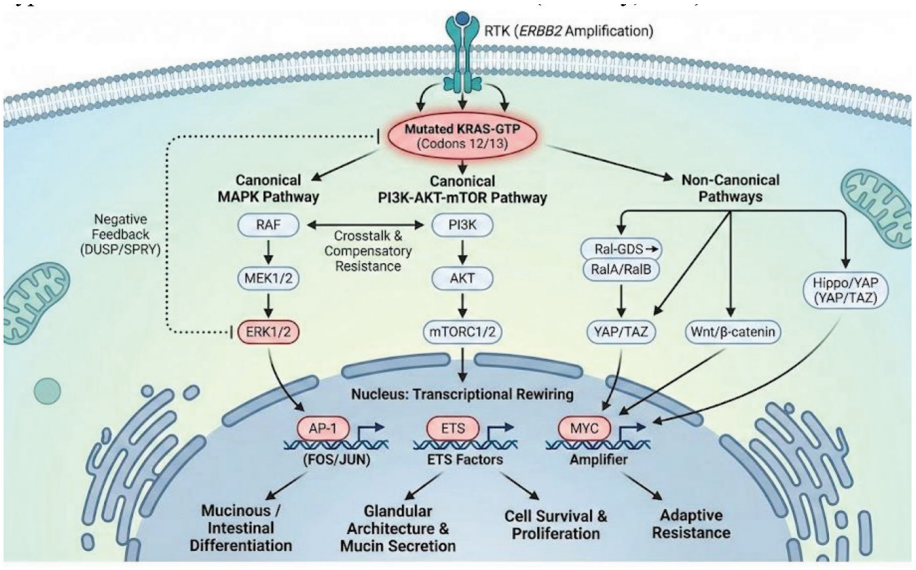

Figure 1. KRAS-driven Signaling Networks and Transcriptional Rewiring Underlying Mucinous Lineage Programs in Mucinous Ovarian Carcinoma.

KRAS/MAPK-Directed Reprogramming Toward a Secretory, Intestinal-Like State

Oncogenic KRAS activation may promote mucinous differentiation through two non-mutually exclusive mechanisms: selection and instruction. In a selection model, KRAS-driven fitness advantages expand pre-existing subclones already primed toward mucinous/intestinal differentiation. In an instruction (reprogramming) model, KRAS/MAPK signaling actively reconfigures transcriptional circuitry and epigenetic landscapes to induce transdifferentiation or state switching toward an intestinal-like identity. This distinction is clinically relevant because instruction implies ongoing dependence on transcription factor networks and epigenetic machinery, potentially exposing vulnerabilities not captured by growth-centric models. Consistent with MAPK-linked epigenomic remodeling in oncogene-driven contexts, MEK perturbation can remodel active chromatin landscapes and alter transcription factor recruitment in MAPK-driven tumors [27]. Phenotypically, KRAS/MAPK-dependent rewiring manifests as coordinated secretory outputs, including induction of mucin programs (notably MUC2 and MUC5AC) that shape barrier properties and local tissue ecology, and as goblet-cell–like differentiation representing a mature secretory intestinal program expressed in an ovarian context [28].

Transcription Factor Circuits that Stabilize Mucinous/Intestinal Programs

The execution and persistence of this lineage state require transcription factor circuitry that translates upstream KRAS/MAPK signaling into durable gene-expression programs. CDX2, a master regulator of intestinal differentiation, can function as both a lineage marker and a mechanistic node coordinating intestinal programs; importantly, CDX2 positivity and related intestinal-like features should not be interpreted as proof of gastrointestinal origin in isolation, as they may reflect reprogrammed intestinal identity reinforced within ovarian epithelium [26]. This interpretive caution is reinforced by work emphasizing that marker overlap can occur between primary MOC and gastrointestinal-derived mucinous tumors, underscoring the need for integrated assessment when origin is in question [29,30]. Beyond CDX2, HNF4α supports endodermal differentiation and integrates metabolic/secretory programs that may reinforce mucinous transcriptional states under KRAS/MAPK contexts, while FOXA pioneer factors provide a plausible enabling layer by opening compacted chromatin and establishing enhancer/promoter accessibility necessary for stable enhancer usage. GATA factors further contribute to glandular and secretory differentiation circuits and may help stabilize the glandular architecture characteristic of mucinous histology [27,31]. Together, these observations support a model in which KRAS/MAPK-driven transcriptional rewiring biases ovarian epithelial cells toward a mucinous/intestinal-like lineage state, with durable maintenance likely requiring enhancer reconfiguration and sustained chromatin accessibility changes—providing a direct bridge to the next section on epigenetic and chromatin remodeling mechanisms [27].

Epigenetic and Chromatin Remodeling Mechanisms

Epigenetic "locking" of mucinous lineage identity

As discussed before transcription factors such as CDX2, HNF4α, FOXA, and GATA can initiate lineage shifts toward mucinous and intestinal programs, but durable identity typically requires an epigenetic "lock" implemented through chromatin remodeling. A coherent mechanistic sequence links oncogenic signaling to stable lineage output: KRAS/MAPK signaling activates kinase-responsive transcription factor hubs (AP-1, ETS, MYC) together with pioneer factors (FOXA), which recruit chromatin remodelers and epigenetic writers to reshape regulatory DNA and consolidate lineage programs. Although the strongest mechanistic evidence for this cascade comes from KRAS-driven tumors outside the ovary, these conserved paradigms provide a useful framework for interpreting how mucinous ovarian carcinoma (MOC) may stabilize mucinous/intestinal identity while MOC-specific epigenomic mapping continues to emerge [27,32].

Chromatin accessibility and histone-based encoding of lineage programs

Chromatin accessibility denotes nucleosome-depleted regulatory DNA that permits transcription factor binding at promoters and enhancers—an essential prerequisite for establishing and maintaining mucinous programs. MAPK signaling can promote enhancer opening through activation of AP-1 components (FOS/JUN), while FOXA pioneer factors facilitate engagement of compacted chromatin to establish regulatory competence. These activities are executed in part through ATP-dependent remodeling complexes (e.g., SWI/SNF/BAF) that reposition nucleosomes. Across KRAS-driven transition states, profiling approaches such as ATAC-seq, DNase-seq, and ChIP-seq demonstrate that MAPK perturbation can alter enhancer accessibility and transcription factor recruitment, consistent with a model in which KRAS generates an "open" regulatory substrate that supports mucin/secretory outputs and intestinal transcription factor modules, including programs linked to MUC2 and MUC5AC [30,32,33]. Once accessible, histone modifications act as a writing system that consolidates these regulatory states. KRAS/MAPK signaling can promote recruitment of co-activators such as p300/CBP, increasing H3K27ac at lineage-defining enhancers and super-enhancer regions, while H3K4me1 and H3K4me3 mark primed enhancers and active promoters, respectively. In parallel, repression of alternative epithelial programs may be reinforced through Polycomb-associated mechanisms, including EZH2-mediated H3K27me3, thereby constraining lineage-inappropriate transcription. The balance between writers and opposing erasers (e.g., HDACs and KDMs) can progressively stabilize a mucinous transcriptional state, providing a mechanistic rationale for exploring epigenetic interventions (including HDAC- or EZH2-directed strategies) to disrupt lineage maintenance under KRAS control [30,33].

DNA methylation, super-enhancers, and microenvironmental sensitivity

Beyond histone-based regulation, DNA methylation provides a more stable layer of epigenetic memory that can reinforce

long-term transcriptional constraints. DNMT-mediated methylation may lock in repression of alternative epithelial identities or tumor-suppressive programs that would destabilize mucinous state maintenance, whereas TET-dependent demethylation can contribute to sustained activation of secretory and intestinal networks. While MOC-specific methylome maps remain less comprehensive than in other KRAS-driven cancers, methylation-mediated memory remains a plausible mechanism by which lineage programs are stabilized over time and may become increasingly actionable as the evidentiary base matures 30,33. A mechanistic focal point of lineage stabilization is the super-enhancer (SE): clustered enhancer assemblies with exceptionally high H3K27ac and dense transcription factor occupancy that control cell-identity genes. In KRAS/MAPK-driven reprogramming, oncogenic signaling may consolidate SE activity around mucinous/intestinal transcription factor modules and secretory programs through coordinated recruitment of AP-1 and FOXA and subsequent p300/CBP-dependent acetylation, creating "transcriptional addiction" to SE-regulated circuits. Cross-context evidence from lung and pancreatic cancers indicates that super-enhancer driven core regulatory circuitry can shape tumor identity and therapeutic vulnerability. If MOC exhibits similar dependencies, pharmacologic disruption of super-enhancer machinery, such as BRD4/BET or CDK7 targeting, may weaken lineage-sustaining transcriptional networks. Finally, these epigenomic states remain environmentally sensitive: enhancer usage and SE activity can be reshaped by microenvironmental inputs such as inflammatory cues, cytokine signaling, and tissue mechanics that feed back into KRAS/MAPK pathways and chromatin regulators. This interplay provides a direct bridge to the next section on how tumor microenvironmental pressures cooperate with KRAS-driven remodeling to shape progression and therapeutic response in MOC [30,33].

Tumor Microenvironment and KRAS-Driven Reprogramming

The tumor microenvironment (TME) serves as both an initiator and an amplifier of this reprogramming (**Figure 2**). Rather than acting as a passive scaffold, the TME—comprising cancer-associated fibroblasts (CAFs), immune cells, and extracellular matrix components—forms an active inflammatory niche. In KRAS-driven settings, these stromal signals integrate seamlessly with oncogenic epithelial activity to support continuous enhancer engagement and transcription factor stabilization. Inflammatory cues within this niche potentiate the transcriptional programs (such as AP-1, ETS, and MYC) and pioneer factor activity required to physically reconfigure chromatin landscapes, thereby providing the continuous stimuli necessary to reinforce mucinous identity modules over time [30,31,34,35].

A primary conduit for this stromal-epithelial communication is cytokine signaling, most notably the IL-6/JAK/STAT axis. Across multiple KRAS-driven cancer contexts, CAFs secrete abundant inflammatory cytokines, prominently Interleukin-6 (IL-6), which binds to receptors on the tumor cells and activates the JAK2/STAT3 signaling cascade. While direct mapping of the IL-6/STAT3 axis specifically in primary MOC is still an active area of investigation, the broader pan-cancer literature supports a convergent model. KRAS-driven tumors actively leverage this CAF-derived inflammatory signaling to stabilize their reprogrammed identities. STAT3, acting in concert with KRAS-activated MAPK networks, helps sustain the transcriptional circuitry that drives continuous mucin production, secretory programs, and subsequent invasive traits [35–37].

Beyond inflammatory signaling, oncogenic KRAS fundamentally reprograms tumor metabolism, a shift that directly shapes the surrounding microenvironment. KRAS mutations drive enhanced glucose uptake, accelerated glycolysis, and a profound dependence on glutaminolysis. This metabolic rewiring serves a dual purpose: it supplies the necessary biomass to sustain the highly energy-demanding process of continuous mucin production, and it alters the availability of extracellular metabolites. The depletion of specific nutrients and the accumulation of metabolic byproducts, such as lactate, can suppress anti-tumor immune cells while further recruiting and activating pro-inflammatory CAFs. Consequently, KRAS-driven metabolic shifts act as a feed-forward loop, reinforcing the very inflammatory niche that supports mucinous lineage reprogramming [37–44].

Ultimately, the synthesis of these domains reveals a highly coordinated system where KRAS/MAPK activation, metabolic rewiring, and TME-derived cytokines (like IL-6) perpetually reinforce one another to lock in the super-enhancers that maintain the mucinous identity. Although much of the mechanistic scaffolding linking these elements arises from studies in lung, colorectal, and pancreatic cancers—underscoring the need for targeted MOC epigenomic studies—this framework opens new translational avenues. Given the reliance on metabolic-inflammatory

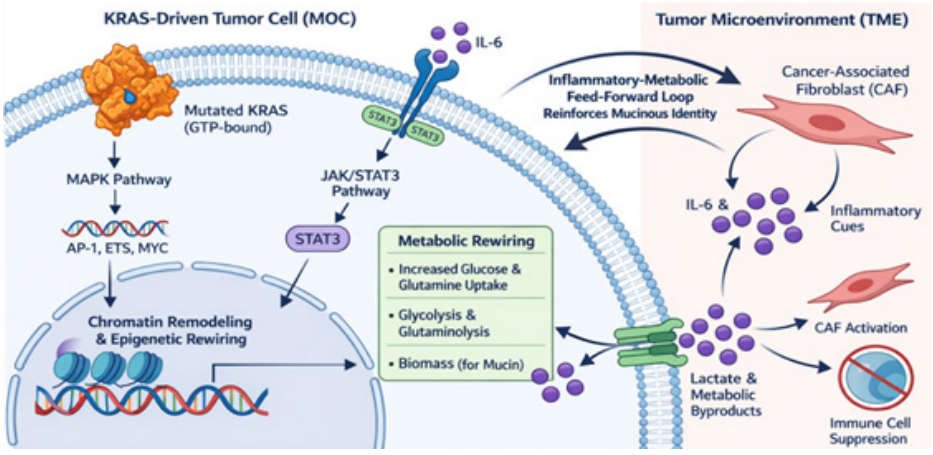

Figure 2. TME–KRAS Crosstalk: A Metabolic–Inflammatory Circuit Driving Mucinous Identity in MOC.

crosstalk, targeting glutaminase (GLS) or glycolytic flux could sensitize MOC tumors. Combinatorial strategies that disrupt these metabolic dependencies alongside epigenetic inhibitors represent a promising frontier for dismantling the resilient KRAS-driven mucinous identity [38,39,41,42,45].

Therapeutic Implications

Direct KRAS Targeting

The central translational challenge in mucinous ovarian carcinoma (MOC) is that the dominant driver—KRAS/MAPK—has historically been difficult to drug, while conventional chemotherapy trials have been hampered by rarity and diagnostic complexity. Notably, the randomized mEOC/GOG-0241 trial closed early because of slow accrual, and retrospective central pathology review confirmed primary mucinous ovarian cancer in only ~45% of evaluable cases, underscoring why biomarker-driven strategies and rigorous case definition are essential for future therapeutic development [46]. Direct KRAS inhibition is currently most mature for KRAS G12C, where covalent inhibitors have achieved regulatory approvals in other tumor types, including sotorasib in KRAS G12C-mutated NSCLC and adagrasib plus cetuximab in KRAS G12C-mutated metastatic colorectal cancer, with additional approvals/expansions for sotorasib plus panitumumab in KRAS G12C-mutated colorectal cancer. However, the relevance of G12C inhibitors to MOC is constrained by genotype frequency: in a large molecular profiling dataset of mucinous ovarian carcinoma, G12D and G12V were most common and G12C was rare (reported at ~4% among KRAS-mutant cases), implying that only a small subset of MOC would be eligible for current G12C-directed drugs [47]. This motivates emphasis on (i) allele-specific inhibitors for non-G12C variants and (ii) broader KRAS strategies. In practice, non-G12C approaches remain investigational; for example, a clinical study of the KRAS G12D inhibitor MRTX1133 reports termination prior to phase 2 initiation, highlighting development hurdles even for highly prevalent KRAS alleles [48,49]. More recently, "pan-KRAS" and "RAS(ON)" approaches have entered clinical development to address non-G12C mutations, representing a plausible path for MOC genotypes enriched for G12D/G12V, although MOC-specific clinical efficacy remains to be established [50].

Targeting downstream KRAS pathways

Given limited applicability of direct KRAS inhibition in MOC, targeting downstream signaling remains a rational, genotype-informed strategy. A recent mucinous ovarian cancer-focused synthesis emphasizes near-universal MAPK pathway hyperactivation as a defining biological feature and outlines a framework for MAPK-pathway targeting, while also noting the scarcity of direct prospective clinical data specific to MAPK-targeted therapy in mucinous ovarian cancer to date [51]. Mechanistically, the principal obstacles mirror other KRAS-driven malignancies: adaptive resistance through compensatory pathway activation (e.g., RTK reactivation, PI3K/AKT signaling), intratumoral heterogeneity, and lineage plasticity that can blunt single-agent pathway blockade [51]. These considerations support combination logic (e.g., co-targeting upstream RTKs such as EGFR/HER2 when relevant, or parallel survival pathways) rather than monotherapy. At the distal end of MAPK, ERK inhibitors provide an alternative way to suppress pathway output. Ulixertinib (BVD-523), an ERK1/2 inhibitor, demonstrated target engagement and clinical activity in MAPK-altered solid tumors in a multicenter phase I trial, supporting the feasibility of ERK blockade in RAS/MAPK-driven settings [52]. Additional ERK inhibitors (e.g., KO-947) have been evaluated in first-in-human trials, further illustrating clinical interest in ERK-directed strategies, though toxicity profiles and optimal combinations remain active questions [53]. For MOC, the translational implication is not that ERK (or MEK) inhibition is "proven," but that downstream targeting is biologically aligned with KRAS/MAPK dominance and should be pursued within trial designs that incorporate molecular stratification and early pharmacodynamic endpoints.

Targeting lineage programs and epigenetic dependencies

Because MOC's clinical behavior appears linked to a mucinous/intestinal-like lineage state, a complementary strategy is to target lineage maintenance mechanisms—especially where direct driver inhibition is not feasible. First, pathway-aligned, lineage-associated actionable targets already exist in subsets of MOC, including HER2/ERBB2 alterations (supporting HER2-directed strategies in biomarker-selected patients) and broader precision approaches discussed in recent MOC therapy reviews [4]. Second, lineage identity may create therapeutic dependencies at the level of transcriptional and chromatin regulation (e.g., enhancer/super-enhancer addiction), providing rationale for epigenetic or transcriptional interventions; while the optimal agents and combinations for MOC are not defined, contemporary reviews emphasize that targeted therapy, antibody–drug conjugates, and synthetic lethality approaches are reshaping the mucinous ovarian cancer landscape and should be evaluated in molecularly selected cohorts 4 . Third, lineage biomarkers may themselves enable therapeutic targeting. For example, claudin18.2 has been evaluated as a potential biomarker/target in primary ovarian mucinous carcinoma and metastatic GI-derived mucinous ovarian tumors, supporting exploration of lineage-informed targets that are already actionable in other mucinous GI cancers 29. Finally, recurrent genomic events that couple lineage and vulnerability—such as CDKN2A/MTAP locus loss—may open synthetic lethal opportunities (e.g., MAT2A/PRMT5-axis targeting) that are being clinically investigated across solid tumors and could be relevant to MOC subsets with such deletions [54].

Future Perspectives

Integrating the paradigms of KRAS signaling, epithelial reprogramming, chromatin remodeling, and microenvironmental reinforcement highlights critical imperatives for the biological understanding and clinical management of MOC. While current profiling supports the KRAS/MAPK cascade as the dominant biological axis, marked therapeutic and biological heterogeneity, including ERBB2-amplified subgroups and diverse progression-associated alterations, suggests that KRAS activation is often a necessary initiating event but rarely sufficient on its own to

sustain the mucinous lineage over time. Furthermore, the lineage-plasticity model implies that mucinous differentiation is conditionally reversible, cautioning that targeted pathway inhibition may induce transient state shifts rather than true tumor eradication. Consequently, future clinical evaluations must move beyond standard response rates to incorporate longitudinal, paired transcriptomic and epigenomic profiling that dynamically tracks lineage transitions before, during, and after therapy. Ultimately, implementing precision oncology for this lineage-defined disease requires overcoming historical diagnostic pitfalls, such as the low confirmation rates seen in GOG-0241 in the absence of central pathology review. A modern precision framework must mandate the rigorous confirmation of a primary ovarian origin, intrinsically coupled with comprehensive molecular stratification encompassing specific KRAS alleles (noting the rarity of the G12C mutation), ERBB2 status, CDKN2A/MTAP loss, and emerging lineage-specific biomarkers like claudin-18.2. Only through this unified diagnostic and molecular strategy can patients be rationally assigned to targeted combination trials, allowing the field to therapeutically exploit lineage-state dependencies as a newly actionable layer of tumor biology.

CONCLUSIONS

The integration of oncogenic *KRAS* signaling, epithelial reprogramming, and chromatin remodeling establishes primary mucinous ovarian carcinoma (MOC) fundamentally as a lineage-driven disease. While *KRAS* mutation serves as the foundational event initiating the shift toward a mucinous and intestinal identity, the durable maintenance of this phenotype is highly contingent upon epigenetic "locking" via super-enhancer regulation and continuous pro-inflammatory feedback from the tumor microenvironment. This mechanistic understanding not only underscores the absolute necessity of stringent diagnostic workflows to accurately distinguish primary MOC from gastrointestinal metastases, but it also compels a critical paradigm shift in its clinical management. Moving forward, precision oncology strategies for MOC must transcend conventional platinum-based chemotherapy; they must actively exploit specific vulnerabilities within transcriptional circuits, metabolic dependencies, and targetable molecular subgroups (such as *ERBB2* amplification) to effectively dismantle the resilient cellular identity of this recalcitrant tumor.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest about this article

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REFERENCES

1. Dundr P, Bazalová B, Bártů M, Bosse T, Drozenová J, Fabian P, et al. The cytokeratin 17 expression in primary ovarian tumors has diagnostic but not prognostic significance. Virchows Archiv. 2022;481(2):201–12. doi:10.1007/s00428-022-03338-z
2. Hegazy S, Bhargava R, Roy S, Elishaev E. Synchronous Mucinous Carcinomas of Ovary and Appendix: A Case Report With Diagnostic Pitfalls and Review of Corresponding Literature. AJSP Rev Rep. 2022;27(3):103–6. doi:10.1097/PCR.0000000000000505
3. Benitz S, Steep A, Nasser MM, Preall J, Mahajan UM, McQuithey H, et al. ROR2 Regulates Cellular Plasticity in Pancreatic Neoplasia and Adenocarcinoma. Cancer Discov. 2024;14(11):2162–82. doi:10.1158/2159-8290.CD-24-0137
4. Przywara G, Biegańska O, Biczak E, Białoń A, Fidorowicz D, Dankowska A, et al. Recent Therapies and Biomarkers in Mucinous Ovarian Carcinoma. Cells. 2025;14(16):1232. doi:10.3390/cells14161232
5. Kawecka W, Bielak M, Urbanska K. Molecular alterations in mucinous ovarian tumors – a review. Current Issues in Pharmacy and Medical Sciences. 2024;37(3):190–4. doi:10.2478/cipms-2024-0031
6. Reyes-González JM, Quiñones-Díaz BI, Santana Y, Báez-Vega PM, Soto D, Valiyeva F, et al. Downstream Effectors of ILK in Cisplatin-Resistant Ovarian Cancer. Cancers (Basel). 2020;12(4):880. doi:10.3390/cancers12040880
7. Ackroyd SA, Goetsch L, Brown J, Houck K, Wang C, Hernandez E. Pancreaticobiliary metastasis presenting as primary mucinous ovarian neoplasm: A systematic literature review. Gynecol Oncol Rep. 2019;28:109–15. doi:10.1016/j.gore.2019.03.012
8. El Ghondakly RA, El Haddad SI, AbdelSalam MM, Nada OH, Farid RM, Farid LM. Immunohistochemical expression of <scp>SATB2</scp> and <scp>PAX8</scp> in differentiating primary from metastatic ovarian mucinous neoplasms. APMIS. 2024;132(10):706–17. doi:10.1111/apm.13449
9. Moh M, Krings G, Ates D, Aysal A, Kim GE, Rabban JT. SATB2 Expression Distinguishes Ovarian Metastases of Colorectal and Appendiceal Origin From Primary Ovarian Tumors of Mucinous or Endometrioid Type. American Journal of Surgical Pathology. 2016;40(3):419–32. doi:10.1097/PAS.0000000000000553
10. Dundr P, Bazalová B, Bártů M, Bosse T, Drozenová J, Fabian P, et al. The cytokeratin 17 expression in primary ovarian tumors has diagnostic but not prognostic significance. Virchows Archiv. 2022;481(2):201–12. doi:10.1007/s00428-022-03338-z
11. Wang F, Yang Y, Du X, Zhu X, Hu Y, Lu C, et al. Claudin18.2 as a potential therapeutic target for primary ovarian mucinous carcinomas and metastatic ovarian mucinous carcinomas from upper gastrointestinal primary tumours. BMC Cancer. 2023;23(1):44. doi:10.1186/s12885-023-10533-x
12. Van Nieuwenhuysen E, Busschaert P, Laenen A, Moerman P, Han SN, Neven P, et al. Loss of 1p36.33 Frequent in Low-Grade Serous Ovarian Cancer. Neoplasia. 2019;21(6):582–90. doi:10.1016/j.neo.2019.03.014
13. Cheasley DA. Comprehensive genomic analysis of mucinous ovarian cancer reveals unique therapeutic vulnerabilities. Journal of Clinical Oncology. 2019;37(15_suppl):5571–5571. doi:10.1200/JCO.2019.37.15_suppl.5571
14. Moujaber T, Etemadmoghadam D, Mapagu C, Kennedy C, Chiew YE, Kan C, et al. Abstract 2584: Mutations in low-grade serous ovarian cancer and response to *BRAF* and *MEK* inhibitors. Cancer Res. 2018;78(13_Supplement):2584–2584. doi:10.1158/1538-7445.AM2018-2584
15. Jarratt A, Polidano J, Scott CL, Barker HE. Genomics of ovarian cancers and the potential of precision medicine. Ther Adv Med Oncol. 2025;17. doi:10.1177/17588359251396651
16. Kim YN, Chung YS, Park E, Lee ST, Lee JY. Human epidermal growth factor receptor-2 expression and subsequent dynamic changes in patients with ovarian cancer. Sci Rep. 2024;14(1):7992. doi:10.1038/s41598-024-57515-y
17. Knigin D, Yang BW, Matanes E, Yasmeen A, Gotlieb W. EP244/#718 Poly-(ADP-ribose)-glycohydrolase localizes to the cytoplasm following neoadjuvant chemotherapy in ovarian serous carcinoma. In: E-Posters. BMJ Publishing Group Ltd; 2022. p. A148.2-A149. doi:10.1136/ijgc-2022-igcs.335
18. Chui MH, Kang EY, Kahn RM, Chiang S, Zhou Q, Iasonos A, et al. Data from Clinicopathologic Features, Molecular Landscape, and Prognostic

Implications of Ovarian Low-grade Serous Tumors with Histologic Transformation. 2025. doi:10.1158/1078-0432.c.7928410
19. De Thaye E, Van de Vijver K, Van der Meulen J, Taminau J, Wagemans G, Denys H, et al. Establishment and characterization of a cell line and patient-derived xenograft (PDX) from peritoneal metastasis of low-grade serous ovarian carcinoma. Sci Rep. 2020;10(1):6688. doi:10.1038/s41598-020-63738-6
20. Maiorano MFP, Maiorano BA, Cormio G, Loizzi V. Mucinous Ovarian Carcinoma: Integrating Molecular Stratification into Surgical and Therapeutic Management. Biomedicines. 2025;13(5):1198. doi:10.3390/biomedicines13051198
21. Gorringe KL, Wakefield M, Hunter SM, Ryland GL, Cheasley D, Anglesio MS, et al. Abstract B08: Genomics analyses of less common epithelial ovarian cancer subtypes. Clinical Cancer Research. 2016;22(2_Supplement):B08–B08. doi:10.1158/1557-3265.OVCA15-B08
22. Knigin D, Yang BW, Matanes E, Yasmeen A, Gotlieb W. EP244/#718 Poly-(ADP-ribose)-glycohydrolase localizes to the cytoplasm following neoadjuvant chemotherapy in ovarian serous carcinoma. In: E-Posters. BMJ Publishing Group Ltd; 2022. p. A148.2-A149. doi:10.1136/ijgc-2022-igcs.335
23. Chamberlain SG, Owen D, Mott HR. Membrane extraction by calmodulin underpins the disparate signalling of RalA and RalB. BioEssays. 2022;44(6). doi:10.1002/bies.202200011
24. Seibold M, Stuehmer T, Mottok A, Scholz CJ, Chatterjee M, Leich E, et al. Activated Ral and Mutated RAS Are Independent Drivers of Multiple Myeloma Cell Survival. Blood. 2018;132(Supplement 1):3217–3217. doi:10.1182/blood-2018-99-119804
25. Aldaoud N, Erashdi M, AlKhatib S, Abdo N, Al-Mohtaseb A, Graboski-Bauer A. The utility of PAX8 and SATB2 immunohistochemical stains in distinguishing ovarian mucinous neoplasms from colonic and appendiceal mucinous neoplasm. BMC Res Notes. 2019;12(1):770. doi:10.1186/s13104-019-4816-9
26. Ates Ozdemir D, Usubutun A. PAX2, PAX8 and CDX2 Expression in Metastatic Mucinous, Primary Ovarian Mucinous and Seromucinous Tumors and Review of the Literature. Pathology & Oncology Research. 2016;22(3):593–9. doi:10.1007/s12253-016-0040-2
27. Fufa TD, Baxter LL, Wedel JC, Gildea DE, Loftus SK, Pavan WJ. MEK inhibition remodels the active chromatin landscape and induces SOX10 genomic recruitment in BRAF(V600E) mutant melanoma cells. Epigenetics Chromatin. 2019;12(1):50. doi:10.1186/s13072-019-0297-2
28. Matson DR, Xu J, Huffman L, Barroilhet L, Accola M, Rehrauer WM, et al. KRAS and GNAS Co-Mutation in Metastatic Low-Grade Appendiceal Mucinous Neoplasm (LAMN) to the Ovaries: A Practical Role for Next-Generation Sequencing. American Journal of Case Reports. 2017;18:558–62. doi:10.12659/AJCR.903581
29. Wang F, Li Y, Cui Y, Zhao L. Expression of CLDN18.2, CDX2, SATB2, and PAX8 in Primary and Gastrointestinal-Derived Mucinous Ovarian Carcinoma. Advances in Obstetrics and Gynecology Research. 2025;3(3):76–83. doi:10.26689/aogr.v3i3.11130
30. Niwa K, Niwa K, Isobe M, Kyogoku R, Tanaka T. Pseudomyxoma Peritonei Arising From a Mucinous Ovarian Borderline Tumor Treated With Paclitaxel, Cisplatin, and Bevacizumab: A Case Report. Cureus. 2024. doi:10.7759/cureus.67554
31. Razia S, Nakayama K, Yamashita H, Ishibashi T, Ishikawa M, Kanno K, et al. Histological and Genetic Diversity in Ovarian Mucinous Carcinomas: A Pilot Study. Current Oncology. 2023;30(4):4052–9. doi:10.3390/curroncol30040307
32. Fort G, Arnold H, Camolotto S, Tariq R, Waters A, O'Toole K, et al. Opposing lineage specifiers induce a pro-tumor hybrid-identity state in lung adenocarcinoma. 2024. doi:10.1101/2024.12.02.626384
33. Matson DR, Xu J, Huffman L, Barroilhet L, Accola M, Rehrauer WM, et al. KRAS and GNAS Co-Mutation in Metastatic Low-Grade Appendiceal Mucinous Neoplasm (LAMN) to the Ovaries: A Practical Role for Next-Generation Sequencing. American Journal of Case Reports. 2017;18:558–62. doi:10.12659/AJCR.903581
34. Saggese P, Sellitto A, Martinez CA, Giurato G, Nassa G, Rizzo F, et al. Metabolic Regulation of Epigenetic Modifications and Cell Differentiation in Cancer. Cancers (Basel). 2020;12(12):3788. doi:10.3390/cancers12123788
35. Ruiz CF, Montal ED, Haley JA, Bott AJ, Haley JD. SREBP1 regulates mitochondrial metabolism in oncogenic *KRAS* expressing NSCLC. The FASEB Journal. 2020;34(8):10574–89. doi:10.1096/fj.202000052R
36. Wu X, Tao P, Zhou Q, Li J, Yu Z, Wang X, et al. IL-6 secreted by cancer-associated fibroblasts promotes epithelial-mesenchymal transition and metastasis of gastric cancer via JAK2/STAT3 signaling pathway. Oncotarget. 2017;8(13):20741–50. doi:10.18632/oncotarget.15119
37. Hutton JE, Wang X, Zimmerman LJ, Slebos RJC, Trenary IA, Young JD, et al. Oncogenic KRAS and BRAF Drive Metabolic Reprogramming in Colorectal Cancer. Molecular & Cellular Proteomics. 2016;15(9):2924–38. doi:10.1074/mcp.M116.058925
38. Kealey J, Düssmann H, Llorente-Folch I, Niewidok N, Salvucci M, Prehn JHM, et al. Effect of TP53 deficiency and KRAS signaling on the bioenergetics of colon cancer cells in response to different substrates: A single cell study. Front Cell Dev Biol. 2022;10. doi:10.3389/fcell.2022.893677
39. Hatipoglu A, Menon D, Levy T, Frias MA, Foster DA. Inhibiting glutamine utilization creates a synthetic lethality for suppression of ATP citrate lyase in KRas-driven cancer cells. PLoS One. 2022;17(10):e0276579. doi:10.1371/journal.pone.0276579
40. Suzuki T, Kishikawa T, Sato T, Takeda N, Sugiura Y, Seimiya T, et al. Mutant KRAS drives metabolic reprogramming and autophagic flux in premalignant pancreatic cells. Cancer Gene Ther. 2022;29(5):505–18. doi:10.1038/s41417-021-00326-4
41. Mukhopadhyay S, Goswami D, Adiseshaiah PP, Burgan W, Yi M, Guerin TM, et al. Undermining Glutaminolysis Bolsters Chemotherapy While NRF2 Promotes Chemoresistance in KRAS-Driven Pancreatic Cancers. Cancer Res. 2020;80(8):1630–43. doi:10.1158/0008-5472.CAN-19-1363
42. Pupo E, Avanzato D, Middonti E, Bussolino F, Lanzetti L. KRAS-Driven Metabolic Rewiring Reveals Novel Actionable Targets in Cancer. Front Oncol. 2019;9. doi:10.3389/fonc.2019.00848
43. Zhao H, Wu S, Li H, Duan Q, Zhang Z, Shen Q, et al. ROS/KRAS/AMPK Signaling Contributes to Gemcitabine-Induced Stem-like Cell Properties in Pancreatic Cancer. Mol Ther Oncolytics. 2019;14:299–312. doi:10.1016/j.omto.2019.07.005
44. Brunelli L, Caiola E, Marabese M, Broggini M, Pastorelli R. Comparative metabolomics profiling of isogenic KRAS wild type and mutant NSCLC cells in vitro and in vivo. Sci Rep. 2016;6(1):28398. doi:10.1038/srep28398
45. Gillis K, Orellana WA, Wilson E, Parnell TJ, Fort G, Dadzie HE, et al. FoxA1/2-dependent epigenomic reprogramming drives lineage switching in lung adenocarcinoma. 2023. doi:10.1101/2023.10.30.564775
46. Gore M, Hackshaw A, Brady WE, Penson RT, Zaino R, McCluggage WG, et al. An international, phase III randomized trial in patients with mucinous epithelial ovarian cancer (mEOC/GOG 0241) with long-term follow-up: and experience of conducting a clinical trial in a rare gynecological tumor. Gynecol Oncol. 2019;153(3):541–8. doi:10.1016/j.ygyno.2019.03.256
47. Nasioudis D, Gysler S, Latif N, Ko E, Cory L, Giuntoli R, et al. Molecular profiling of mucinous ovarian carcinoma reveals actionable mutations and a unique genomic profile (1282). Gynecol Oncol. 2023;176:S176–7. doi:10.1016/j.ygyno.2023.06.188
48. Wei D, Wang L, Zuo X, Maitra A, Bresalier RS. A Small Molecule with Big Impact: MRTX1133 Targets the KRASG12D Mutation in Pancreatic Cancer. Clinical Cancer Research. 2024;30(4):655–62. doi:10.1158/1078-0432.CCR-23-2098
49. Isermann T, Sers C, Der CJ, Papke B. KRAS inhibitors: resistance drivers and combinatorial strategies. Trends Cancer. 2025;11(2):91–116. doi:10.1016/j.trecan.2024.11.009
50. Feng J, Xiao X, Lian Z, Zhang A, Pang X. Pan-KRAS inhibition: unlocking broad-spectrum targeted therapy for KRAS-mutant cancers. Cancer Biol Med. 2026;1–7. doi:10.20892/j.issn.2095-3941.2025.0612
51. Bartl T, Cacsire Castillo-Tong D. Targeting RAS–RAF–MEK–ERK signaling in mucinous ovarian cancer: a translational evidence synthesis and clinical framework. International Journal of Gynecological Cancer. 2026;104485. doi:10.1016/j.ijgc.2026.104485
52. Sullivan RJ, Infante JR, Janku F, Wong DJL, Sosman JA, Keedy V, et al. First-in-Class

ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study. Cancer Discov. 2018;8(2):184–95. doi:10.1158/2159-8290.CD-17-1119

53. Schram AM, Boni V, Adjei AA, Olszanski AJ, Vieito M, Francis JH, et al. A phase I, first-in-human trial of KO-947, an ERK1/2 inhibitor, in patients with advanced solid tumors. ESMO Open. 2025;10(3):104300. doi:10.1016/j.esmoop.2025.104300

54. Kalev P, Hyer ML, Gross S, Konteatis Z, Chen CC, Fletcher M, et al. MAT2A Inhibition Blocks the Growth of MTAP-Deleted Cancer Cells by Reducing PRMT5-Dependent mRNA Splicing and Inducing DNA Damage. Cancer Cell. 2021;39(2):209-224.e11. doi:10.1016/j.ccell.2020.12.010

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