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OVERCOMING CHEMORESISTANCE IN MUCINOUS ADENOCARCINOMA: THE IMPACT OF TUMOR MICROENVIRONMENT AND GENETIC ALTERATIONS

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ABSTRACT
Background: Mucinous adenocarcinoma (MAC) is a rare, aggressive subtype of adenocarcinoma, distinguished by excessive extracellular mucin production. This feature impairs drug penetration and contributes to poor chemotherapy response and chemoresistance. Genetic mutations (e.g., KRAS, BRAF, PI3K/AKT), epithelial-to-mesenchymal transition (EMT), alterations in the tumor microenvironment, and mucin barriers contribute to this resistance. ***Objective:*** This narrative review aims to comprehensively summarize the molecular and microenvironmental mechanisms behind chemoresistance in MAC and highlight emerging therapeutic strategies to overcome it. **Results:** Chemoresistance in MAC arises from oncogenic signaling, immune evasion, hypoxia, and mucin-mediated drug exclusion. Promising approaches include mucolytic agents, small-molecule inhibitors, immune checkpoint inhibitors, RNA-based therapies, and nanoparticle-assisted drug delivery. Precision medicine, which utilizes genomic and transcriptomic profiling, is advancing individualized treatment; however, clinical translation remains limited. ***Conclusion:*** Resistance in MAC stems from both genetic and microenvironmental factors. Understanding these mechanisms is crucial for developing more effective, personalized therapies to improve patient outcomes. Future efforts should focus on validating novel therapies through clinical trials, discovering predictive biomarkers, and exploring tumor heterogeneity with multi-omics technologies. Integrating targeted therapies with advanced delivery systems may offer significant advances in treating chemoresistant MAC.

INTRODUCTION

Cancer is a heterogeneous disease marked by uncontrolled proliferation, invasion, and metastasis, originating from various tissues and organs with distinct histological and molecular features [1,2]. Mucinous adenocarcinoma (MAC), or colloid carcinoma, is a distinct adenocarcinoma subtype, defined by over 50% extracellular mucin containing dispersed malignant epithelial cells. Tumors with less than 50% mucin are classified as adenocarcinomas with a mucinous component. Mucin, a high-

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molecular-weight glycoprotein composed of oligosaccharides linked to a core protein, is physiologically secreted by epithelial cells for lubrication and barrier protection [3]. It stores bioactive molecules important in wound healing and inflammation [4]. Dysregulated mucin expression in adenocarcinomas promotes immune evasion and tumor progression through altered signaling [3, 5], thereby disrupting cell adhesion and facilitating invasion and metastasis [6]. A related subtype, signet ring cell carcinoma (SRCC), exhibits intracellular mucin accumulation, which causes the nucleus to be pushed peripherally, resulting in a characteristic signet ring appearance [7]. SRCCs often coexist with MACs in gastrointestinal malignancies, distinguished histologically by mucin localization [2]. Epidemiologically, MAC accounts for 10–20% of colorectal and gastric adenocarcinomas, often presenting at advanced stages with poor prognosis and lower five-year survival rates compared to non-mucinous counterparts [8]. Although most prevalent in colorectal cancer (10–15%) [9], MAC also occurs in the lung [13], ovary [12], stomach [11], and breast [10] [Figure 1]. Despite organ-specific differences, MACs share standard histopathological and molecular features, including frequent mutations in the KRAS, BRAF, and PI3K/AKT pathways, as well as mucinous barriers that impede drug penetration. This review adopts a histology-driven, cross-cancer perspective to examine shared chemoresistance mechanisms in MAC and to evaluate emerging therapeutic strategies.

By focusing on molecular similarities rather than organ origin, we aim to bridge knowledge gaps and identify unified intervention strategies. While clinicopathological characteristics of MACs are increasingly reported [14–16], gaps remain regarding incidence trends and prognostic outcomes, with conflicting findings on survival rates [17,18]. In mucinous breast cancer, however, outcomes are consistently better than in infiltrating ductal carcinoma [19,20]. Debates persist regarding the impact of tumor site on MAC-specific survival, underscoring the need for molecularly targeted therapeutic strategies across various organs. Alternatives to standard treatments, such as fluorouracil-based chemotherapy, are being explored [21,22]. Phase II trials have shown promising responses with irinotecan and mitomycin in platinum-refractory mucinous carcinoma [23,24], and oxaliplatin combined with 5-fluorouracil has demonstrated clinical benefit in heavily pretreated ovarian cancer patients [25]. Preclinical studies in mucinous ovarian cancer cell lines further support the potential synergy of these regimens [21]. Excessive mucin production creates a hypoxic microenvironment that fosters metastasis and chemotherapy resistance. Given MAC's frequent late diagnosis and poor standard therapy response, innovative treatment strategies are crucial. This review focuses on the fundamental mechanisms of chemoresistance in MAC, highlighting emerging therapeutic approaches, including immunotherapy, targeted therapies, nanomedicine-based drug delivery, and combination strategies. It also discusses future directions for developing individualized treatments for patients with MAC.

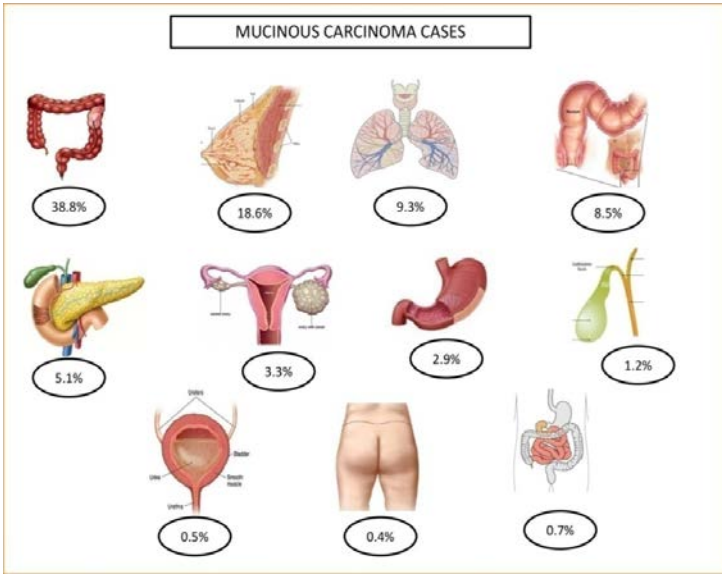

Figure 1: Organs and mucinous carcinoma cases

MECHANISM OF CHEMORESISTANCE

While this review emphasizes shared chemoresistance mechanisms in mucinous adenocarcinoma (MAC), it also notes organ-specific differences. Colorectal MAC often features KRAS/BRAF mutations and MSI; pancreatic MAC commonly exhibits KRAS and TP53 co-mutations; breast MAC is usually hormone receptor-positive with a better prognosis; and lung MAC, though rare, may involve ALK or EGFR alterations. Mucin gene expression also differs, with MUC2 predominant in colorectal and pancreatic MAC, and MUC5AC more frequent in breast and lung MAC. These distinctions are addressed where relevant to maintain a comprehensive yet focused analysis.

Tumor Microenvironment (TME)

Mucin as a Physical and Biochemical Barrier

By creating a physical and biochemical barrier that encourages tumor survival and resistance to treatment, mucin plays a crucial role in shaping the tumor microenvironment [26]. When mucin

is produced in excess, especially in mucinous adenocarcinoma, a thick extracellular matrix forms around the cancer cells, physically blocking the penetration of medication and decreasing the effectiveness of chemotherapy. In addition to restricting drug diffusion, this mucin-rich environment offers structural support that improves tumour cell adherence, proliferation, and invasion [27]. Beyond its physiological function, mucin plays an active role in biochemical signaling by interacting with critical oncogenic pathways, such as the PI3K/AKT, Wnt/β-catenin, and EGFR pathways, which promote tumor growth and resistance mechanisms [28]. By hiding tumor-associated antigens and preventing immune cell recognition, several mucins, including MUC1, MUC4, and MUC16, aid in immune evasion. Furthermore, mucin controls the release of growth factors and cytokines, creating a hypoxic and immunosuppressive environment that increases tumour aggressiveness [29]. To overcome chemoresistance and enhance treatment outcomes in mucinous adenocarcinoma, mucin-targeted therapies, including mucolytic agents, inhibitors of mucin production, and nanoparticle-based drug delivery systems, are being investigated.

Hypoxia

A variety of neoplastic cells are affected by hypoxia, a key factor in tumor therapeutic resistance [30] [Figure 2]. HIF-1 inactivation amplifies the inhibitory effects of etoposide and carboplatin in mouse embryonic fibroblasts [31]. Overexpression of HIF-1α in several solid cancers, including breast, colon, gastric, lung, ovarian, pancreatic, prostate, and renal malignancies, results in a poor prognosis [32]. High HIF-1α expression is a survival signal in various studies, and it is used therapeutically to evaluate prognosis in pancreatic cancer [33]. Immunohistochemical analysis revealed elevated expression of VEGF, HIF-1α, and glucose transporter protein 1 in pancreatic cancer tissues; Cox regression analysis validated HIF-1α as an independent prognostic predictor. The prognostic relevance of HIF-1α was demonstrated by the markedly shorter survival rates of patients with increased levels of this protein [34]. In addition, hypoxia causes an acidic tumour microenvironment (TME), which in turn causes p53 mutations, decreased apoptosis, increased P-glycoprotein (P-gp) activity, and multidrug resistance (MDR) through ion trapping. The intracellular accumulation of pH-dependent medications is impacted by the acidic extracellular pH, which lowers the effectiveness of chemotherapy. Benzoate mustard was shown to be 2.3 times more effective than doxorubicin; however, sodium bicarbonate alkalinisation decreased the potency of nitrogen mustard [35]. Despite being unaltered at the mRNA level, P-gp activity dramatically increased under acidic and hypoxic environments, which reduced the lethality of drugs [36]. Furthermore, immune cell infiltration and genomic instability induced by hypoxia promote tumor resistance and malignancy [37]. A promising strategy to combat hypoxia-induced resistance and improve the effectiveness of chemotherapy is the use of targeted nanoparticles [38]. Due to its role in tumour growth, HIF-1 overexpression is recognized as a significant contributor to treatment resistance in various malignancies, including head and neck, lung, breast, prostate, and pancreatic cancers.

Hypoxia in MAC vs. Non-Mucinous Tumors

In MAC, the dense mucin matrix creates a more hypoxia-prone microenvironment than in non-mucinous adenocarcinomas. The viscous extracellular mucin impedes oxygen diffusion, exacerbating local hypoxia. This persistent hypoxia activates HIF-1α more robustly, leading to increased expression of VEGF, EMT markers, and drug efflux pumps, enhancing chemoresistance.

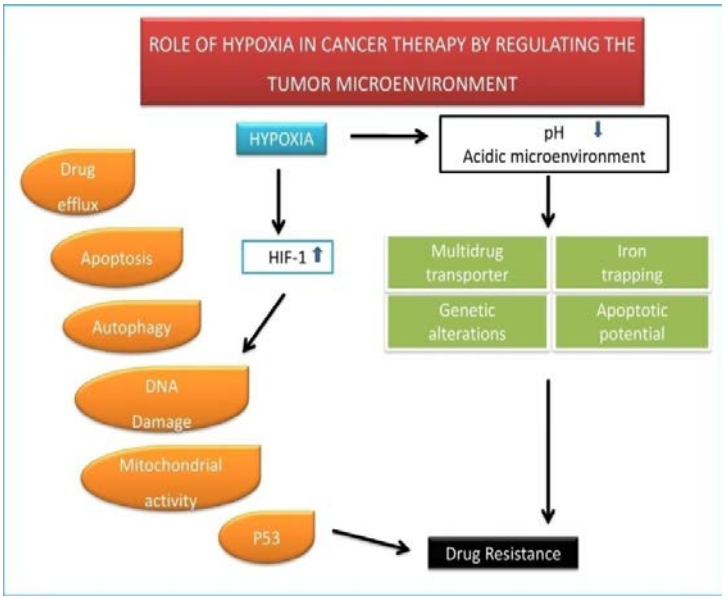

Figure 2: Role of Hypoxia in Cancer Therapy Resistance

Role of CAFs and Stromal Interactions in Tumor Progression

Cancer-associated fibroblasts (CAFs) promote adenocarcinoma growth and chemotherapy resistance by remodeling the tumour microenvironment through extracellular matrix (ECM) deposition, cytokine release, and immune suppression [Figure 3]. They enhance resistance by inducing epithelial-mesenchymal

transition (EMT), activating PI3K/Akt and Wnt/β-catenin pathways, and increasing stromal stiffness and hypoxia. Targeting CAFs through depletion, reprogramming, or signalling inhibition presents strategies to overcome chemoresistance. In pancreatic ductal adenocarcinoma (PDAC), CAFs and cancer cells mutually stimulate growth and differentiation. PDAC cell supernatants promote pancreatic stellate cell (PSC) proliferation and ECM production [39], while co-injection of PSCs with PDAC cells accelerates tumour growth, and CAF-conditioned media enhances PDAC cell migration and proliferation [40]. In 3D cultures on collagen and Matrigel, PSCs modulate adhesion molecule expression, increasing invasiveness, downregulating E-cadherin, and upregulating β-catenin [41]. Standard co-cultures show downregulation of epithelial markers (E-cadherin, cytokeratin 19, β-catenin), upregulation of mesenchymal markers (vimentin, snail), and enhanced migration [42]. In an orthotopic xenograft model, co-injected PSCs followed PDAC cells to metastatic sites, indicating a role in metastasis [43].

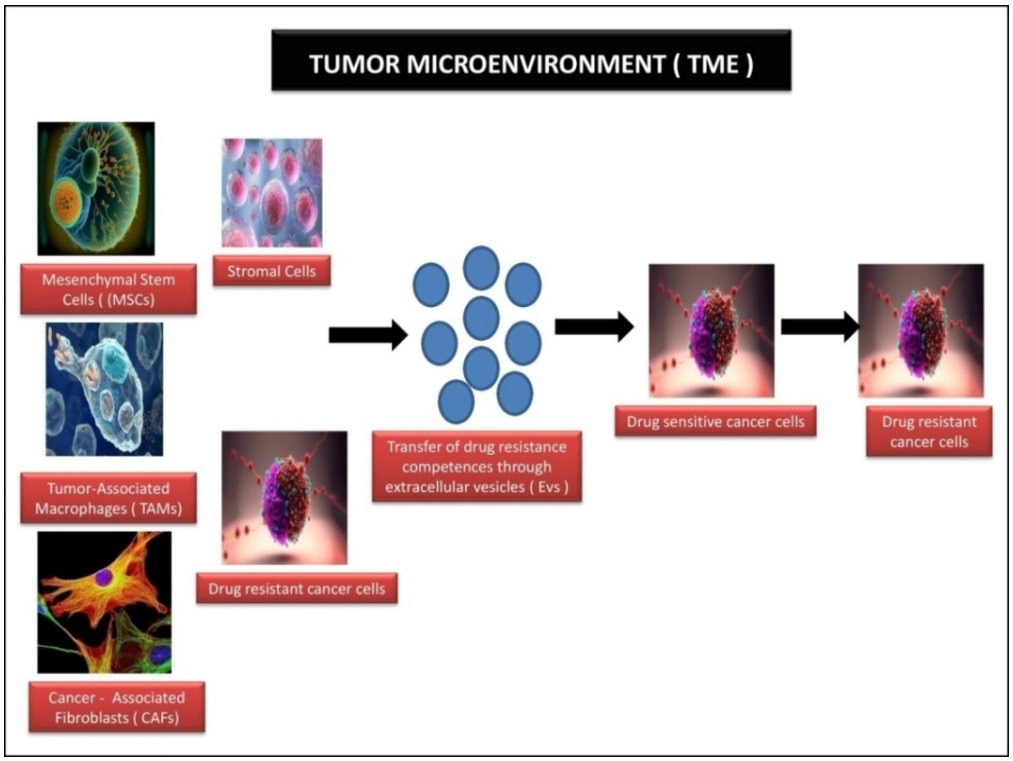

Figure 3: Role of Tumor Microenvironment in Drug Resistance

GENETIC ALTERATIONS

KRAS, BRAF, PIK3/AKT, TP53 mutations

Mutations in key tumour suppressor and oncogene genes, particularly KRAS and TP53, are frequently found in mucinous adenocarcinoma. KRAS mutations drive unchecked proliferation and oncogenic signaling, while TP53 mutations impair genomic stability and DNA repair, thereby accelerating tumor growth. Additional mutations in GNAS, BRAF, and SMAD4 also influence tumour behaviour and treatment outcomes. Understanding these molecular changes is essential for targeted therapies. TP53 encodes p53, a crucial tumor suppressor that maintains genomic integrity [44]. TP53 mutations are major drivers of lung carcinogenesis [45, 46] and are more prevalent than EGFR or KRAS mutations in LUAD [46], with similar mutation rates observed across Western and Asian patients [45]. TP53 mutations, arising from genetic or epigenetic errors [46], lead to an increased somatic mutation burden [47] and correlate positively with KRAS mutations in LUAD [48], thereby enhancing neoantigen production and inflaming the tumour microenvironment, which theoretically favours PD-1/PD-L1 inhibition [49]. However, KRAS/TP53 co-mutant LUADs may not consistently benefit from immune checkpoint inhibitors (ICIs) alone [50], underscoring the need for further investigation. In mucinous adenocarcinoma (MAC), TP53 mutations frequently co-occur with KRAS mutations, synergistically driving mucin production, EMT, and CSC-like traits. TP53 loss also dysregulates mucin genes (MUC2, MUC5AC), contributing to the mucinous phenotype unique to MAC. Epigenetic regulators, including DNA methylation and histone modifications, drive treatment resistance in mucinous

adenocarcinoma [Figure 4]. Aberrant DNA methylation, such as the hypermethylation of MLH1 and CDKN2A, promotes chemotherapy resistance, while hypomethylation activates oncogenes. Histone modifications alter chromatin structure, influencing survival pathways and resistance to apoptosis. Early PDAC lesions (PanIN-1A) exhibit DNA methylation changes [51]. DNA methyltransferases (DNMTs) mediate gene silencing by methylating CpG islands [52]. Overexpressed genes, such as SERPINB5, CLDN4, and S100P, affect adhesion, proliferation, and differentiation [53]. Histone acetylation, methylation, phosphorylation, and ubiquitylation regulate chromatin accessibility and transcription [54]. Though limited by small cohorts, combining gemcitabine with HDAC inhibitors shows synergistic effects [55].

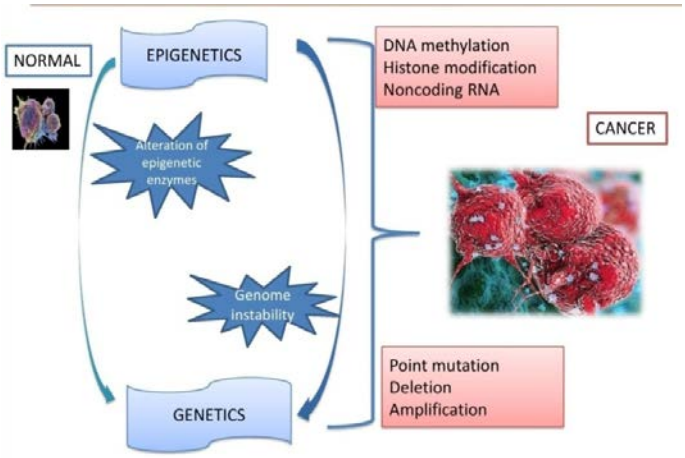

Figure 4: Epigenetic Regulation and Cancer

The MAPK (RAS/RAF/MEK/ERK) and PI3K/AKT/mTOR pathways are major contributors to drug resistance in mucinous adenocarcinoma [Figure 5]. PI3K/AKT/mTOR, often activated by PIK3CA mutations or PTEN loss, enhances survival and proliferation, while MAPK, commonly driven by KRAS mutations, promotes tumour growth and adaptive feedback. Crosstalk between these pathways, immune evasion, and EMT further amplify resistance, highlighting the need for combination therapies. In pancreatic cancer (PC), pathways such as the PI3K/AKT/mTOR, Notch, Wnt, and Hedgehog pathways are critical [56,57], with frequent overexpression of the PI3K/AKT/mTOR pathway [58]. AKT1, PIK3CA mutations, and PTEN loss are common [59], with PTEN loss observed in 25–70% of cases [60]. KRAS mutations drive PI3KCA overexpression [61]. AKT1 promotes proliferation in 10–20% of PDAC patients [61], while AKT2 and AKT3 enhance invasion and migration [62]. The PI3K/AKT/mTOR pathway regulates key processes, including motility, metabolism, and proliferation [63, 64], and influences transcription and translation through phosphorylation [65]. AKT also regulates Bcl-XL and NF-kB, promoting survival, making it an important therapeutic target in PDAC [66].

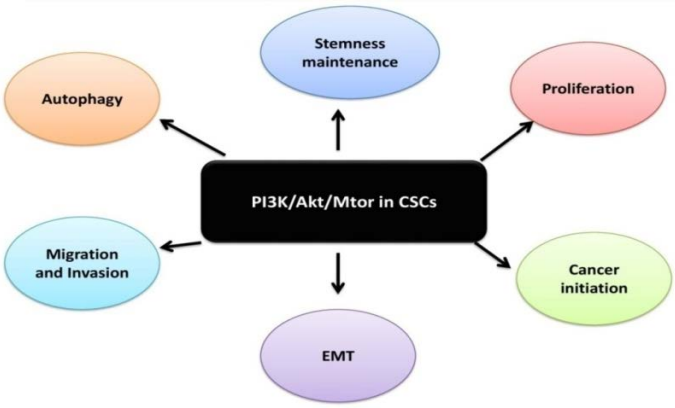

Figure 5: Key signaling pathways (e.g., PI3K/AKT/mTOR, MAPK) in drug resistance

CANCER STEM CELLS (CSCS)

Drug efflux mechanisms

The upregulation of drug efflux pumps, particularly ATP-binding cassette (ABC) transporters, is a significant contributing factor to treatment resistance in mucinous adenocarcinoma [Figure 6]. ABC transporters, such as P-glycoprotein (ABCB1), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP/ABCG2), actively transport chemotherapy drugs out of cancer cells. This lowers intracellular drug concentrations, thereby diminishing the effectiveness of treatment.

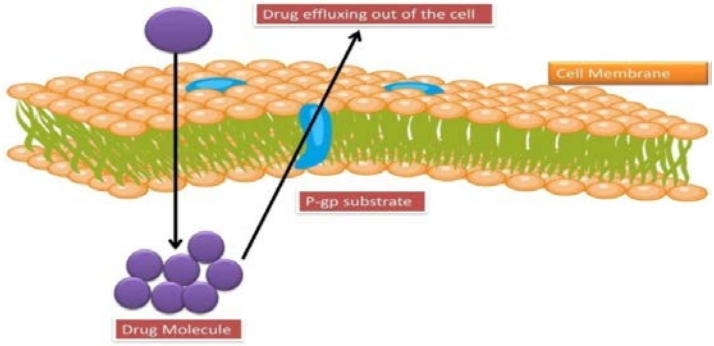

Figure 6: Overexpression of drug efflux pumps (ABC transporters)

This process is crucial in determining resistance to targeted medicines and platinum-based chemotherapy. ABC transporters are a promising target for combination therapy aimed at

overcoming drug resistance in mucinous adenocarcinoma (as listed in Table 1), as their overexpression is frequently regulated by oncogenic signaling pathways and epigenetic changes [67]. Cancer stem cells (CSCs) drive tumour heterogeneity, therapy resistance, metastasis, and recurrence in adenocarcinomas [Figure 7]. Their self-renewal and differentiation enable them to survive against radiation, chemotherapy, and targeted therapies. Resistance mechanisms include enhanced drug efflux (ABCB1, ABCG2), activation of survival pathways (PI3K/AKT, Wnt/β-catenin, Notch), resistance to apoptosis, and quiescence, which limit sensitivity to proliferative-targeted treatments. Targeting CSCs is crucial for enhancing long-term outcomes. In 1997, Bonnet and Dick identified a leukemia subpopulation (CD34+/CD38−) that initiates tumor growth in NOD/SCID mice [68]. CSCs were later found across various solid tumours [69], with clonogenic glioma cells demonstrated in vitro in 2002 [70] and CD44+ CD24−/lowLineage− breast cancer cells shown in vivo in 2003 [69]. CSCs have since been isolated from ovarian, breast, brain, lung, liver, pancreatic, colon, and melanoma cancers, among others [72].

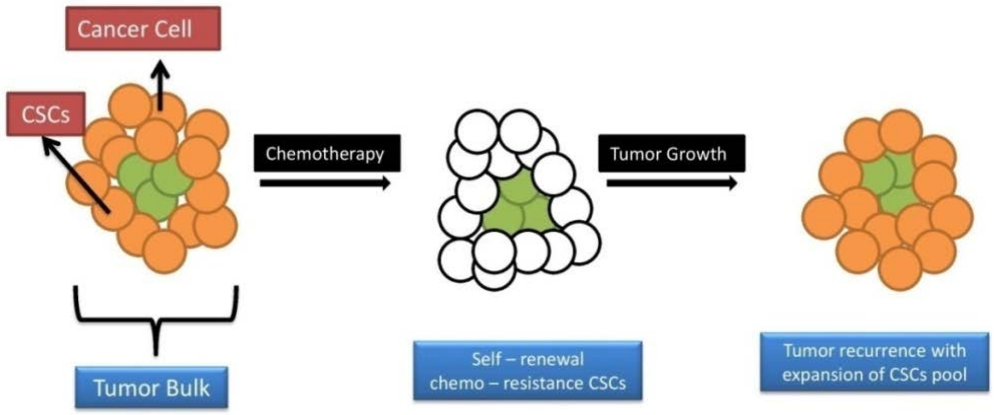

Figure 7: Role of cancer stem cells in tumor growth

EMERGING STRATEGIES TO OVERCOME CHEMO-RESISTANCE

Targeted Therapies

Targeted inhibitors against overexpressed or mutant oncogenes offer promising strategies to overcome drug resistance in mucinous adenocarcinoma. KRAS G12C mutations, common in lung and colorectal MACs, are targeted by KRAS inhibitors (sotorasib, adagrasib) [73]. PI3K/AKT/mTOR inhibitors (alpelisib, everolimus) counteract survival signalling from PTEN loss or PIK3CA mutations [74], while MEK inhibitors (trametinib, selumetinib) suppress MAPK pathway-driven tumour growth [75]. EGFR-targeted therapies, including monoclonal antibodies (cetuximab, panitumumab) & TKIs (osimertinib, erlotinib), are effective against EGFR-mutant MACs [76]. Combining these inhibitors with immunotherapy or chemotherapy enhances efficacy and supports personalized treatment strategies. In mucinous ovarian cancer, oncogenic drivers such as KRAS and BRAF mutations, EGFR and MYC amplifications, and ERBB2 amplification have been implicated [77, 78, 80]. BRAFV600E mutations aid in diagnosis and prognosis across several cancers [77, 83, 84, 86], while harmful KRAS mutations occur in 60–70% of cases [77]. ERBB2 amplification and KRAS mutations may co-occur in ~11% of cases, though c-MYC amplification appears mutually exclusive [80,83,85]. Monoclonal antibodies and small-molecule inhibitors further target tumour-promoting pathways. VEGF inhibitors (bevacizumab, ramucirumab) and EGFR inhibitors (cetuximab, panitumumab) block surface receptors [76]. HER2-targeted therapies (trastuzumab, pertuzumab) improve outcomes in HER2-overexpressing tumours, especially when combined with chemotherapy or immunotherapy. Trastuzumab is well-tolerated and effective as a first-line or post-chemotherapy agent [86], with combination therapy improving response rates, progression-free time, and overall survival in HER2+ cancers [87–89].

COMBINATION THERAPY APPROACHES

Because it provides a novel method that can improve treatment efficacy, reduce toxicity, and potentially overcome medication resistance, the use of phytochemicals or plant extracts in conjunction with complementary therapy for cancer treatment is highly regarded. It may be able to improve lung cancer patient outcomes and open the door for future treatment options that are more individualised and effective by utilising the special

qualities of natural substances and their capacity to enhance the effects of chemotherapeutic medications [90]. In the treatment of lung cancer, the use of natural substances in conjunction with traditional chemotherapy medications has demonstrated encouraging outcomes. Natural substances have been shown in preclinical research to increase the anticancer activity of chemotherapeutic medications by sensitising lung cancer cells to them [91,92]. Furthermore, the potential of natural agents to overcome drug resistance when paired with traditional chemotherapy has been emphasised, underscoring their translational importance in cancer treatment [93].

Table 1. Chemoresistance mechanisms in mucinous adenocarcinoma

Mechanism	Therapeutic Agent/Strategy	Status	Limitations
Mucin barrier	Mucolytics	Preclinical	Limited penetration in vivo; short systemic half-life
Hypoxia-driven resistance	HIF-1α inhibitors, hypoxia-activated prodrugs	Preclinical/ Clinical	Tumor heterogeneity; limited clinical efficacy so far
KRAS/BRAF mutations	KRAS G12C inhibitors, BRAF inhibitors	Clinical (specific cases)	Resistance mutations; efficacy varies by organ type
TP53 dysfunction	p53 reactivators	Clinical trials	Limited efficacy in mucinous tumors
EMT & stemness	TGF-β inhibitors, CSC-targeted therapies	Preclinical	Off-target toxicity; poor CSC specificity
Drug efflux (ABC transporters)	ABC transporter inhibitors	Preclinical	High toxicity; poor clinical translation
Immune evasion	Immune checkpoint inhibitors (PD-1, CTLA-4 blockers)	Clinical	Less effective in MAC due to immunosuppressive microenvironment
Gene editing	CRISPR-Cas9, RNA interference	Preclinical	Delivery challenges, off-target effects

Potential new treatment approaches for lung cancer may be found by investigating and comprehending the synergistic interactions between natural substances and traditional chemotherapeutic medications [94]. The synergistic interaction of plants, plant-derived substances, and chemotherapeutic drugs has been the subject of numerous investigations. For example, when paired with the chemotherapies sorafenib, afatinib, cisplatin, paclitaxel, gemcitabine, and endoxifen, the phytocompound emodin exhibited synergistic effects, resulting in improved anticancer activity against lung adenocarcinoma and non-small cell lung cancer [90]. A multimodal approach is essential for treating mucinous adenocarcinoma to prevent compensatory pathways that promote tumour growth and drug resistance. Although targeted therapies against drivers like EGFR, KRAS, & PI3K/AKT/mTOR are effective, they often trigger adaptive resistance through alternative survival mechanisms. Combining radiation, targeted therapies, chemotherapy, and immunotherapy helps overcome these escape routes [Figure 8]. In colorectal cancer (CRC), targeted therapies, especially angiogenesis inhibitors like bevacizumab, have become critical [95]. The combination of encorafenib and anti-EGFR agents, such as cetuximab, shows promise for BRAF V600E-mutated tumors by disrupting multiple growth pathways [96]. Immunotherapies targeting CTLA-4 (ipilimumab) and PD-1 (pembrolizumab, nivolumab) enhance T-cell responses, particularly benefiting MMR-deficient and MSI-H CRC cases [97]. Numerous FDA-approved treatments now target molecular alterations in CRC. RAS wild-type tumors respond to anti-EGFR antibodies (cetuximab, panitumumab), and HER2-targeted therapies, such as trastuzumab, are under investigation for HER2-positive CRC.

Immunotherapies, such as nivolumab and pembrolizumab, are effective for patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors. Encorafenib plus cetuximab offers a vital alternative for BRAF V600E-mutant CRC, traditionally treated with chemotherapy [98]. However, therapeutic resistance remains a challenge, prompting exploration of combination therapies. The SUNLIGHT Phase 3 trial evaluates bevacizumab with trifluridine/tipiracil (FTD/TPI) to extend survival in resistant CRC, with FTD/TPI offering better tolerability compared to irinotecan. Emerging treatments, such as fruquintinib, a selective VEGFR inhibitor, have shown promising results in studies like FRESCO-2 [99].

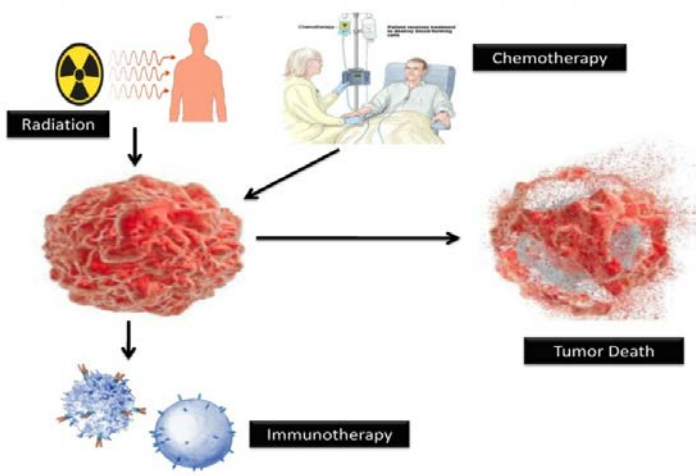

Figure 8: Role of Radiotherapy, Chemotherapy and Immunotherapy in Cancer Treatment

IMMUNOTHERAPY

Immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1, anti-CTLA-4)

Examples of immune checkpoint inhibitors (ICIs) that have demonstrated promise as treatments for mucinous adenocarcinoma include anti-PD1 (nivolumab, pembrolizumab) [100], anti-PD-L1 (atezolizumab, durvalumab) [101], and anti-CTLA-4 (ipilimumab, tremelimumab) [102], particularly in tumours with high tumour mutational burden (TMB), microsatellite instability (MSI-H), or expression of PD-L1. By providing T cells with inhibitory signals, these drugs enhance the immune system's capacity to recognise and eliminate cancer cells. Tumor-infiltrating lymphocytes (TILs) and PD-L1 upregulation in mucinous adenocarcinoma suggest the potential benefits of PD-1/PD-L1 inhibition. Furthermore, tumors with defective mismatch repair (dMMR) have a higher neoantigen load, which increases their sensitivity to anti-PD-1 medications, such as pembrolizumab. Immune responses are further enhanced by anti-CTLA-4 therapy (ipilimumab), which is frequently used in conjunction with PD-1 inhibitors to improve T-cell priming and activation. Combination techniques with chemotherapy, targeted therapy, or other immunomodulators are being investigated to enhance efficacy and overcome resistance in mucinous adenocarcinoma, despite ICIs having demonstrated lasting responses in a small number of patients.

Adoptive T-cell therapies (e.g., CAR-T cells)

Adoptive T-cell therapies, particularly chimeric antigen receptor T-cell (CAR-T) therapy, offer a promising immunotherapeutic approach for patients with mucinous adenocarcinoma who are unresponsive to conventional treatments [Figure 9]. CAR-T cells are engineered to recognize tumor-specific antigens, enhancing immune targeting of cancer cells. Potential targets include mesothelin, EGFR, MUC1, and HER2, commonly overexpressed in mucinous tumors. HER2-directed CAR-T therapy has shown success in HER2-positive adenocarcinomas, while EGFR- and MUC1-targeted CAR-T cells are under investigation for broader applications. TCR-T and tumor-infiltrating lymphocyte (TIL) therapies are also being explored to target mutant neoantigens in high-TMB tumors [103]. Despite promising preclinical outcomes, challenges such as tumor heterogeneity, immunosuppressive microenvironments, and CAR-T cell exhaustion remain. Combination strategies with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) or cytokine support (e.g., IL-15, IL-21) are being evaluated to enhance therapeutic efficacy. Ongoing clinical trials will further define the role of adoptive T-cell and CAR-T therapies in mucinous adenocarcinoma [104].

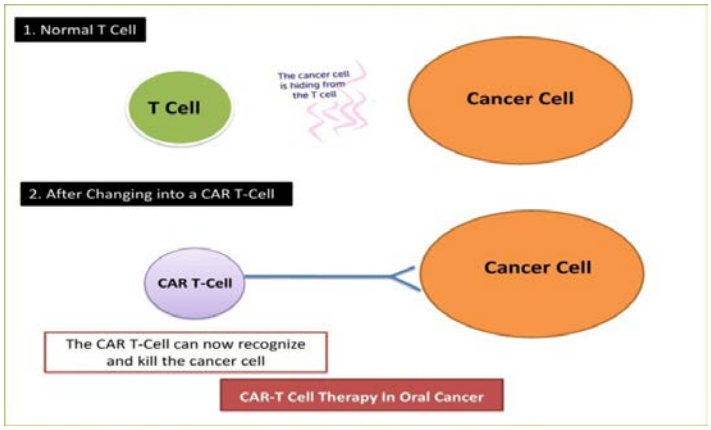

Figure 9: CAR-T therapy in mucinous adenocarcinoma

Cancer vaccines

Because they encourage the immune system to identify and target tumour cells, tumor-associated antigens (TAAs) are essential in the development of cancer vaccines for mucinous adenocarcinoma. The glycoprotein MUC1, which is abundantly expressed in mucinous tumours, is one of the TAAs that dendritic cell and peptide-based vaccines target. Similarly, CEA-based vaccines have been investigated for carcinoembryonic antigen (CEA), which is frequently overexpressed in gastrointestinal mucinous adenocarcinomas. Furthermore, KRAS mutation-specific vaccines (e.g., targeting G12D and G12V mutations) aim to enhance immune responses in KRAS-driven tumors, while HER2-targeted vaccines have shown promise in HER2-positive mucinous adenocarcinomas. To induce long-lasting anti-tumor immunity, various

vaccination platforms are being investigated, including dendritic cell vaccines, mRNA vaccines, peptide vaccines, and viral vector-based vaccines. By combating immune evasion, these vaccines may be even more effective when used in conjunction with immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4) or adoptive T-cell therapy. These tactics are still being investigated in ongoing clinical trials with the goal of enhancing survival rates for patients with mucinous adenocarcinoma [105].

Nanotechnology-Based Drug Delivery

To improve drug delivery in mucinous adenocarcinoma, the use of nanoparticles, liposomes, and polymeric systems has shown promise in addressing issues such chemoresistance, rapid drug clearance, and poor drug penetration [Figure 10]. Through the increased permeability and retention (EPR) effect, drug carriers based on nanoparticles, including as liposomes, polymeric nanoparticles, and inorganic nanoparticles, enhance drug stability, bioavailability, and tumor-specific accumulation. Chemotherapeutic drugs are encapsulated in liposome-based formulations (such as liposomal doxorubicin and irinotecan) [106] to improve tumour targeting and lessen toxicity. Therapeutic efficacy is increased by the regulated and sustained drug release provided by polymeric nanoparticles (e.g., PLGA, chitosan-based systems)[107]. Furthermore, active targeting in mucinous adenocarcinoma is made possible by functionalised nanoparticles with ligands that target tumor-associated antigens (such as MUC1, EGFR, and HER2) [108]. Stimuli-responsive nanocarriers, activated by temperature, pH, or enzymes, ensure targeted medication release in the tumor microenvironment, thereby enhancing the accuracy of treatment. As a potential remedy for the adverse effects of chemotherapy, nanotechnologies may prove highly beneficial in addressing nonspecific drug release through both passive and active approaches [109]. Bioadhesion is a crucial strategy for enhancing drug residence time and targeted delivery. Mucosal secretion, mucosal microbiota, low absorptive surface area, and mucosal thickness are all crucial considerations for developing a mucoadhesive system with the best potential therapeutic response [110].

Both natural and synthetic polymers have been investigated as potential drug delivery systems for treating bladder cancer, owing to their diverse mucoadhesive properties. The bulk of current research, however, still requires additional in vitro and in vivo tests. Furthermore, because in vitro and in vivo studies only provide a limited amount of information, clinical trials are necessary to evaluate treatment effects and safety-related issues. Improvements in these areas of innovative and sophisticated drug delivery techniques will lead to better bladder cancer treatment [111]. When combined with nanoparticle-based drug delivery, chemotherapy, immunotherapy, and targeted therapy may greatly improve treatment outcomes and overcome resistance in mucinous adenocarcinoma.

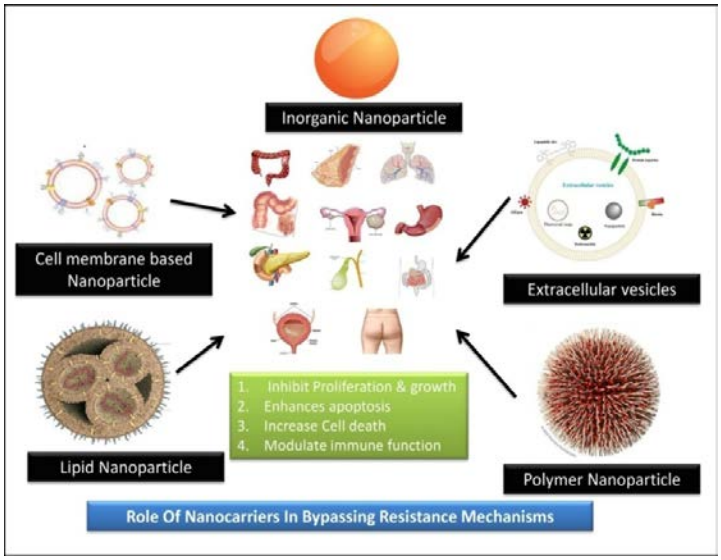

Figure 10: Role of nanocarriers in Bypassing Resistance mechanisms

Tumor-specific delivery systems

Overcoming the molecular and physical barriers of the tumour microenvironment (TME) is crucial for enhancing drug delivery and therapeutic efficacy in mucinous adenocarcinoma. The dense extracellular matrix (ECM), rich in mucin, collagen, and hyaluronic acid, restricts immune infiltration and the penetration of drugs. Enzymatic degradation (e.g., hyaluronidase, mucolytic agents) and nanoparticle-based carriers improve drug diffusion. Hypoxia and immunosuppressive factors (TGF-β, IL-10) further promote resistance. Targeting hypoxia-inducible factors (HIFs) and normalizing vasculature with anti-angiogenic agents, such as bevacizumab, enhances oxygenation and delivery. Immunotherapies, including checkpoint inhibitors (anti-PD-1, anti-CTLA-4) and TME-modulating agents (CXCR4 inhibitors, TGF-β blockers), help reprogram the suppressive microenvironment. Engineered CAR T and CAR NK therapies improve antigen specificity and anti-tumour responses [112]. Tailoring immunotherapy based on biomarkers (PD-1/PD-L1/IL4I1, TIL/Treg ratio) and mutational profiles (MSI, BRCA, p53/KRAS/PTEN mutations) is critical. Most HGSOCs harbor

mutant p53, which promotes immunosuppressive TGF-β signaling. Anti-p53 vaccines combined with chemotherapy have improved PFS in ovarian cancer responders [113], and trials are assessing p53 vaccines with pembrolizumab [114]. Tumor metabolic reprogramming impairs immune function; metformin, by inhibiting mitochondrial complex 1, enhances CD8+ T-cell activity and boosts ICB efficacy [115]. Hypoxia-activated HIF signalling recruits MDSCs and Tregs, and elevates PD-L1 expression, thereby fostering immune suppression.

Blocking AhR reverses TME suppression and synergizes with ICB to inhibit tumour growth. Combining immunotherapy with targeted therapies, chemotherapy, and nanotechnology holds promise for overcoming tumor microenvironment (TME)-driven resistance. Epigenetic therapies also show potential [Figure 11]. HDAC inhibitors (vorinostat, panobinostat, romidepsin) reactivate tumour suppressor genes, suppress oncogenes, and enhance apoptosis, improving responses to immunotherapy and chemotherapy. DNMT inhibitors (azacitidine, decitabine, guadecitabine) demethylate tumour suppressor promoters, restoring function and enhancing immune recognition. DNMTis are approved for AML and MDS, benefiting patients with TP53 mutations [116-118]. HDACis exhibit anticancer activity in pancreatic cancer models, showing synergy with proteasome inhibitors and gemcitabine [119-122]; however, clinical efficacy is limited by toxicity [123]. Combining HDACis and DNMTis with checkpoint inhibitors or targeted therapies may help overcome resistance; however, further investigation is needed in mucinous adenocarcinoma.

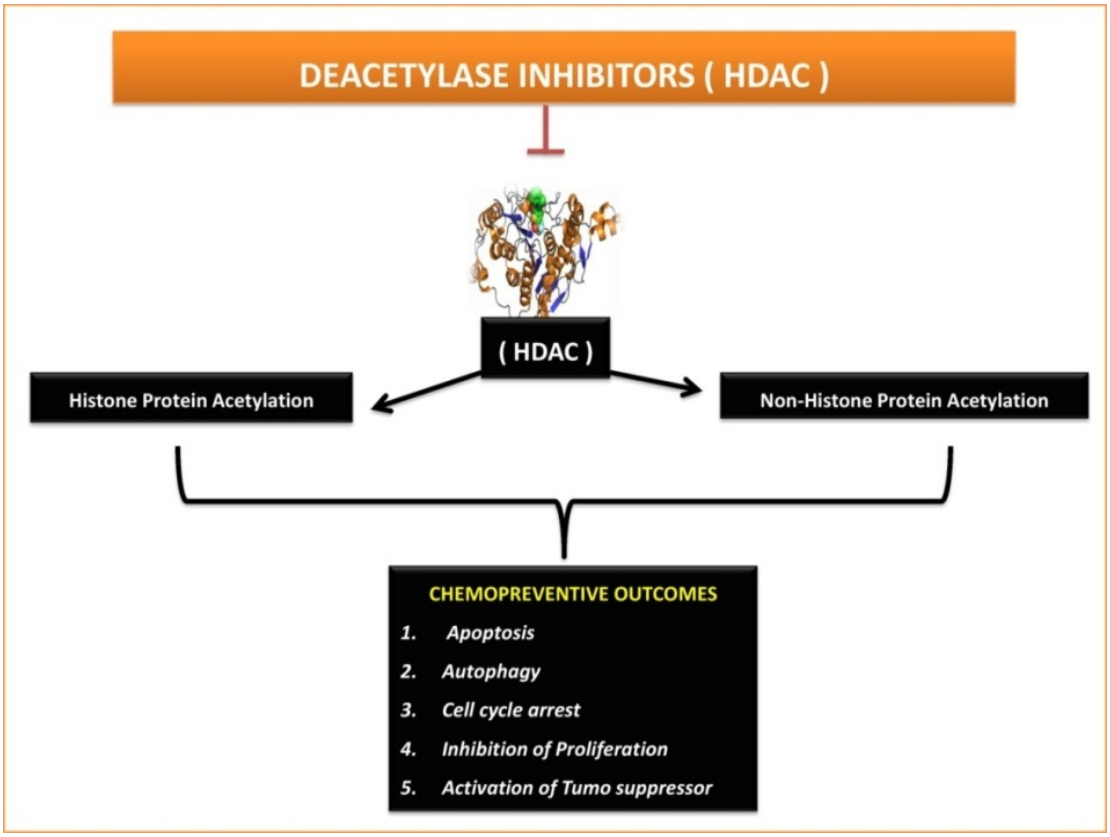

Figure 12: Role of HDAC in cancer treatment

RNA-Lipid Nanoparticles (LNPs)

Small interfering RNA (siRNA) and microRNA (miRNA) therapies target treatment resistance in mucinous adenocarcinoma by modulating gene expression post-transcriptionally. siRNAs restore chemotherapy sensitivity by silencing oncogenes and resistance-related genes, such as KRAS, ABC transporters (ABCB1, ABCC1) [124], and components of the PI3K/AKT/mTOR pathway. miRNAs act as tumour suppressors or oncomiRs; for example, miR-34a and miR-200c suppress chemoresistance and EMT, while miR-21 promotes resistance via anti-apoptotic pathways. Blocking oncomiRs or delivering tumour-suppressive miRNAs can reverse resistance mechanisms [125]. Nanoparticle-based delivery systems enhance the stability, uptake, and tumor specificity of siRNA/miRNA, addressing issues related to degradation and bioavailability. Combining RNA therapies with immune checkpoint inhibitors (anti-PD-1/PD-L1), targeted therapies (e.g., KRAS or EGFR inhibitors), or chemotherapy can

synergistically overcome resistance [104]. Ongoing studies and clinical trials are evaluating the potential of RNA therapies to enhance treatment efficacy. RNA-lipid nanoparticle (LNP) systems offer a cutting-edge approach for targeted RNA delivery, addressing drug resistance, immune evasion, and tumor heterogeneity. LNPs protect siRNA, miRNA, and mRNA from degradation, thereby improving tumor-specific uptake. Functionalization with ligands (e.g., antibodies, peptides) enables the targeting of receptors such as integrins, MUC1, or EGFR. LNPs deliver siRNAs to silence resistance-related genes (KRAS, ABC transporters, PI3K/AKT/mTOR) or tumour-suppressive miRNAs (miR-34a, miR-200c), enhancing therapy response. mRNA-loaded LNPs encoding cytokines or tumor-suppressor proteins boost anti-tumor immunity and sensitize tumors to immunotherapy. LNPs offer two advantages: (1) achieving efficacy at lower doses [126] and (2) improving pharmacokinetics by reducing toxicity and dosing frequency. Examples include 5-FU-loaded solid lipid nanoparticles showing dose-dependent cytotoxicity in Caco-2 cells [127], DOX-loaded ginger-derived nanovectors enhancing tumor uptake and reducing cardiotoxicity [128], anti-EGFR antibody-modified PSL nanoparticles increasing plasma half-life and tumor accumulation [129], and IRI-loaded SLNs with chitosan coating protecting against gastric degradation [130]. Combining LNP-mediated RNA therapy with immunotherapy or chemotherapy holds great promise for overcoming resistance. Preclinical and clinical research continues to advance LNP-based RNA therapies for mucinous adenocarcinoma.

FUTURE PERSPECTIVES AND CHALLENGES

Precision and personalised medicine, in which treatments are customised according to each patient's unique molecular profile, hold the key to the future of treating mucinous adenocarcinoma [131]. More accurate targeted therapy selection is made possible by advancements in liquid biopsy, next-generation sequencing (NGS), and biomarker discovery, which reduce the development of resistance and off-target consequences. By transforming our knowledge of tumour heterogeneity and adaptive resistance mechanisms, multi-omics technologies such as transcriptomics, proteomics, metabolomics, and genomics are opening the door to more potent combination treatments. High-throughput screening (HTS) platforms enable the rapid identification of novel drug candidates and resistance modifiers, accelerating the discovery of new therapeutic targets. Meanwhile, artificial intelligence (AI) and machine learning (ML) are revolutionizing cancer research by predicting resistance mechanisms, optimizing drug combinations, and personalizing treatment regimens through the analysis of large datasets. AI-driven models can analyze tumor evolution, immunotherapy responses, and drug interactions, providing valuable insights for clinical decision-making. However, significant challenges remain in translating these advancements into clinical practice.

Drug toxicity, tumor heterogeneity, and acquired resistance to emerging therapies pose barriers to long-term efficacy. Additionally, regulatory hurdles, cost constraints, and patient-specific variability complicate the widespread clinical adoption. Addressing these challenges requires a multidisciplinary approach, integrating oncologists, molecular biologists, bioinformaticians, and pharmaceutical researchers to develop comprehensive, patient-centered treatment strategies. Moving forward, the combination of precision medicine, AI-driven analytics, innovative drug delivery systems, and immune-based therapies holds great promise in overcoming resistance and improving patient outcomes in mucinous adenocarcinoma.

CONCLUSION

This review highlights the complex mechanisms behind chemoresistance in mucinous adenocarcinoma, including genetic mutations (KRAS, TP53), epigenetic alterations, tumor microenvironment-driven resistance, drug efflux pumps, and cancer stem cell-mediated therapy evasion. Key survival pathways, such as the PI3K/AKT/mTOR and MAPK pathways, along with dysregulation of apoptosis and immune evasion, further complicate treatment. Emerging strategies, such as epigenetic modulators, immune checkpoint inhibitors, RNA-based therapies, CAR-T therapy, and tumor antigen vaccines, offer promising solutions. Advances in nanotechnology, including RNA-lipid nanoparticles and polymeric carriers, have enhanced drug delivery.

However, challenges remain in optimizing treatment combinations, identifying predictive biomarkers, and addressing tumor heterogeneity and adaptive resistance. Limited clinical validation of emerging therapies underscores the need for further research. Integrating precision oncology, advanced drug delivery, and immunomodulation is essential. Future efforts should focus on multi-omics, novel combinations, and patient-specific strategies to improve outcomes and survival for patients with mucinous adenocarcinoma.

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NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Kaniga Pandi wrote the original draft. Binoy Varghese Cheriyan contributed to supervising and looking after the administration. Vishali Ramesh contributed to analyzing the literature and developing methodologies. Sowparnika Murugavel and Jaya Surya Venkatesan were involved in collecting data, data curation, and accessing various resources.

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