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Current Trends in Therapeutics for Colon Cancer

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ABSTRACT: Colon cancer (CC) is the third most common cancer diagnosed worldwide, making it a serious global challenge. Metastasis is mainly responsible for high mortality in CC patients. In CC patients, a mutation in Kirsten rat sarcoma (KRAS), adenomatous polyposis coli (APC), and tumor protein 53 (TP53) mainly drives the metastasis, mediates drug resistance, and promotes tumor recurrence by maintaining stem cell phenotype. Recently, long noncoding RNAs (lncRNAs) were reported to mediate KRAS-, APC-, and TP53-dependent CC progression and metastasis. In the present review, we have discussed the current updates on lncRNAs dependent on KRAS, APC, and TP53 in CC progression and metastasis. We also presented current trends in targeted therapies, immune therapies, redox-based therapies, and phytochemical-based therapies for CC. Finally, nanosystems for targeted delivery of therapeutic agents, which limit drug resistance and drug toxicities, were discussed. Therefore, targeted therapeutics can be used for CC treatment at the clinical stage.

KEY WORDS: colon cancer, targeted therapies, immunotherapy, redox-based therapies, phytochemicals

ABBREVIATIONS: APC, adenomatous polyposis coli; **CC**, colon cancer; **CSCs**, cancer stem cells; **KRAS**, Kirsten rat sarcoma; **LINC**, long intergenic non-protein coding RNA; **lncRNAs**, long non-coding RNAs; **MAPK**, mitogen-activated protein kinase; **mTOR**, mammalian target of rapamycin complex 1; **PI3K**, phosphatidylinositol-3-kinase; **STAT**, signal transducer and activator of transcription; **TGFβ**, transforming growth factor-β; **TP53**, tumor protein 53; **VEGF**, vascular endothelial growth factor; **Wnt**, Wingless-related integration; **5-FU**, 5-fluorouracil

I. INTRODUCTION

Colon cancer (CC), a large intestine or colon tumor, is the third most prevalent cancer and second most leading cause of death worldwide.[1] According to GLOBOCON (2020), CC represents one in 10 cancer cases and deaths, including 1.9 million new cases of CC and 935,000 new deaths. The major symptoms of CC including stools with blood, change in bowel movement, pain in the stomach. Early detection by a regular screening test for small tumors called polyps and cancer in healthy people having 50 years or more with the symptoms mentioned above can save the lives of the people with CC. The most common CC screening tests including a fecal immunochemical test at once a year, colonoscopy at 10 years, guaiac-based fecal occult blood test once a year, multitargeted stool DNA test (FIT-DNA) once every 3 years, flexible sigmoidoscopy once every 5 years and a recently developed CT colonography or virtual or X-ray colonoscopy are recommended for people who have a higher risk of CC development due to history of advanced adenomas, inflammatory bowel disease or genetic polyposis in the family. Also, persons who have CC in first-degree relatives likely to have more risk of CC development also recommended regular screening.[2]

The risk of polyps and CC can be reduced by eating calcium-rich dietary and dairy foods and regular physical activity, avoiding being overweight.[3] Besides these strategies, better treatment modalities can further reduce the mortality rate of CC. Despite the developments in diagnostic methods and treatment strategies, the overall incidence rate of CC is increasing worldwide. The criteria that are useful for predicting the likeliness of CC metastasis in stage II including detection of microsatellite instability, microRNAs, loss of 18q heterozygosity, Kirsten rat sarcoma (KRAS) mutation status, v-RAF murine sarcoma viral oncogene homolog B1 (BRAF) mutation status, gene expression profiling, circulating

tumor DNA, and laterality. The curative surgery of CC by laparoscopy minimizes the invasion.

Metastasis is mainly responsible for the increased death of CC patients. The mutation in KRAS, adenomatous polyposis coli (APC), and tumor protein 53 (TP53) drives the metastasis in CC, mediates drug resistance, and promotes tumor recurrence by maintaining stem cell phenotype. The CC with KRAS mutation preferentially metastasizes to the lung whereas, with wildtype to liver indicating the role of KRAS in site-specific metastasis of CC. The mutant KRAS expression is closely correlated with EGFR levels at primary as well as metastatic sites in CC tissue. It is also associated with aggressive invasiveness in CC patients. However, KRAS mutation had a different correlation with the right side and left side CC as well as lymph node metastasis as well as heterogeneity. KRAS mutation status also had prognostic importance in CC patients.[4]

In CC, metastasis is driven by various genes, including ATP-citrate lyase (ACLY), which facilitates CC metastasis by stabilizing the β-catenin 1.[5] In KRAS mutant cells, ACLY abundantly expressed and mediates KRAS-driven reprogramming in metabolism as well as tumor development via generation of acetyl-CoA, which is required for acetylation of histone as well as mevalonate pathway, a key pathway of cell plasticity.[6] Further, genotypes TT and GT of rs712 polymorphism in KRAS significantly contributed to CC lymph node metastasis, poor differentiation, and poor chemotherapy response in CC patients.[7] KRAS dependency and caspase 3 induction in KRAS mutation promotes lung metastasis.[8] Caspase 3, through promoting epithelial to mesenchymal transition (EMT) facilitates CC metastasis via increasing E-cadherin expression and decreasing zinc finger E-box binding homeobox 1 (ZEB1), N-cadherin, and Snail expression.[9]

Long non-coding RNAs (lncRNAs) regulate the stability of mRNA, splicing RNA, modulate the function of chromatin, and control the miRNA-dependent regulation of genes. They are implicated in various cellular and molecular mechanisms. Dysregulated lncRNAs are reported to promote oncogenic transformation by interacting with other regulatory molecules. They can also function as an enhancer of RNAs, decoys, and scaffolds. lncRNAs mediates hallmarks of cancer via diverse signaling pathways.[10] The CC patients with stage III or higher risk stage II are usually curative by colectomy and adjuvant chemotherapy.[11] Also, the inclusion of oxaliplatin in the adjuvant chemotherapy benefited some patients.[12] The treatment options for CC have endured a rapid development with advanced surgical and medical regimes and the launching of targeted treatments.

lncRNA mediates CC metastasis by regulating KRAS, APC, and mutant TP53 (Fig. 1). lncRNAs upregulate KRAS expression via microRNA-dependent mechanisms. For example, long intergenic non-protein coding RNA (LINC) 01420 requires KRAS for facilitating metastasis by binding to Myc.[13] However, KRAS is also regulated by lncRNA brain cytoplasmic RNA 1 (BCYRN1). Many lncRNAs regulate metastasis via different mechanisms. Linc00152 (CYTOR) promotes metastasis by impeding the casein kinase 1 via binding with cytoplasmic β-catenin,[14] B3GALT5 antisense RNA 1 (B3GALT5-AS1) inhibits liver metastasis of CC by binding with miRNA-203,[15] LINC00662 promotes metastasis by regulating co-expression of claudin 8/interleukin 22 (CLDN8/IL22) and triggering extracellular signal-regulated kinase signaling through competitive interaction with miRNA-340-p.[16] A tumor suppressor microRNA-543 inversely regulates the KRAS expression. Studies also reported that KRAS mutation associate with Piezo1- R-spondin 2 fusion protein. Piezo1 regulates metastasis by inhibiting the hypoxia inducing factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) expression,[17] exosomes by crosstalk with macrophages, and fibroblasts.[18] Studies also reported that CC metastasis is promoted by tissue inhibitor matrix metalloproteinase 1 (TIMP) via focal adhesion kinase (FAK)-PI3K/AKT and mitogen-activated protein kinase (MAPK) pathway,[19] stimulation of Wnt, and KRAS along with repression of signaling mediated by TGFβ.[20] These studies suggest that KRAS-dependent mechanisms are primarily mediated metastasis in CC, and therefore, they are promising targets of CC metastasis.

APC is a tumor suppressor gene highly mutated in CC. Mutant APC promotes metastasis via various pathway mediators, including lncRNAs. Genetic

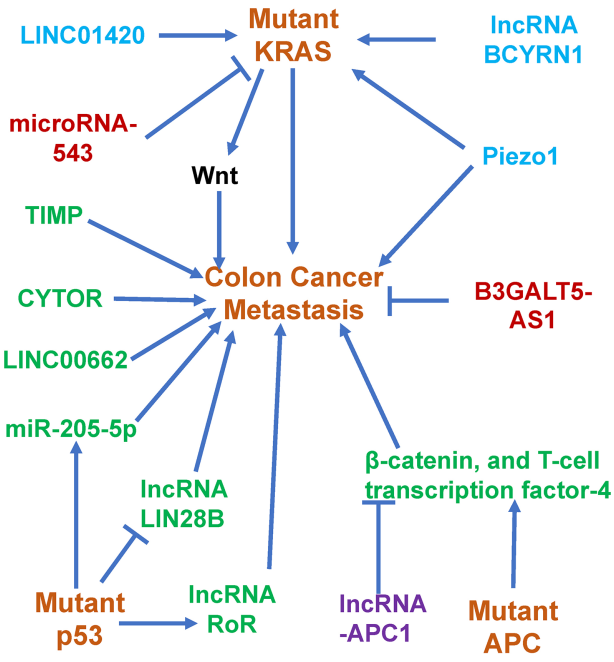

FIG. 1: lncRNAs mediate mutant KRAS-, APC-, and TP53-dependent CC metastasis. KRAS is regulated by lncRNA BCYRN1. CYTOR promotes metastasis by impeding the casein kinase 1 via binding with cytoplasmic β-catenin, LINC00662 by regulating co-expression of CLDN8/IL22 and triggering ERK signaling. KRAS mutation related Piezo1-RSPO2 fusion protein regulates metastasis by inhibiting the HIF-1α and VEGF expression. TTIMP promotes metastasis via FAK-PI3K/AKT and MAPK pathway. Wnt and KRAS along with repression of signaling mediated by TGFβ promotes CC metastasis. B3GALT5-AS1 inhibits liver metastasis of CC by binding with miRNA-203. Mutant APC promotes metastasis by activating β-catenin, and T-cell transcription factor-4 and lncRNA-APC1 inhibits lymph node or distinct metastasis by activating the MAPK pathway. Mutant TP53 promotes metastasis by inducing miR-205-5p expression, translocating RoR into the nucleus and inhibiting the expression of lncRNAs.

modifiers change the phenotype in APC mutant CC to promote carcinogenesis. APC mutant proteins exert various cellular mechanisms controlling cell migration, cell adhesion, proliferation, differentiation, and chromosome segregation in CC. The mutant APC promotes β-catenin and T-cell transcription factor-4 mediated metastasis in CC. It is one of the components of the β-catenin destruction complex, a control switch of the Wnt pathway mediated by lncRNAs.[21] APC activating lncRNAs impedes CC metastasis via reducing the production of exosomes. For example, lncRNA-APC1 correlates positively with lymph nodes or distinct metastasis by activating the MAPK pathway.[22] It regulates miRNA17-92 cluster via inhibiting β-catenin binding to transcription factor at promoter site, which in turn inhibits phosphatase and tensin homolog (PTEN), p21, bcl-2-interacting mediator of cell death (Bim)–dependent invasion.[23]

The combination of mutant TP53 and other drivers promotes metastasis by gain-of-functions. The mutant TP53 activates nuclear factor kappa B (NF-κB) by enhancing the promoter activity through the remodeling of chromatin and subsequent induction of epithelial to mesenchymal transition.[24] Mutant TP53 regulates diverse lncRNAs to achieve oncogenic nature via the formation of complex networks. It induces miR-205-5p expression to repress the genes associated with DNA repair mechanisms. Yet, it inhibits the expression of microRNAs such as miR-34 and miR-223, lncRNA Lin-28 Homolog B (LIN28B) to promote metastasis.[25] DNA damage-induced lncRNA regulator of reprogramming (RoR) represses TP53 via heterogeneous nuclear ribonucleoprotein in the cytoplasm. This study reported that RoR has a 28-base sequence, which is required for the repression of TP53. Interestingly, this study reported that TP53 could also regulate RoR through an autoregulatory feedback loop.[26] It also regulates several lncRNAs, including taurine-upregulated gene 1 (TUG1), GUARDIN, PGM5 antisense RNA 1 (PGM5-AS1), and nuclear enriched abundant transcript 1 (NEAT1).

The advanced proteogenomic analysis uncovered the novel therapeutic prospects for CC. Systemic treatments for CC patients have extended largely from 5-fluorouracil (5-FU)–based chemotherapy. The treatment of CC patients with adjuvant chemotherapy must consider several factors, including the risk of recurrence, survival benefits, toxicity, and multiple medical conditions of patients. In the metastatic setting, biomarkers such as mutant KRAS/TP53/APC have shown benefits to tailor-made systemic treatments such as chemotherapy, targeted therapy, and immunotherapy. Therefore, this review

presents the current trends in chemotherapeutics, redox-based therapeutics, targeted therapeutics, and immune therapeutics for CC. This review also uncovers the recent developments in drug delivery systems for the targeted therapeutics.

II. TARGETED THERAPEUTICS

Targeted chemo- and immune therapeutics are frequently used in cancer treatment, but their clinical efficacy is limited due to drug resistance, side effects, harmfulness, and refractory to immune checkpoint inhibitors in immunotherapy. KRAS, APC, and TP53 are frequently mutated in patients with metastatic CC and imply a potential therapeutic target. KRAS mutations transform oxidative phosphorylation to aerobic glycolysis by metabolic reprogramming in CC cells. KRAS inhibitor MRTX849, in combination with inhibitors that target receptor tyrosine kinases and mTOR, showed a marked reduction of CC growth in various tumor models.[27] The combination of borussertib, an allosteric AKT inhibitor, with trametinib showed antitumor activity in the patient-derived xenograft model.[28] However, the combination of small molecules ABT263 and axitinib synergistically induced apoptosis in RAS-mutant CC cells targeting AKT and Wnt/β-catenin pathways *in vitro* and *in vivo* models.[29] Monotherapy using nitro-coumarin derivate reduced the growth of CC cells by exerting the cytotoxicity, inhibiting the proliferation, and inducing the apoptosis via mitochondrial-mediated pathway.[30]

Antifungal antibiotic trichostatin A (TSA) reduces the expression of oncogenic markers by targeting HDAC in CC. The combination of TSA and 5-FU suppressed the viability of CC stem cells by targeting KRAS via β-catenin, NF-κB, Akt/mTOR pathway.[31] The CC patients with KRAS exon 2 wild-type, showed significant response with targeted therapy of FOLFIRI and cetuximab or bevacizumab in FIRE3 clinical trials.[32] The combination of palbociclib and PD0325901 is efficacious in CC by downregulating gene signature associated with KRAS mutation, including cyclin dependent kinase 4/6 (CDK4/6), forkhead box protein M1 (FOXM1), and mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK).[33] The monoclonal antibodies of EGFR, such as cetuximab and panitumumab, either individual or combination, effectively suppressed the metastasis of CC by targeting KRAS via tensin4 (TNS4) dependent MAPK pathway.[34] However, MEK1/2 inhibitor selumetinib, along with cetuximab, showed antitumor activity in CC by inhibiting metastasis via targeting KRAS in phase I clinical study.[35]

A novel polycyclic antibiotic from actinomycetes, pradimicin showed cytotoxicity by targeting mutant TP53 and KRAS. It inhibited metastasis by damaging the DNA, blocking the cell cycle, and inducing apoptosis by activating p21, reducing the phosphorylation of Rb, inhibiting the expression of cyclin A and B as well as activating the caspase 3, respectively, in CC cells.[36] miRNA-based therapy using miR-29b-3p induced apoptosis in KRAS mutant CC cells by downregulating B-cell lymphoma 2 (Bcl2), B-cell lymphoma-extra large (Bcl-xL), and myeloid cell leukemia-1 (MCL1) via the NF-κB signaling pathway.[37] These studies reveal that selective targeting mutant KRAS signifies a prospective therapeutic intervention for the prevention of CC.

Mutant APC is very frequent in patients with metastatic CC and implies a potential therapeutic target. In one study, truncated APC selective inhibitor-1 (TASIN-1) impeded the growth of CC with mutant APC in xenograft models. Further, analogs of TASIN-1 demonstrated selectively targeted action for mutant APC in CC patients.[38] In ApcMin/+ mice, fisetin and 5-FU substantially decreased the tumorigenesis by targeting PI3K/AKT/mTOR signaling. The mitochondria targeting compounds 3-carboxyl peroxyl nitroxide and metformin impeded ATP-associated O_2 utilization via 5' AMP-activated protein kinase (AMPK) and ribosomal protein S6 kinase B1. They induce mitophagy by releasing Unc-51 like autophagy activating kinase (ULK1) from mTOR-dependent blocking, changing the morphology and membrane potential of mitochondria.[39]

Recent studies reported that targeting CC stem cells using small molecule inhibitors effectively reduced the CC. For example, a novel class of gamma-secretase inhibitor, RO4929097 showed

a significant response against CC by activating cytochrome p450 in phase II clinical trials.[40] Cyclooxygenase (COX)-2 increase the growth of CC, promotes apoptotic resistance, mediates metastasis by generating prostaglandin E2 (PGE2). Studies suggest that COX-2 and PGE2 promote CC metastasis by a positive feedback loop mechanism through E-type prostanoid (EP) receptors. For example, rofecoxib, a selective inhibitor of COX2, showed a significant response against CC patients.[41] Cinobufacini is widely used in Chinese medicine, inhibiting CC cell metastasis by downregulating EMT promoting genes such as N-cadherin, matrix metalloproteinase (MMP) -2, and -9 and suppressing the Wnt/β-catenin signaling pathway.[42]

III. IMMUNE-TARGETED THERAPEUTICS

A recent study reported that myeloid-targeted therapeutic such as anti-colony stimulating factor 1 receptor (CSF1R) and cluster of differentiation (CD) 40 agonist, which is under clinical trial, showed improved tumor immunity.[43] Loss of Werner syndrome ATP-dependent helicase (WRN) is lethal to deficiency of mismatch repair (dMMR) in CC. Thus, Picco et al. demonstrated WRN dependency in preclinical models with WRN knockout or knockdown in CC with dMMR and suggested WRN as a potential marker for CC.[44] The use of T cell receptor (TCR)-therapy in CC by directing CEA antigens has certain limitations since normal colon cells contain CEA. In another attempt to develop targeted therapy against metastatic CC, use of humanized T cells aiming TGF β- receptor type II (TGFβII) frameshift antigen, which is expressed in dMMR CC. The current TCR therapies with CT03190941 for targeting KRAS G12V + tumor or NCT03745326 for targeting KRAS G12D + tumor are under phase I/II clinical trials.[45]

Wang et al. reported that cetuximab could be used to treat KRAS wild-type CC cells by targeting EGFR and inhibiting the activation of downstream signaling pathways. It exhibits little therapeutic effect on KRAS mutant CC cells. It is well known that natural killer (NK) cells show anticancer activities but lack inherent tumor-targeting abilities. The humanized NK-92 cells with surface-bound cetuximab are significantly compared to their parental counterpart in protecting against tumor development in a KRAS mutant mouse tumor model resistant to cetuximab treatment.[46]

Bahmani et al. reported that the anticancer effects of T-cell immune checkpoint inhibitors in CC are effective in a small subset of patients with microsatellite-unstable tumors. Thus, the binding of aberrantly expressed CD47 on tumor cells to signal regulatory protein-α (SIRP-α) on macrophages allows tumor cells to evade immune destruction. Based on this, drugs targeting the macrophage checkpoint can be developed with anticancer effects against T-cell immune checkpoint inhibitor-refractory tumors. CD47, SIRP-α, CD68, and CD163 expression can assess the predictive utility and the applicability of CD47-SIRP-α axis-modulating drugs. CCs contained various numbers of tumor-associated immune cells (TAIs) with SIRP-α, CD68, or CD163 expression. Based on the log-rank test, it is well known that patients with CD47-positive CCs had significantly worse survival than CD47-negative patients with high SIRPA-positive TAI counts favorable severity of the disease.[47] Abnormal acetylation of protein is associated with tumorigenesis, and thus modifying acetylation via inhibiting histone deacetylase (HDAC) using small molecule inhibitors can be effective on CC.

Recently, Blaszczak et al. identified CXD101 as a novel inhibitor for HDAC. CC cell lines responded to a varied set of changed gene expression upon CXD101 treatment. Global profiling showed the involvement of cytotoxic immune response correlated with antigen processing (AP) and natural killer (NK) cells. The capacity of CXD101 to influence immune regulating gene expression concurred to variations in the tumor microenvironment (TME), particularly in CD4 and CD8 tumor-infiltrating T cells. The changed TME signifies the improved antitumor potential of CXD101 in combination with PD1 and CTLA4 inhibitors. The capacity of CXD101 to re-establish with immune-regulating gene expression in the TME in combination with ICIs provides a

potent logic for investigation on combinational therapy.[48]

IV. REDOX-BASED TARGETED THERAPIES

Emerging theranostics precursor drug is extremely advantageous for precision cancer therapy. Redox-based therapeutics can be used for targeted therapy of CC (Table 1). Bao et al. employed the glutathione (GSH)-dependent transformation of 2,4-dinitrobenzenesulfonates into phenols and established it as an antitumor theranostic precursor drug pro-catechol-type diphenyl polyenes. It has three exclusive advantages: (1) release of enhanced GSH levels in cancerous cells by oxidation to o-quinone, causing redox disparity, which includes the release of H_2O_2 and diminution of GSH and induction of cytotoxicity selectively to CCs (2) allowing monitoring of its release based on fluorescence, aiming mitochondria with high therapeutic efficiency (3) proficiently targeting mitochondria without additional mitochondria-directed groups.[49]

The nanoparticles-based covalent organic framework (COF) generates free radicals under laser radiation. The COF with the polymer of Fe^{3+} and p-phenylenediamine could be utilized as an oxidant in photothermal therapy. In cancer cells, H_2O_2 decomposes to hydroxyl radicals by the Fenton reaction. Interestingly, the surge of photothermal therapy can hasten the generation of hydroxyl radicals. Furthermore, the tumor antigen-mediated stimulation of antitumor immune response efficiently prevented tumor metastasis using anti-PD-L1 inhibitors. Such a COF-based multitasking NPs offers an effective therapy for both the primary and metastatic tumors.[50]

It is well known that genistein (Gn) induces genotoxicity by blocking the activity of type II topoisomerase. It is metabolized to 3'-hydroxygenistein and 6-hydroxygenistein based on the oxidation site, which amplifies the toxic effect Gn on

TABLE 1: Nanoparticle-based strategies for targeted delivery of therapeutics in CC

Strategy	Effect
Doxorubicin with carrier liposomes	Site-specific delivery and decrease systemic toxicity
5-fluorouracil and miR-21i with carrier as exosomes	Site specific and reduces drug resistance
Graphene oxide nanocomposite conjugated to curcumin-capped gold nanoparticle	Cytotoxic and powerful antioxidant
AS1411 DNA aptamer tagged mesoporous rod-shaped nanoparticle loaded with camptothecin and serve as shRNA	Regulated the delivery of camptothecine, synergistic induction of cytotoxicity and apoptosis and antitumor effect in a nucleolin dependent uptake
Epirubicin containing nano-emulsion of algae and cinnamon oil	Induce apoptosis by fragmenting DNA via generating ROS
Dextran nanoparticles conjugated with modified spermine loaded with nutlin-3a and granulocyte-macrophage colony-stimulating factor (GM-CSF)	Antiproliferative
Silk fibroin-based nanoparticles	Antiinflammatory and wound healing inhibitory activity by lysosomal-dependent controlled release of drugs
Cholesterol based liposome formulation containing siRNA for c-myc	Reduced the c-myc expression and viability of cancer cells
Evo-encapsulated poly (amino acid) nanoparticles with EGFR	Anti-invasion and anti-metastatic activities in cancer cells by lowering the expression of EGFR, VEGF, and MMP proteins
pH responsive mesoporous silica coated gold nanorod based nanocomposite with poly-histidine/tocopherol polyethylene glycol/DOX coating	Photothermal conversion in the region of NIR and induced cytotoxicity by intracellular release of Dox in cancer cells

topoisomerase II.[51] Vidimar et al. showed that the effect of the redox ability of a ruthenium organometallic complex on CC. This complex stimulated cytotoxicity in a TP53-independent manner and decreased the angiogenesis of platinum drug-resistant patient-derived tumor explants. Mechanistically, the ruthenium complex modifies the redox enzymes as well as intracellular redox condition by enhancing the ratio of NAD+/NADH as well as ROS production. Further, analysis of the pathway indicated that HIF-1 is highly modified. Ruthenium complex diminishes the HIF-1α expression. The decrease of HIF-1α levels is also due to the direct interaction of the ruthenium compound with the redox enzyme PHD2, a master regulator HIF-1α. The downregulation of HIF-1α caused reduced vascularization in human colon tumors.[52]

Glucose-6-phosphate dehydrogenase (G6PD) is a key enzyme that produces NADPH to sustain decreased glutathione (GSH), which removes free radicals to shield cancer cells from radical-mediated damage. Ju et al. studied the possible roles of G6PD in CC advancement and drug resistance. This research stated that G6PD expression is enhanced in CC cells and patients samples. Elevated expression of G6PD expects poor prognostication of disease and associated with poor outcome of oxaliplatin-based chemotherapy in patients with CC. Silencing of G6PD reduced NADPH generation, and impairs ROS scavenging capacity, and improves oxaliplatin-stimulated apoptosis in CC. This study indicates that G6PD is a probable predictive biomarker for CC therapy.[53]

V. PHYTOCHEMICAL TARGETED THERAPEUTICS

Phytochemicals showed promising results in the treatment of CC at preclinical and clinical experiments. The progression of CC results from malfunctioning of cytoplasmic transcription factors involving signal transducer and activator of transcription (STAT) proteins that are implicated in the Janus kinase (JAK)-STAT pathway. The STAT proteins are therapeutic targets for many drugs as it is linked with the pathogenesis of cancer including CC. Genistein is an effective chemo-protective plant-based drug for CC. Dariya et al. explored the molecular communication between diverse STAT proteins with genistein using a computational biology approach. The molecular dynamic (MD) simulation was also performed. The molecular docking result showed that the interface of STAT2 proteins and genistein is effective with high binding efficacy. Furthermore, this study also stated that targeting STAT3 could be an effective therapeutic target for CC progression.[54]

Ganesan et al. suggested that diet-derived phytochemicals modulate the microbiome as well as targeting CC stem cells (CSCs). The effectiveness of CC can be reduced using various dietary phytochemicals or modulating microbiome that reduces or inverses the progression of a tumor as well as CSCs, which could be a promising and efficient way to reduce the burden of CC. Phytochemicals with modulation of gut microbiome continue to be auspicious investigations in CC through noticeable anti-tumorigenic effects and goals to CSCs, which provides new openings for cancer inhibition and treatment.[55] Yapasert et al. reported the anticancer of piperine, xanthotoxol, and dihydrogambogic acid. These compounds significantly induced the extrinsic and intrinsic apoptotic pathways in CC cells. Moreover, BJA-95 promoted ROS production via ER stress-mediated apoptosis.[56] Extracts from natural products have been customarily shown anticancer activity against different forms of cancer. These extracts can target distinct pathways selectively in cancer cells. Lemongrass isolates are efficient at causing apoptosis in human lymphomas. The effectiveness of isolates on CC was explored by Ruvinov et al., and they stated that ethanolic extract stimulated apoptosis in CC cells in a time and dose-dependent manner.[57]

VI. STRATEGIES FOR TARGETED DELIVERY OF THERAPEUTICS

The delivery of targeted therapeutics to the tumor site in the colon in a predictable and reproducible manner is a major challenge. Another challenge of effective targeting of therapeutics to CC is absorption and degradation of the drug in the upper gastrointestinal tract. Nanotechnology-based therapies

are considered as next-generation tools to target ever-increasing mortality by cancers. Specially designed nanoparticles have the ability of site-specific delivery of chemotherapeutics (Table 2). In addition, recent advancements in engineered exosomes facilitate co-delivery of chemotherapeutics and gene targeting therapeutics. Liang et al. demonstrated that systemic delivery of 5-fluorouracil and miR-21i using exosomes efficiently reduced the drug-resistant CC growth in cell lines as well as animal models.[58]

Graphene oxide nanocomposite conjugated to curcumin-capped gold nanoparticle showed concentration-dependent cytotoxicity to CC cells by acting as a powerful antioxidant.[59] AS1411 DNA aptamer tagged mesoporous rod-shaped NPs loaded with camptothecin (CT), and surviving shRNA showed controlled the release of CT with potent synergistic induction of cytotoxicity and apoptosis as well as *in vivo* antitumor effect in a nucleolin dependent uptake. This system also suppressed tumor growth in mice bearing C26 tumors by increasing survival rate as well as pharmacokinetics. This study recommended nucleolin-targeted nanomedicine as a versatile nanotherapeutic system for co-delivery of CT and iSur-DNA for CC treatment.[60] Epirubicin (EPI) containing nanoemulsion of algae and cinnamon oil inhibited cell proliferation, induced apoptosis by fragmenting DNA via generating ROS, and inhibited invasion of CC cells with an efficient release of epirubicin.[61] Dextran NPs conjugated modified spermine loaded with nutlin-3a, and granulocyte-macrophage colony-stimulating factor (GM-CSF)–induced antiproliferative effect in 3D model of multicellular tumor spheroids consisting of CC cells, intestinal fibroblasts, and monocytes by partial polarization of M1 macrophages.[62] Silk fibroin-based NPs exhibited antiinflammatory and wound healing inhibitory activity in CC cells by lysosomal-dependent controlled release of drugs.[63]

Cholesterol-based liposome formulation containing siRNA for *c-myc* markedly reduced the *c-myc* expression and viability of CC cells better than Lipofectamine™ 3000 by inducing apoptosis.[64] Evo-encapsulated poly (amino acid) NPs with EGFR targeting ability exhibited significant anti-invasion and anti-metastatic activities in CC cells by lowering the expression of EGFR, VEGF, and MMP proteins. They also decreased the tumor volume and growth as well as metastasis in tumor-bearing nude mice.[65] Self-assembled hydrocortisone containing doxorubicin (DOX)/docetaxel and TP53 gene selectively inhibited the CC by reducing the expression of Bcl-2, poly (ADP-ribose) polymerase (PARP), vimentin, and N-cadherin. It also inhibited the tumor

TABLE 2: Redox-based targeted therapeutics for CC

Target	Effect
Glutathione-activated catechol	Used to develop a phenol to protect a catechol moiety and developed stable pro-catechol-type diphenylpolyenes as small molecule-based prooxidative anticancer theranostic prodrugs.
Nanoparticles based covalent organic framework (COF)	Generate free radicals under laser radiation. The COF with polymer of Fe^{3+} and p-phenylenediamine is utilized as oxidant in photothermal therapy to generate free radical.
Genistein induced genotoxicity against type II topoisomerase	Genistein is metabolized to 3'-hydroxygenistein and 6-hydroxygenistein based on the oxidation site.
Ruthenium organometallic complex	Stimulated cytotoxicity in TP53-independent manner and decreased the angiogenesis of platinum drug resistant tumor. Ruthenium complex alters the redox enzymes as well as intracellular redox state by enhancing the ratio of NAD+/NADH as well as ROS production. Ruthenium compound with the redox enzyme PHD2 and decrease of HIF-1α levels.
G6PD silencing	Reduces NADPH generation and impairs ROS scavenging capacity and improves oxaliplatin-stimulated apoptosis.

progression by enhancing the activity of caspases.[66] The liposomes containing copper- 1,10-phenanthroline complex induced antiproliferative activity in CC in a pH-sensitive release manner by reducing the expression of aquaglyceroporins, reduced tumor progression in a murine model.[67]

pH-responsive mesoporous silica-coated gold nanorod-based nanocomposite with poly-histidine/tocopherol polyethylene glycol/DOX coating showed well-characterized photothermal conversion in the region of near infrared (NIR) and induced cytotoxicity by the intracellular release of Dox in CC cells.[68] Nano-assembly of N-heterocyclic carbene silver complexes functionalized with pyrazole/pyridine sensitized cisplatin-resistant CC cells by inducing caspase-independent necrosis via generating reactive oxygen species (ROS) and depletion of mitochondrial membrane potential as well as inhibited tumor progression in a xenograft model.[69] Installed redox-active NPs with tissue plasminogen activator (tPA) inhibited CC growth by reducing ROS via the NF-κB pathway in a fibrin-dependent degression of tumor vessels.[70] A self-assembled thiolated maytansine derivative coupled with polyethylene glycol-block-polylactide dramatically reduced the CC in the xenograft nude mice model.[71] These studies provide novel strategies for enhanced delivery of therapeutics into CC.

VII. CONCLUSION

CC is the third most frequently diagnosed cancer worldwide, represents one in 10 cancer cases and deaths and making it a serious global challenge. Metastasis is mainly responsible for the increased death of CC patients. The mutation in KRAS, APC, and TP53 drives the metastasis in CC, mediates drug resistance, and promotes tumor recurrence by maintaining stem cell phenotype. lncRNAs mediates hallmarks of cancer via diverse signaling pathways. lncRNAs mediates KRAS, APC, and TP53 dependent CC progression and metastasis. CC patients with stage III or higher risk stage II are usually curative by colectomy and adjuvant chemotherapy, and the inclusion of targeted therapeutics in the adjuvant chemotherapy benefited some patients. The treatment options for CC have endured a rapid development with advanced surgical and medical regimes and the launching of targeted treatments. However, delivery of targeted therapeutics to the tumor site in the colon in a predictable manner is a major challenge. NPs with targeting capacities present an innovative approach for site-specific delivery of therapeutics. Targeted therapeutics, redox-based therapeutics, and immunotherapeutic are clinically effective in limiting drug resistance and drug toxicities, and most patients are well responsive. Therefore, targeted therapeutics can be used for CC treatment at the clinical stage.

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