### EDITORIAL

#### Leveraging electrochemical sensors to improve efficiency of cancer detection
**Fu L, Karimi-Maleh H**

#### Mechanisms and potential applications of COPS6 in pan-cancer therapy
**Wu T, Ji MR, Luo LX**

#### High-dose methotrexate and zanubrutinib combination therapy for primary central nervous system lymphoma
**Yadav BS**

#### Role of targeting ferroptosis as a component of combination therapy in combating drug resistance in colorectal cancer
**Xie XT, Pang QH, Luo LX**

#### Approaches and challenges in cancer immunotherapy pathways
**Kapritsou M**

### MINIREVIEWS

#### Current interventional options for palliative care for patients with advanced-stage cholangiocarcinoma
**Makki M, Bentaleb M, Abdulrahman M, Suhooll AA, Al Harthi S, Ribeiro Jr MA**

### ORIGINAL ARTICLE

#### Ferroptosis biomarkers predict tumor mutation burden's impact on prognosis in HER2-positive breast cancer

#### Clinical application of reserved gastric tube in neuroendoscopic endonasal surgery for pituitary tumor

#### Nomogram based on multimodal magnetic resonance combined with B7-H3mRNA for preoperative lymph node prediction in esophagus cancer
## Contents

### Clinical and Translational Research

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
</table>

### META-ANALYSIS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>447</td>
<td>Transarterial chemoembolization plus stent placement for hepatocellular carcinoma with main portal vein tumor thrombosis: A meta-analysis</td>
<td>Sui WF, Li JY, Fu JH</td>
</tr>
</tbody>
</table>

### CASE REPORT

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>456</td>
<td>PD-1 antibody in combination with chemotherapy for the treatment of SMARCA4-deficient advanced undifferentiated carcinoma of the duodenum: Two case reports</td>
<td>Shi YN, Zhang XR, Ma WY, Lian J, Liu YF, Li YF, Yang WH</td>
</tr>
</tbody>
</table>
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Role of targeting ferroptosis as a component of combination therapy in combating drug resistance in colorectal cancer

Xiao-Ting Xie, Qiang-Hu Pang, Lian-Xiang Luo

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Abstract
Colorectal cancer (CRC) is a form of cancer that is often resistant to chemotherapy, targeted therapy, radiotherapy, and immunotherapy due to its genomic instability and inflammatory tumor microenvironment. Ferroptosis, a type of non-apoptotic cell death, is characterized by the accumulation of iron and the oxidation of lipids. Studies have revealed that the levels of reactive oxygen species and glutathione in CRC cells are significantly lower than those in healthy colon cells. Erastin has emerged as a promising candidate for CRC treatment by diminishing stemness and chemoresistance. Moreover, the gut, responsible for regulating iron absorption and release, could influence CRC susceptibility through iron metabolism modulation. Investigation into ferroptosis offers new insights into CRC pathogenesis and clinical management, potentially revolutionizing treatment approaches for therapy-resistant cancers.

Key Words: Colorectal cancer; Ferroptosis; Immunotherapy; Drug resistance; Chemotherapy; Nanodrug delivery systems

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Core Tip: Drug resistance poses a challenge to the treatment of colorectal cancer (CRC). In this paper, we offer novel perspectives on tackling this issue by focusing on ferroptosis in CRC cells. This approach holds promise in overcoming tumor cell resistance caused by CRC genome instability and changes in the tumor microenvironment, thereby providing innovative therapeutic strategies to break through the clinical drug resistance in CRC.
INTRODUCTION

Colorectal cancer (CRC) is a serious and aggressive form of cancer. Unfortunately, the majority of patients are diagnosed at advanced stages, with 50% of cases being prone to liver metastasis, leading to a poor prognosis and high mortality rate. The inflammatory tumor microenvironment (TME) and genomic instability in CRC make it resistant to existing treatments such as chemotherapy, targeted therapy, and immunotherapy. Ferroptosis emerges as a novel type of programmed cell death that is dependent on iron-induced lipid peroxidation. Cancer cells can evade ferroptosis signaling pathways, resulting in uncontrolled disease progression and drug resistance. Recently, ferroptosis has been proposed as a potential solution to the issue of cancer cells bypassing apoptosis and anti-apoptosis-induced drug resistance and metastasis[1].

The adenomatous polyposis coli (APC) tumor suppressor protein, forming a complex with GSK-3β and AXIN1, plays a significant role in the frequent mutation occurrence in CRC. Deactivation of this protein stands as a common CRC trigger. Studies indicate that pretreating HeLa cells with a GSK-3β inhibitor can thwart erastin-induced ferroptosis[2]. AMER1 is recognized as part of a complex that recruits AXIN1, β-TrCP, and APC to facilitate β-catenin ubiquitination and degradation. In CRC cells with wild-type status, AMER1 binds to SLC7A11 and FTI, recruiting β-TrCP1/2 to expedite FTI and SLC7A11 ubiquitination and degradation. This leads to an escalation in the labile free iron pool and a decline in cystine uptake, causing reactive oxygen species (ROS) overload and ferroptosis induction. However, AMER1 absence in vivo shields metastatic CRC cells from ferroptosis triggered by elevated blood oxygen levels, fostering CRC cell metastasis. This underscores a correlation between AMER1 mutations and CRC metastasis[3]. Studies have showed that KRAS mutations are one of the most common mutations in CRC. A recent study found that in male CRC patients, untargeted metabolomics data revealed that tumors with KRAS mutations have several pathways that inhibit ferroptosis. Furthermore, targeted metabolomics of RSL3 MC38 cells harboring KRAS mutations confirmed this finding by identifying iron metabolite precipitation. Inadequate administration of cetuximab is to KRAS mutant cell lines can increase lipid peroxides or induce ferroptosis. Additionally, when used in combination with cetuximab and RSL3, cetuximab increases ROS production and the malondialdehyde enhanced RSL3 cytotoxic effect[4]. This suggests the clinical potential of ferroptosis inducers as a component of combination therapies to target tumor antioxidant status and treat CRC.

Chemotherapy is widely used in the clinical treatment of CRC. Oxaliplatin (OXA), as a chemotherapeutic drug, is frequently used in the treatment of CRC, but patients frequently develop drug resistance, which limits its therapeutic effect. Some studies have found that cyclin dependent kinase 1 (CDK1) may be a key factor in OXA resistance. The mRNA and protein levels of CDK1 were significantly up-regulated in OXA-resistant CRC tissues, while the number of clones formed by CDK1 knockout cells treated with OXA was decreased, indicating that the depletion of CDK1 could overcome OXA resistance in CRC patients. Moreover, the physical interaction of CDK1 with ACSL4 led to ACSL4 degradation in OXA-resistant CRC cells, thwarting tumor cell ferroptosis. Thus, inhibiting ACSL4 lipid peroxidation and promoting ferroptosis through CDK1 interaction create essential conditions for managing OXA-resistant CRC patients. CDK1 inhibitors synergistically enhance the anti-tumor effect of OXA in OXA-resistant CRC[5]. Additionally, research has unveiled that the ferrophilic short-chain fatty acid butyrate can enhance the ferroptphilic ability of OXA and induce ferroptosis in CRC. Butyrate can also inhibit xct mediated ferroptosis resistance by inducing c-Fos expression, reverse the resistance of cancer stem cells to ferroptosis, and promote the occurrence of ferroptosis[6].

The conventional treatment of metastatic CRC, however, is still limited by the adverse reactions associated with chemotherapy drugs and the biological characteristics of tumors. Immune checkpoint blockade holds considerable promise in malignancy treatment. Regrettably, immunotherapy achieves notable curative outcomes only in a minority of patients with high microsatellite instability, with most patients displaying a certain level of resistance. Research indicates that CYP1B1 enhances tumor cell resistance to ferroptosis by increasing ACSL4 ubiquitination and promoting its degradation, and the therapeutic effect of anti-PD-1 therapy may be enhanced by inhibiting CYP1B1[7]. Moreover, through in vivo analysis, some researchers have identified the role of the APOL3-LDHA axis in promoting CRC cell ferroptosis and enhancing CD8+ T cell cytotoxicity by increasing IFNγ levels and reducing lactate concentration in the TME[8]. These findings suggest that targeting ferroptosis in CRC cells might effectively combat immune checkpoint blockade resistance.

Because targeting ferroptosis has shown great potential in CRC treatment, enhancing the selectivity of ferroptosis inducers and mitigating unnecessary side effects emerge as pressing concerns in clinical transformation. In this regard, the development of nanotechnology provides new possibilities for ferroptosis induction in cancer treatment. Nanodrug delivery systems (nano-DDSs) leverage the unique physical and chemical properties of nanomaterials for efficient targeted drug delivery to achieve more precise therapeutic effects[9]. Zhang et al[10] coordinated and assembled ions with 6-[2-(3-methyl)-naphthoquinyl]-hexanoic acid (NQA), a derivative of vitamin K3, to obtain multifunctional Fe-NQA nanopolymer particles, which reduced Fe2+ to Fe3+ while producing a large amount of ROS. In addition, the Fenton reaction occurred and ferroptosis was induced. The nano-DDS exhibited remarkable tumor inhibitory effect and inhibited tumor metastasis in the CT26 mouse tumor model. Most importantly, some studies have suggested that nano-DDSs may improve the multidrug resistance of CRC cells and the treatment effect in CRC patients[11]. These findings proved that
nano-therapy has great potential in targeting ferroptosis in CRC cells. However, since nano-DDSs are still in the emerging stage of research, more clinical studies are needed to further explore their efficacy.

**CONCLUSION**

This editorial emphasizes the potential of targeting ferroptosis in CRC cells to reduce the drug resistance of tumor cells due to CRC genomic instability and inflammatory TME, and presents a potential new approach for the treatment of this malignancy by combining ferroptosis targeting with chemotherapy, targeted therapy, radiotherapy, and immunotherapy.

**FOOTNOTES**

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**Country/Territory of origin:** China

**ORCID number:** Lian-Xiang Luo 0000-0002-3391-9713.

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