JANECZEK, Maksymilian, PLEWNIOK, Julia, PARTYKA, Maria, WÓJCIK, Julia, KANTOR, Karolina Kinga, CHOLEWA, Marcin, SZYMAŃSKA, Wiktoria Maria, JAGLARZ, Karolina, KUCA, Maciej and PAMUŁA, Kacper Wojciech. Molecular mechanisms of resistance and new therapeutic approaches in the treatment of colorectal cancer - a review of the literature. Journal of Education, Health and Sport. 2024;66:55620. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.66.55620
https://apcz.umk.pl/JEHS/article/view/55620

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 13.10.2024. Revised: 13.10.2024. Accepted: 20.10.2024. Published: 21.10.2024.

Molecular mechanisms of resistance and new therapeutic approaches in the treatment of colorectal cancer - a review of the literature

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ABSTRACT

Introduction and aim

CRC occupies one of the leading positions among gastrointestinal malignancies and is a significant problem in Europe since it is the third most frequently diagnosed cancer. Recent developments in diagnostic techniques have led to higher chances of early diagnosis and survival; nevertheless, CRC is highly likely to relapse in the survivorably younger individuals. The importance of the current chemotherapy treatment and potential key therapeutic targets are identified in this review so that the molecular alterations causing drug resistance in CRC can be studied.

Material and methods

Current literature formed the basis of this review by reviewing the molecular processes that underlie CRC, with emphasis on the mutational alterations in genes such as SENP1, KRAS, APC, TP53, and BRAF that play critical roles in CRC and resistance to treatment. Chemotherapy for CRC, targeting therapies, and immuno therapies have been discussed particularly with reference to their effectiveness for treatment and overcoming resistance.

Analysis of the literature

Genomic alterations in some important genes are involved in the onset of CRC and also determined the response to therapies. The KRAS mutations are associated with the resistance to EGFR inhibitors; however, BRAF mutations require BRAF/MEK inhibitors. Lack of MMR system SSR as a trigger for MSI-H status suggests a better response to immunotherapies. In addition, new molecules including SENP1, which involved the DNA

repair pathway, and combination using CDK4/6 inhibitors are currently under development to overcome resistance and enhance the patients' benefits.

Conclusion

Colorectal cancer is still a problem, primarily because of its genetic character and high rates of recurrence. Even though chemotherapy and targeted therapies offer helpful results, the problem of resistance stands in the way. Subsequent studies should aim at symptomatic treatment outcomes and combine different drugs in order to enhance long-term treatment outcomes.

Keywords

Colorectal cancer, chemotherapy, therapeutic targets, KRAS, BRAF, MMR deficiency, resistance mechanisms, immunotherapy, SENP1

Introduction

Colon cancer is the most common gastrointestinal cancer. In 2022 colorectal cancer was ranked 3rd in terms of occurrence, especially in Europe. [1] These data are becoming more precise due to the development of diagnostic technologies. This gives the additional effect of increasing survival and treatment effectiveness, which allows a 5-year survival rate of 90% in the case of localized colon cancer. [2,7]

However, the high development of society brings with it disadvantages in the form of a sedentary lifestyle and, very often, an inappropriate diet. This contributes to the incidence of colon cancer. [1] Young age also contributes to this, these people have a more severe course than others.[23] Moreover, it is estimated that within the next decade it will be the main cancer killer. [3] Different mutations have a fundamental position in the development of the tumor, as well as in the treatment response in colorectal cancer (CRC) pathophysiology. In the majority of cases, these changes involve alterations in such genes as SENP1, KRAS, APC, TP53 and BRAF (encoding for proteins playing a role in cell growth regulation processes that include proliferation or apoptosis). For example, mutations in KRAS are associated with resistance to EGFR receptor therapies that render drugs such as cetuximab less effective. Conversely, mutations in APC and TP53 cell cycle control pathways, ultimately leading to uncontrolled cancer-cell growth. In addition, the range of DNA replication- and damage-related genes that contribute to heightened genomic instability due to impaired DNA error repair (which includes deficiencies in the MMR system as well as CIMP) directly affect chemotherapy responsiveness. Comprehension of these molecular resistance mechanisms enables personal genuine individual therapy adaptation in order to increase cancer treatment

success rates. [25] Recovery does not mean getting rid of the problem. Relapse of the disease may turn out to be more dangerous than the disease itself, due to too late detection. Approximately 20% of patients experience recurrence despite resection and chemotherapy. [4] For this reason, frequent level marking H&P, CEA, CT scanning of the chest/abdomen/pelvis and colonoscopies are recommended for the first 5 years.[2] The problem with these tests is the need to perform them in order to obtain the result. Just as in the case of cure, they are performed, in the case of screening diagnostics, these tests are performed only when the condition is really serious and qualifies for emergency surgery. [5] The current standard of treatment includes chemotherapy and surgery. We have two types of chemotherapy to choose from. Adjuvant chemotherapy, administered after surgery and reducing toxicity, and new neoadjuvant therapy, administered before and after surgery. However, these models do not differ much from each other and have similar effectiveness, but the newer one exposes patients to a greater risk of overdose. However, despite all this, relapse is a common problem. [6]

Analysis of the literature

Mutation influence and resistance to chemotherapy

There are several potential mutations that cause changes in the cell that affect the occurrence as well as the effectiveness of treatment. The most common problems were changes in SENP1, KRAS, APC, TP53, BRAF. Problems with DNA mismatch repair (MMR) or CpG island methylator phenotype (CIMP) are also common. By comparing the causes of resistance, their pathophysiological mechanism and the effect of potential chemotherapy, we are able to select a drug that will be effective in combating cancer.

SENP1

One of the known mechanisms of chemotherapy resistance is the impairment of non-homologous DNA end joining (NHEJ) repair. Double-strand breaks (DSBs) are a serious type of DNA damage that require repair through the activation of the NHEJ pathway. Increased mobilization of the NHEJ pathway in colorectal cancer can be a significant problem in halting the development of cancer cells. Mutations in this pathway can contribute to increased tumorigenesis. Therefore, some therapies are targeted at NHEJ. One such therapy involves administering the TBX20 factor, which impairs repair via NHEJ, potentially inhibiting tumor growth. [11] SENP1, which reduces the SUMOylation of RNF168, is associated with NHEJ.

SENP1 has become a potential therapeutic target because it promotes resistance to DNA damage, significantly limiting the effectiveness of radiotherapy and chemotherapy. It reduces the recruitment of RNF168 to damage sites, which in turn decreases H2A ubiquitination and results in the inability to repair non-homologous DNA ends. Focusing on SENP1 leads to a situation where the cell becomes susceptible to radiotherapy and chemotherapy by blocking the cell's self-repair abilities, thus making the treatment harmful to cancer cells. [8,11]

Chromosomal instability

Another pathway involving KRAS and APC is chromosomal instability (CIN). This group is based on disruption of the WNT pathway. APC mutations cause loss of control over the cell life cycle and lead to carcinogenesis. This mechanism can often be driven by the occurrence of both mutations (APC and KRAS), which promote abnormal cell growth and proliferation by activating downstream signaling pathways such as the MAPK/ERK pathway. [9+] The problem is the KRAS mutation located in the EGFR pathway. Unending promotion of activation leads to the ineffective action of Panitumumab. KRAS is additionally characterized by maintaining low levels of P53. Only in combination with Sotorasibe does it become effective by inhibiting KRAS and allowing the action of Panitumumab. [10,11] The problem, however, can be the recurrence of the disease, as a link has been shown between the presence of KRAS mutations and the recurrence of colorectal cancer. [12] Mutations are not always beneficial to the cancer, as indicated by the results of the analysis, in which high levels of CIN were a good prognosis. Mutations are not always beneficial for the tumor, as shown by the results of the analysis, in which a high level of CIN was a good prognosis. They can also affect the effectiveness of therapy. High CIN significantly sensitized the tumor to oxaliplatin and paclitaxel. Therefore, an attempt was made to combine overexpression of YY2, which causes a high level of CIN, with oxaliplatin. The effect of the action was a significant delay in the formation of tumor cells. [13]

MMR

Cancers that lack mismatch repair (MMR) proteins in their nucleus and/or MMR activity are referred to as mismatch repair-deficient (dMMR) cancers, or high-frequency microsatellite instability (MSI-H) tumors. Fifteen percent of colorectal cancers (CRCs) are caused by dMMR (DNA mismatch repair) deficiency. One Tumor DNA can be used for MSI testing and immunohistochemistry (IHC) to determine MMR status. Numerous investigations have demonstrated that due to mutations or epigenetic modifications in DNA MMR genes, dMMR demonstrated an improved antitumor immune response and decreased tumor cell development

in colorectal cancer. [26,27] It is evident that predictive characteristics for dMMR/MSI-H CRC patients are varied. Patients with dMMR/MSI-H colorectal cancer (CRC) had longer disease-free survival (DFS) and overall survival (OS) than those with pMMR/MSS tumors. This is likely because dMMR/MSI-H tumors have more lymphocyte infiltration. Tumor microenvironment (TME) inflammation in dMMR/MSI-H CRC may make the patient more susceptible to immune checkpoint inhibitors (ICIs). [28] Clinical trials of dMMR/MSI-H CRC have not yet clearly distinguished differences in immunotherapy efficacy between LS, LLS and sporadic patients and do not have uniform classification criteria. Therefore, molecularly based differential treatments cannot yet be provided and treatment still follows standard protocols for dMMR/MSI-H CRC. KRAS/BRAF, as independent prognostic markers, guide targeted therapy for CRC, but no direct association with immunotherapy has been found. Preliminary results indicate that BRAFV600E mutation cannot predict the outcome of dMMR/MSI-H metastatic CRC (mCRC) patients receiving ICI therapy. Therefore, for patients with dMMR/MSI-H mCRC accompanied by BRAFV600E mutation, ICI should be considered as the standard first-line treatment. [29]

Microsatellite instability

Determining MSI may prove crucial in the choice of treatment type, an example being the effectiveness of neoadjuvant immunotherapy in the case of such instability. [14] Accumulating errors in the DNA microsatellite section occur in about 15% of patients., when considering only the IMS cohort, pembrolizumab was found to be more effective. This group achieved an objective response of 45.1%, as opposed to 33.1% for standard chemotherapy, also progression-free survival was higher than with standard chemotherapy. [15,16,17] This drug is focused on PD-1/PD-L1 blockade.

To understand the topic, two mutational states should be distinguished:

- MSS tumors ("cold tumors") that do not cause an immune response, creating a shutdown and controlled immunosuppression nearby, this leads to a lack of clinical response to PD-1/PD-L1 blockades in tumors. Higher PD-L1 expression inhibits cytotoxic T lymphocyte (CTL) function, resulting in immune escape, additionally elevated PD-L1 levels in these tumors result in the exhaustion of CD8+ T cells and an increase in regulatory T cells (Tregs), which further enhances the tumor's ability to evade the immune response. [22,23,24]
- MSI-H, which increases the number of tumor-infiltrating lymphocytes (TIL) and memory T cells, called "hot tumors". Therapies using anti-PD-1 and anti-PD-L1

monoclonal antibodies bring significant benefits, but only for certain groups of patients, because in the case of cold tumors this therapy is not successful. [22,23,24]

The synthetic protein IgP β, which responds to the pH changes of peptide foldamers, effectively reduces neoplastic PD-L1 levels, thereby restoring the activity of CD8+ T cells infiltrating the tumor, enhancing their anti-tumor response. [23]

TP53

The tumor suppressor gene TP53, which stands guard over tumors. It plays a key role in the cell cycle. When DNA damage occurs in cells, this gene initiates apoptosis, eliminating the threat. If it is inactivated, the p53 protein loses these abilities. This leads to uncontrolled cell proliferation, in which cells that would normally undergo programmed cell death. Due to the importance of this gene, therapeutic strategies for colon cancer have been identified that correct this process. However, it turned out that removing the mutated TP53 *in vitro* did not stop the uncontrolled proliferation, nothing changed. Studies have shown that deleting mutant TP53 did not alter the response of cancer cells to anticancer drugs such as etoposide, 5-FU, taxol, or cisplatin. Cancer cells with and without TP53 used similar signaling pathways to adapt in response to treatment. [18,19] According to recent research, TP53 mutations usually occur before other genomic rearrangement events, indicating that p53 inactivation is a key contributor to genomic instability. Researchers have shown that when p53 is absent from cells, the cancer genome evolves in a predictable, ordered, and deterministic manner while causing genomic instability. Furthermore, it is challenging to target mutant p53 proteins due to their structural variations. At the moment, there are two primary categories of study focused on p53: regaining the functionality of wild-type p53 and undoing the consequences of mutant p53. [19]

BRAF

Mutations in the BRAF gene, encoding the B-Raf protein. B-Raf - a serine-threonine kinase, associated with resistance to traditional therapies, including chemotherapy. This protein has an essential role in the regulation of the MAPK signaling pathway that is responsible for controlling cell growth and division. For example, the BRAF V600E mutation is one of the most frequent activating unstoppable proliferation. As such have seen the development of newer targeted therapies combining a BRAF inhibitor- encorafenib, with a MEK inhibitor- binimetinib, and anti-EGFR antibodies. It thern out in BEACON clinical trial demonstrated that these combinations could lead to survival benefits in BRAF V600E-mutant colorectal

cancer compared with conventional chemotherapy. Authors of the trial conclude that that dual therapy (cetuximab and encorafenib) and triple therapy (cetuximab, encorafenib, and binimetinib) were associated with a substantial overall survival benefit over chemotherapy alone, along with better side-effect tolerability. Nonetheless, initial responses are frequently short-lived and drug resistance rapidly ensues through adaptive changes in the MAPK pathway, limiting the clinical efficacy of BRAF V600E mutation-targeted therapy and hence achieving long-term cure in this lethal cancer is a major unmet challenge today, but considerable advances have been made and promise that treatment outcomes for patients with this deadly disease can be markedly improved. Given the fragility of treatment, studies are currently underway to explore combination therapy with CDK4/6 inhibitors, which may restore sensitivity to BRAF and EGFR inhibitors, offering restoration of treatment efficacy. [20, 21]

Conclusion

CRC remains an enormous challenge in global health due to its increasing incidence and mortality regardless of the region of the world, including Europe where it is the third most prevalent cancer. The changes proved in diagnosing have cut down earlier detection and its treatment results through recording an incredible five years survival rate of 90% of those that were localized. However, for better prevention and therapeutic outcomes, the technological advancements, disturbing epidemiological features of CRC as a disease of a younger generation as well as the sedentary lifestyle and poor dietary behaviors of the society raises the need for improved approaches towards the disease. In no other cancer is the genetic heterogeneity, encompassing mutations that not only contribute to tumor formation but also affect response to treatments and therapy related resistance more evident than in CRC. February 2010, SENP1, K-Ras, APC, p53, and BRAF genes are critical genes that are involved in multiple cellular processes including cell division, cell death and DNA fix. For example, SENP1 mutation defects a DNA repair process known as non-homologous end joining (NHEJ) leading to resistance to therapies such as radiotherapy and chemotherapy. The five aspects outlined above, therefore, mean that targeting SENP1 appear to be a viable approach to selectively enhance the death of cancer cells while making the disease manageable by current therapy. CIN along with KRAS and APC mutations also plays significant role in treatment challenge. These mutations interfere with important signaling, especially the MAPK/ERK signaling, making even such traditional targeted therapies as

EGFR inhibitors, i.e., cetuximab, ineffective and increasing relapse rates. That KRAS mutations are related to the higher risk of disease relapse underscores the need for monitoring and creating effective therapeutic strategies which would directly address issues of resistance mechanisms. It is therefore known that, patients with CRC carrying dMMR and MSI-H are a specialized population with increased immunogenicity and favourable survival profile. MSI-H tumors show higher intratumoral infiltration of lymphocytes and memory T cells than MSS or MS-I tumors and are more sensitive to immune checkpoint inhibitors targeting the PD-1/PD-L1 axis. Nonetheless, the variation in the response to these therapies, such as BRAF, means that the current strategy is insufficient. Optimization of the outcomes that are obtained during the treatment of cancer requires that treatment regimes be tailored towards the molecular and immune characteristics of the tumors.

It is noteworthy that the tumor suppressor gene TP53 remains the only sentinel preventing uncontrolled cell division and genomic dysregulation. Aberrantly expressed in CRC, it is often inactivated promoting tumor growth and presenting difficulties for targeted therapy. Present day therapeutic strategies lie in trying to redesign wild-type TP53 functionality or lowering the impact of the TP53 mutations, while these attempts are stillContinue existing in investigations and have not delivered clear standard augmentation yet. BRAF mutations are another factor in the CRC treatment, and V600E is the most common mutation in CRC patients. Although recently, the combination of BRAF inhibitors (for example, encorafenib), MEK inhibitors (for instance, binimetinib), and antibodies against EGFR (for example, cetuximab) have been reported to show efficacy in clinical trials, the inherently prompt development of adaptive changes in the MAPK signaling pathway pose major challenge. On—going effort in combinatorial treatments that include CDK4/6 inhibitors is to enhance its sensitivity and duration of effectiveness of targeted therapy. Even though there has been significant advances in elucidation of molecular characteristics and targeted treatment paradigms of CRC, numerous questions remain to be answered. Possible criticisms involve high rate of relapse, how drug resistance develops, how treatment that is effective in some patients is not always effective in others hence the call for further research/ development. Hence, it remains incumbent on future therapeutic interventions to align molecular diagnosis with the personalized medicine techniques so that treatment accuracy and longevity can be improved. Therefore, after massive advancements in the identification of the genetic and molecular characteristics of colon cancer, making durable therapeutic progress remains a challenge. The genetic variability and plasticity of CRC call for a combined treatment and

control strategy that includes specific treatment, immunotherapy and closely monitored approaches. It has remained for molecular biology to advance further and for clinical science, therefore, to discover how survival duration and quality of life of patients with this deadly cancer might be enhanced.

Disclosure:

Author's contribution: MJ

Conceptualization: MJ, JP and MP

Methodology: MJ

Software: JW, MP

Check: KJ, MK

Formal analysis: MJ, WMS

Investigation: KWP, MJ

Resources: MJ

Data curation: KKK, WMS, MC

Writing-rough preparation: KWP, MP, KKK

Writing-review and editing: MJ, JP, JW

Visualization: MJ, JW

Supervision: KJ, MK

Project administration: MJ

Supplementary Materials: They have not been provided.

Funding Statement: This research received no external funding.

Institutional Review Board Statement: Not applicable.

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