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Original Research Article

Colon Tumor Resistance to Chemotherapy: Review of Principle Findings from Recent Studies

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Abstract: Colon cancer is among the most prevalent and fatal malignancies and among the most deadly type of tumor in the world. Chemotherapy and surgery are the main choices of treatment for cancer patients. However, Resistance to chemotherapy remains one of the greats challenges mostly for patients with metastatic lesions. This study will provide a comprehensive review of different mechanisms of colon cancer chemotherapy resistance in cancer stem cells including, epithelial-mesenchymal transition (EMT), activation of DNA damage checkpoints, hindrance of the over-expression of antiapoptotic regulatory element, the dormant state of colon cancer, ATP-binding cassette (ABC) transporters, 5-fluorouracil resistance mechanisms in colon cancer, and the presence of reactive oxygen species (ROS) levels will be reviewed. In this paper, the possible mechanisms of chemoresistance in colon cancer are systematically described, which will be beneficial to the further research of chemoresistance in colon cancer.

Keywords: Colorectal Cancer, Chemotherapy Resistance, Resistance Mechanism.

INTRODUCTION

Colon cancer is an illness where cancerous tumors develop in the colon. According to research, it is one of the most frequent among cancer patients and among the deadliest type of cancer in the globe [1]. At present, chemotherapy and surgery are among the primary medical care methods and the personal characteristics of a patient [2]. Chemotherapy is applied at varying phases of treatment and it is normally administered as adjuvant management after surgery for patients with chronic colon cancer. It can also be applied as neoadjuvant treatment to minimize the size of a cancerous cell before its extraction from the body. The accessibility of different chemo treatment routines has enhanced the entire endurance rate of individuals with chronic colon cancer in the previous few years. Nevertheless, despite the successful treatment rate for new systematic therapies has reached up to 50%, there have been cases of drug resistance nearly among individuals suffering from colon cancer and there has been a decline in the effective treatment of antitumor agents, hence leading to a non-performance of chemotherapy [3].

Drug counteraction is the reduced effectiveness of a drug. This includes antiviral, antibodies, and chemotherapeutic agents in the treatment or prevention of a certain disease [4]. There has been an extensive

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investigation of the resistance of cancer drugs since the finding of a new form of inhibition related to P-glycoprotein (P-gp) in different hamster ovary cell cycles. This is the resistance to different functionally and structurally chemotherapeutic agents that are not related after they have been exposed to a one cytotoxic agent. To date, cancer inhibition to different types of drugs is still a considerable hindrance to the notable medication of cancer. Many deaths related to cancer is as a result of the failure of chemotherapy that result because of treatment suppression that is experienced in the period of chemotherapy and cancer progression.

Suppression of tumor programmed cell death, differentiation with targeted sites of chemotherapeutic agents, cancer stem cells, change in designated regions of chemotherapeutic mechanisms, and tumor resistance are the main reasons for chemotherapy resistance [5]. Cancer stem cells account for approximately 5% of the tumor cells and can lead to cloning, self-renewing, multi-lineage variation, tumor activation, metastasis, upkeep of tumor behaviors, and proliferation [6]. The study of the mechanism of drug suppression and their methods of reversal have contributed in the successful development and study of cancer chemotherapy methods.

Different biological pathways principal to drug inhibition were studied and developed in the past few decades. They are grouped into two types that are, cellular and non-cellular inhibition pathways. cellular mechanisms are mostly associated with drug targets, transport systems, and enzymes in the cellular cells. Non-cellular mechanisms, on the other hand, are the extracellular elements, such as tumor micro-environment, and inhibited vascular accessibility. Other mechanisms are epithelial-mesenchymal transition (EMT), initiation of DNA damage barriers, hindrance of the over-expression of antiapoptotic regulatory element, the dormant state of colon cancer, ATP-binding cassette (ABC) transporters, 5-fluorouracil inhibition mechanisms in colon tumor, and the presence of reactive oxygen species (ROS) levels. Recent studies have focused on cancer stem cells and natural drug extracts, that can remove CSC and inhibit chemotherapy resistance. Even though there are effective chemotherapeutic treatments for colon cancer, most patients end up developing acquired inhibition to chemotherapeutic agents. In this consideration, we must have an imperative knowledge of the underlying mechanism through which drug repression develops in colon cancer, to create effective therapeutic measures for colon cancer patients. This paper will review different pathways of colon cancer counteraction to chemotherapy.

Mechanisms of colon cancer resistance to Chemotherapy Fluorouracil resistance mechanisms in colon cancer.

5-fluoroucil is a cognate of a fluorine atom at the C5 point as a substitute of hydrogen. The most important catalyst in 5-FU catabolism is thymidylate synthase (TS), belonging to one of the three fundamental routes of 5-FU metabolism. Similar to other enzymes taking part in either 5-FLU catabolism or metabolism, they are always changed, leading to 5-FU resistance. The primary cellular functions (autophagy, apoptosis, cell cycle, glucose catabolism, and respiration) can also be interfered with in colon tumor leading to contact with 5-FU. Drug transporters are the primary elements taking part in multi-drug counteraction. 5-FU-mediated epigenetic changes, epithelial-mesenchymal transition (EMT), and microRNA (miR) dysregulations make up the most vital 5-FU resistance mechanisms. we will review different mechanisms created by colon cancer cells to inhibit 5-FU-activated cytotoxic ramifications.

Alternation of TS and Various Enzymes Associated With 5-Fu Activation and Metabolism

TS mRNA levels increase in 5-FU-repression cells causing heightened TS catalytic activity and inhibition of TS transport [7]. Increased intrinsic values of TS are a product of 5-FU counteraction in patients, in the cells, and in a laboratory setting [8]. It is also clear that after the treatment of 5-FU, the continuity rate of long-suffering individuals with high TS levels, which can be seen in main tumors with lymph node progression and in those with metastasis, is lesser than for patients with low TS levels. Among the main sources of the high level of TS in colon cancer is TS polymorphism [9]. The

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existence of high-level TS ahead 5-FU clinical care leads to disrupted folate streams and results in intrinsic hindrance. On the other hand, acquired suppression is associated with TS gene mutations and amplification. This study indicates that patients with tumors that show the presence of TS amplification should seek alternative treatment methods and should not be treated with 5-FU.

Other mechanisms that have recently been identified as new pathways explaining 5-FU suppression in colon cancer are thymidine kinase and Uridine kinase, orotate phosphoribosyltransferase activities that have a lower cell resistance [[10]]. Changes in the uridine monophosphate synthetase (UMPS) RNA that is subject to the alteration of 5-FU into activated anticancer metabolites in cancer cells. An example is heterozygous splice target alterations and aberrant exon splitting and deterioration that lead to a reduction in its functionality.

Disruption of Cellular Activities by 5-FU

Cancer cells can lead to a chemical mechanism resistance to anticancer drugs. This section will provide a review of how colon cancer can regulate the cell cycle, oxidative stress, glucose metabolism, EMT, and the activities of mitochondrial in order to be able to inhibit cell death induced by 5FU.

Autophagy and Apoptosis Disruptions

These are two regulatory events that are liable for the extermination of cancer cells. However, this process is always counteracted by cancer cells and becomes drug resistant.

Chemotherapy is one among other treatments that enhance apoptosis through the introduction of tumor suppressor gene p53 (pt53). Studies has indicated that, that some colon tumor tend to be more defiant to 5-FU as a result of the alternation of cytoplasmic p53. therefore, hydroxymethyltransferase 2 can marge together cytoplasmic p53 instead of HDM2 limiting the deterioration of cytoplasmic p53 [[11]]. However, research indicated that tp53 is mutated in 50% of cancer since it losses its functionality [[12]]. It has also been found that p53 modulators, like caspase-9 and its elements, apoptotic protease that is responsible for the activation of factor one can be inactivated resulting in resistance to drugs. Other have also been indicated the function of glycogen synthase kinase3β (GSK3β) in cell resistance associated with 5-FU. Studies have also indicated that the prevention of enhancing colon tumors continuity to 5-FU via the suppression of apoptosis activated by 5-FU and evolution of in G2/M and S phase [[13]]. In addition to GSK3β and TP53 involvement of resistance mediated by 5-FU, the expected functions of Maspin (pro-apoptotic protein) and Rho GDP dissociation resistance 2 (RhoGDI2) that are promoted and downgraded correspondingly, in suppressor cells, were also observed. This, therefore, indicates that knockdown of (RhoGdI2) has the ability to improve 5-FU inhibition colon cancer cells to this treatment.

Autophagy can be described as a procedure where cells can be able to thrive via the presence of a self-regulated mechanism of nutrition when the pressure evoked is over expressed. It leads to resistance to treatment and tumor growth. Stimulation of the p38MAPK mechanism has a vital determinant in this pathway and the cellular response to 5FU. It has also been found that the suppression of this mechanism goes in line with a decline in 5-FU-associated apoptosis, which later leads to colon tumor inhibition. The 5-FU inhibition channeled by P38MAPK mechanism suppression is related to an autophagic reaction in places where it evokes a decline in p53-mediated apoptosis in a way that it does not affect p53 driven autophagy. It is also clear that the p38MAPK-mediated mechanism takes a vital function in colon tumor 5-FU inhibition by regulating the equilibrium amidst autophagy and apoptosis.

The activation of autophagy by 5-FU can in the same case be associated with the P53-AMPK-mTOR mechanism. The induction of AMPK leads to the suppression of mTOR by p53 and can lead to autophagy [[14]]. The study indicated that receptor-associated-co-activator 3(RAC3), which is highly found in cancer with

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primary function in cancer progression, induction, survival, and metastasis, enhances 5-FU resistance. RAC3 is over-expressed in colon tumor cells under 5-FU diagnosis. It suppresses both autophagy and apoptosis [[15]]. The induction of PI3/AKt and P38MAPK mechanisms is accompanied by repression of caspase-8 and 9 and an encirclement of apoptosis-activating factor -1 moved to the nucleus from mitochondria.

Interruption of Cellular Roles Taking Part in EMT

Changing growth factor-β (TGF-β) is a vital element of EMT that is associatyed with paradoxical duties in the development of cancer. According to research, it has also been found that it acts as a key modulator of 5-FU inhibition; it is up-regulated in 5-FU-inhibition colon cancer tumors, and its resistance reactivates 5-FU colon cancer cell functionality via the regulation of some RNA expression forms, such as the transcription actor TWIST1 [[16]]. It has also been found that TWIST1 inhibition in colon tumor cells activates them to 5-FU-mediated apoptosis.

It was observed that integrins play a primary function in the intrusion, degradation, and metastasis of ECM of colon tumor cells. It was also found that β-6 integrin is up-regulated after 5-FU diagnosis, shielding colon tumors from the outcomes of 5-FU cytotoxic on cell development resistance and apoptosis, via Bvsl2 over-expression, Bax adverse effect, and ERK/MAPK mechanism activation [[17]]. Connexins, a group member of surface adhesion proteins were found to reduce the effectiveness of 5-FU hazardousness in colon cancer cells [[18]]. Consequently, development of E-cadherin reduces with colon cancer stage after the administration of 5-FU treatment. This element associated with the EMT cycle have adverse effects as a result of the over-expression of hairy catalyst of split-1, a transcription element of a Notch signaling mechanism (HES1) in phase II-III colon cancer treatment through 5-FU activating higher colon cancer recurrence rates [[19]].

Apart from cell surface adhesion molecules, there are other elements of cancer advancement and EMT. It has been implied that cell amalgamation can be successfully applied during the induction, progression, and phenotypic change of tumor. It has also been found that GTP-binding protein, radixin, ADAM 10, RhoA proteins, and myosin controlling light chain were found to enhance cell amalgamation in colon cancer, resulting to the growth of a resilient phenotype to 5-FU.

It was also observed that some mechanisms such as Hedgehog signaling, which had been labelled as vital controllers of embryonic growth, cell differentiation (EMT), and tissue polarity, were also found to be part of colon cancer development and 5-FU resistance cells [[20]].

Oxidation Stress, Glucose Metabolism, and Mitochondrial Process

The pyruvate dehydrogenase (PDH) catalyst is an important intermediary of glucose oxidative metabolism that helps in the conversion of pyruvate to acetyl-CoA. Its functionality is restricted by (PDHK) proteins and PDH kinase. It has been found that the conversion of PDHK4 is completely compatible with 5-FU suppression of colon cancer tumors. It has also been found that 5-FU activates PDHK4 expression in a TGF-β indicating a similar reliant way with the phosphorylation of Survivin expression and Smad2 [[21]]. The protein groups, Prolyl hydroxylase are oxygen-selective catalysts that were first known for their potential to control cellular survival to a very low level oxygen environment by focusing the hypoxia-activatable transcriptional elements HIF-2α and HIF-1α to their proteasomal declining. Through p53 phosphorylation activation, Pyruvate dehydrogenases take part in cell destruction, mediated 5-FU colon cancer recession, and development of metabolic stress. The modification of P53 post-translational activates the reaction amidst XPB and P53, a factor of nucleotide editing restoration process, resulting in 5FU-activated DNA mutilation

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restoration and hence colon cancer proliferation and survival.

Various anticancer elements, for example 5-FU, produce reactive oxygen species (ROS), which activate oxygen adding impairment resulting in tumor cell damage. However, cancer stem cells (CSC) can create cellular adaptive responses to reactive oxygen species to thrive [22]. Some proteins have been marked as new indicators of this colon cancer sub-population with the ability to counteract the 5-FU activated reactive oxygen species: 5-FU activation nuclear rearrangement and induction of Nrf2, identified as being associated with the resistance to treatment via its fundamental induction, which later results to up-regulation of antioxidant enzymes, enhancing the inhibition of cells to the cytotoxic outcomes brought about by this treatment.

Mitochondria supply energies for the cells and led to programmed cell death. Over-expression of ATP synthase restricts the energy flow to the process of respiratory, leading to an higher level of superoxide electrons, triggering DNA mitochondrial-associated cell disintegration and DNA damage, but also changed phenotype [23]. Therefore, mitochondrial ATP synthase flaw could lead to bionergetic elements of cancer as well as a primary factor of chemotherapy-activated hinderance [24]. This will, therefore, reduce the production of the sub-elements of the mitochondrial F1F0-ATP synthesis in 5-FU recession cells. Consequently, an ATP synthase, oligomycin a resistor highly counters 5-FU cytotoxic properties. Recent studies have also indicated that 5-FU hindrance is activated by minimizing mitochondrial metastasis with reference to reduced production of both the large cancer inhibitor kinase 2 (LATS2) Hippo mechanism and mitochondrial extension factor 1.

Cell Cycle Perturbation

5-FU-inhibitor colon tumor cells indicated key cell cycle delay in long DNA synthesis time and G1 and G1/S [25]. It was also found that the levels of protein activation of cyclin-mediated kinase 2(CDK2) and its other phosphorylation levels, were minimized in 5-FU-impediment cells. The outcomes indicated that there is a cell cycle delay, preventing the transformation of 5-FUmetabolites into DNA and giving cancer cells ample period for DNA restoration [26]. Studies also indicated that a colon sub-population that had ideal cancer stem cell elements and resistance to 5-FU has the ability to change into a reversible inactive G0 form after it has been exposed to high 5-FU concentrations. The inactive 5-FU-recession colon cancer cells over-expressed both the membrane-bound and activated tyrosine kinase c-Yes. Consequently, Yes-associated protein (YAP) and YES 1 transcript rates are at a high level in liver metastases of individuals diagnosed with colon tumor done after 5-FU-related neoadjuvant treatment. In addition, YAP and YES1 manuscript factors correlated accordingly with tumor degeneration and reduced patient survival [27].

Membrane Drug Transporters and Multidrug Resistance

MDR can result in hindrance to cytotoxic factors like 5-FU influenced by an increase in the activities and expression of some membrane medicine transporters that will be reviewed below.

The first is the MDR-related protein (MRP) which is made up of nine elements, MRP8/ABCC11, ATP/MRP1 binding cassettes (ABC) subtype ABCC6/MRP6 to C1, MRP9/ABCC12, MRP7/ABCC10. The efflux of anticancer and MRP/ABCs reportedly mediated ATP-dependent transport mediators out of cells, enhancing drug inhibition [28].

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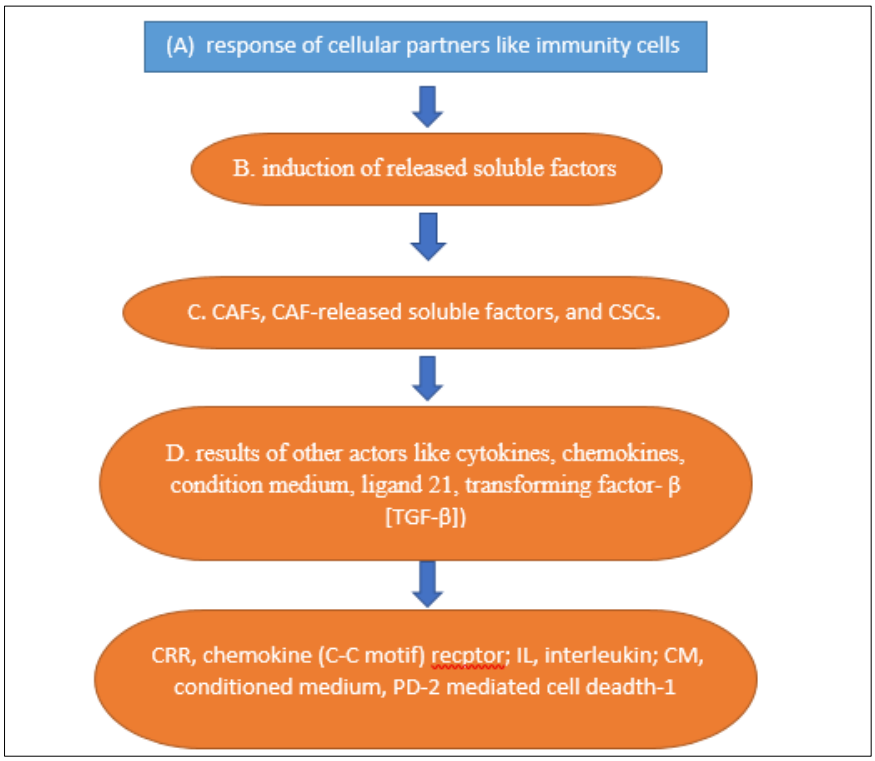
Both ABCC5 and MRP8/ABCC11 have been found as enhancing factors to the resistance of therapies related to 5-FU and its active derived metabolite in colon cancer [29]. Consequently, MRP7/ABCC10 indirectly participates in the 5-FU recession. 5-FU activated up-regulation of Forkhead box M1 (FOXM1) transcription elements, which later up-regulate ABBCC10 in 5-FU-recession cells. Following these findings, the hindrance of ABCC10 and FOXM1 enhance the hindrance of colon tumor to 5-FU.

Tumor Microenvironment

Some 5-FU recession pathways take place in cancer cells and while are moderately modulated by the TME, that assumes a vital function in the bio-availability of chemo-treatment molecules and the overall tumor's factors [30]. The TME is comprised of endothelial cells, cancer-associated fibroblasts (CAFs), cancer cells, and resistant cells with fundamental functions taken by cancer-related macrophages cancer stem cells, and (TAMs).



A. M1 reaction B. induction of released soluble factors and TAMs C. colon cancer stem cells and CAF-released soluble factor D&E. results of varrying actors like cytokines, chemokines, condition medium etc.

C. colon cancer stem cells and CAF-released soluble factor

Vesicles and extracellular soluble molecules perform a major role in carcinogenesis activation and TME-associated recession. A review of the contribution of the two resistant cells CAFs and (TMEs) and the results of their free soluble elements on cancer stem cell preservation and development of 5-FU inhibition will be done.

Subtypes macrophages, released soluble factors, and TAMs

Insoluble tumors, resistant cells, and mostly macrophages have been developed as crucial elements of the cancer stroma, taking a key part in cancer development [31]. Research data on Macrophage subtypes M2 anti-inflammatory 1, M1 pro-inflammatory macrophages, and TAMs have been well documented.

M1 culture media (M1-CM) weakens 5-FU-activated cytotoxic reaction outcomes by minimizing cell

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development and enhancing cell cycle arrests [32]. M1-CM restricts the 5-FU-activated S stage colon cancer cell blockade that concentrates in G2/M and G0/G1, preventing them from medicine-initiated cytotoxic results. Consequently, M1-CM up-regulates protein levels in mRNA, and protein rates of the known element which controls the reaction of p21 that is also overexpressed at protein levels in colon cancer and mRNA affected by M1-CM. The increase of p21 expression has had a direct effect on 5-FU inhibition in a cell line from other parts of the body and from the colon.

Tumor development is enhanced by M2 through metastasis, cell proliferation, immunosuppression, and lymphangiogenesis/angiogenesis [33]. Therefore, it can be well said that TAMs regulate not only tumor development but also chemoresistance, and medical care-guided cytotoxic effects. Research has also indicated that there is a relationship between colon cancer progression and TAM infiltration [34]. 5-FU enhances TAM permeation in colon cancer and the removal of myeloid cells, which are composed of TAMs which increases 5-FU effectiveness on cancer increased resistance. Consequently, the channel of culture from 5-FU-prepared TAMs (TAM-CM) hinders 5-FU-activated cancer development, weight restriction, and size, indicating that 5-FU can lead to the release of TAM elements that act against 5-FU-activated cytotoxicity. TAM-CM metabolic division that has a surplus supply of putrescine is the only metabolic fraction that can do away with 5-FU cytotoxic outcomes by minimizing cleaved caspase-3 and JNK mechanism induction.

Cancer-Associated Fibroblasts, Cancer Stem Cells, and CAF-Released Soluble Factors

Cancer-related fibroblast results from different categories of cells. The most common cells in the group have crucial elements of stroma cancer. They enhance the creation of new tumors by facilitating tumor cell propagation and angiogenesis and incursion performing key functions in inhibition to chemotherapy of various tumors, counting colon cancer. Cancer-mediated fibroblasts propagate various distinct characteristics such as fibroblast growth factor receptor 4(FGFR4) and α-smooth muscle actin. In colon cancer, FGFR4 promotes EMT, takes action in tumor-stroma reactions, and can also be part of a new key factor of 5-FU inhibition in colon cancer [35]. Its hindrance improves cytotoxic paraphernalia of 5-FU via downregulation of indicator converter and catalysts of transcription 3 (STAT3) and later resistance of cFLIP, ensuing in cytochrome c discharge, BAX and caspase-8 and -9 induction, and caspase-9 and -3 and caspase-9 and polymerase divisions and lastly the apoptosis of FGFR4-mediated 5-FUresistant colon cancer cells [36].

Tumor-related fibroblasts also have the ability to release cytokines and chemo- and soluble expression elements that activate JAK and PI3K motion routes to shield cancer cells from chemotherapy treatment elements presently applied in colon cancer [37]. Cancer-mediated fibroblast-associated culture medium (CAF-CM) comprising CAF soluble agents, minimize proliferative and apoptotic levels of colon cancer cells unprotected from 5-FU or not. The colon cancer cell increment is minimized by CAF-CM in the S stage activated by 5-FU, enhancing a longer G1 propagation with cell accretion in G0/G1. Cancer-mediated fibroblast soluble factor, thus enhances cycle arrest of 5-FU-associated colon cancer cells earlier than they enter into mitosis for it to restore cell DNA impairment and keep them ready for mitosis. The cell cycles are associated with the induction of G2/M checkpoint kinase and 2(CHK2) the following reduction in expression of mitosis cycle 25B (CDC25B. Increased levels of phosphorylated CHK2 that are similar to lower CDC25B expression can be found in 5-FU mediated cells formed in CAF-CM [38]. Consequently, CAF soluble elements

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excite and activates STAT/JAK and PI3K/mTOR/ AKT mechanism and the following nuclear translocation of AKT, p38, and STAT triggered states, which enhance the expression of survivin. In this case, STAT3 exhibits a potential point to overrule CAF-associated CRC 5-FU inhibition, as STAT3 resistance enhances colon cancer cells to 5-FU despite the presence of CAF-CM. On the other hand, AKT resistance indicates adversary properties; it does not inform colon tumor cells to 5-FU, which might lead to trosine kinase or MYC receptor mechanism [39]. Cancer-inhibited fibroblasts or colon cancer also eject chemokine (C-C motif) ligand 1 (CCL1), an unhealthy intermediary that has a great contribution to lymph node conversion as well as 5-FU recession, and strongly demonstrates the finger transcript factor snail [40].

Epigenetic Alterations

This is the alteration of gene expression and not changing the nucleotide series. They are among the pathways that lead to 5-FU resistance that will be reviewed in our study.

Histone Posttranslational Modification

Histone structure modification is fundamental in tumor activation and advancement. Histone acetylation or methylation has a direct impact on the chromatic structure and modulates DNA accessibility and gene expression. Histone methylation is related to RNA expression or RNA induction, other the hand, acetylation is only related to RNA induction [41].

The mediated serine-threonine kinase body structure (STRAP) is a a structural protein that binds several molecules together and that epigenetically modulates the Notch route and establishes properties that are related to colon cancer stem cells by working on the polycomb-immune complex 2 (PRC2). The polycomb-resistant complex 2 has trimethylates histone H3 and histone methyltransferase actions on lysine 27 (H3K27me3), a representation of both notch-associated gene inhibition and transcriptionally silent chromatin. However, the activity of methyltransferase is hindered by STRAP, whose mRNA and protein levels are over-copied in colon cancer samples related with ideal tissues. Consequently, STRAP upregulation is related to poor endurance with adjuvant phototherapy, indicating its fundamental duty in 5-FU chemotherapy resistance [42].

DNA Methylation and Demethylation

In the medical care of colon tumor, studies have indicated that some genes that take part in medicine metabolism modulated by cytochrome P450, pyrimidine metabolism, p53 signaling pathways, epidermal development factor receptor, and apoptosis that are hypermethylated and later downregulated leading to 5-FU repression [43]. Some characteristics of microsatellite instability are lack of sufficient incongruity repair (MMR) MLH1 RNA, that result from its catalytic hypermethylation. Despite being identified by advanced appearance MSI colon cancer usually have a promising medical diagnosis. 5-FU metabolism leads to the formation of 5-FUTP, that is consequently incorporated into DNA, producing a discrepancy identified by the MMR structure. This lead to cell cycle apoptosis and arrest in situations where cases of irreversible cuts. In cases where patients are suffering from MLH1 gene deficiency, the damage is not recognized, therefore, conferring repression to 5-FU [44].

Lack of Methylation Hypomethylation-Modulated Gene Upregulation

Prooncogenes genes of recurrent colon cancer take part in the cell production mechanism as well as cell series, resulting in higher rates of production, shielding cells from phototherapeutic cytotoxicity, and the growing danger of return [45].

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DNA Demethylation

As described in previous studies, improvement of ROS production after the drug treatment of 5-FU is observed in 5-FU repression of colon tumor cells. Indeed, ROS production has a relationship with DNA methylation cycles through maximizing levels of 10-11 translocation (TET) enzymes, with no interference in DNMT protein levels. DNA demethylation is, therefore, enhanced through the oxidization of 5-methylcytosine by TET enzymes [46]. It was also observed that there was the presence of hypomethylation of NRF2 in 5-FU-associated colon tumor cells that were in line with the increase in protein levels and mRNA. When treated with 5-FU, Nrf2 is transited into the colon cancer nucleus and reacts with the OH-1 catalytic site, activating cellular stability. Combined, these findings indicate that upregulation of HO-1 and Nrf2 expression through epigenetic DNA demethylation activates the activation of 5-FU hindrance in colon tumor cells [47].

Noncoding RNA-miRNA

FU restricts the amalgamation of DNA and RNA and changes the protein formation profile of miR in colon tumor cells. MicroRNA can control the production of target RNAs and 1 RNA can also be governed by numerous miR. The first example of the molecular mechanism is where they can modulate colon cancer cell 5-FU-medicine reactivity by creating a reaction with the 3′-UTR of their desired RNA's mRNA. In the process of ideal alkaline conjugation amid miR and mRNA, the aim is split. When microRNA is at the basis of translational reproduction, it can lead to the production of steric hindrance on the mRNA site or translocation efficiency transcription. Evaluation of miR expression amidst colon cancer cells and hale and hearty ones indicated upregulation and downregulation of miR after exposure to 5-FU. After chemotherapeutic treatment, the variation in miR expression a possibility of their involvement in the regulation of 5-FU response in colon tumor. With respect to their target, some miR performance as oncogenes and others as cancer inhibition genes [48].

Tam1 chemoresistance and tumor invasiveness

A. The bar shows mRNA formation of protein copies of TIAM1 in colon cancer cell cycles caused transfection by siRNA counter to TIAM1 B. the figure indicates how formation of protein copies of TIAM1 in colon tumor cell line caused transfection by siRNA against TIAM1. C. the cell lines are indicated as the medical cured cell ratio with the bar graph indicating IC50. D. illustrates the potential of invasion of colon cancer cell line transfected by TIAM1 siRNA [49].

In patients with chemoresistance colon cancer, TIAM1 is frequently overexpressed. Wnt-signaling pathways are well-modulated for their role in both drug stemness and resistance. Six are mostly associated with drug stemness, they are also highly related to Ocy4. One of these genes metastasis-activating protein-1, and T-lymphoma invasion (TIAM1) indicate the most key correlation [50]. Recent studies have identified TIAM1 as an oncogene in various cancer.

Studies to determine the expression of TIAM1 gene mRNA correlation with medical care results indicated that TIAM1 is highly upregulated in patients with chemotherapeutic resistance. The use application of Kaplan-Meier examination indicated that patients suffering from colon cancer having high-TIAM1 expression have lower endurance, both overall disease-free survivals. High formation of protein copies of TIAM1 is correlated with poorer sensitivity to phototherapeutic factors.

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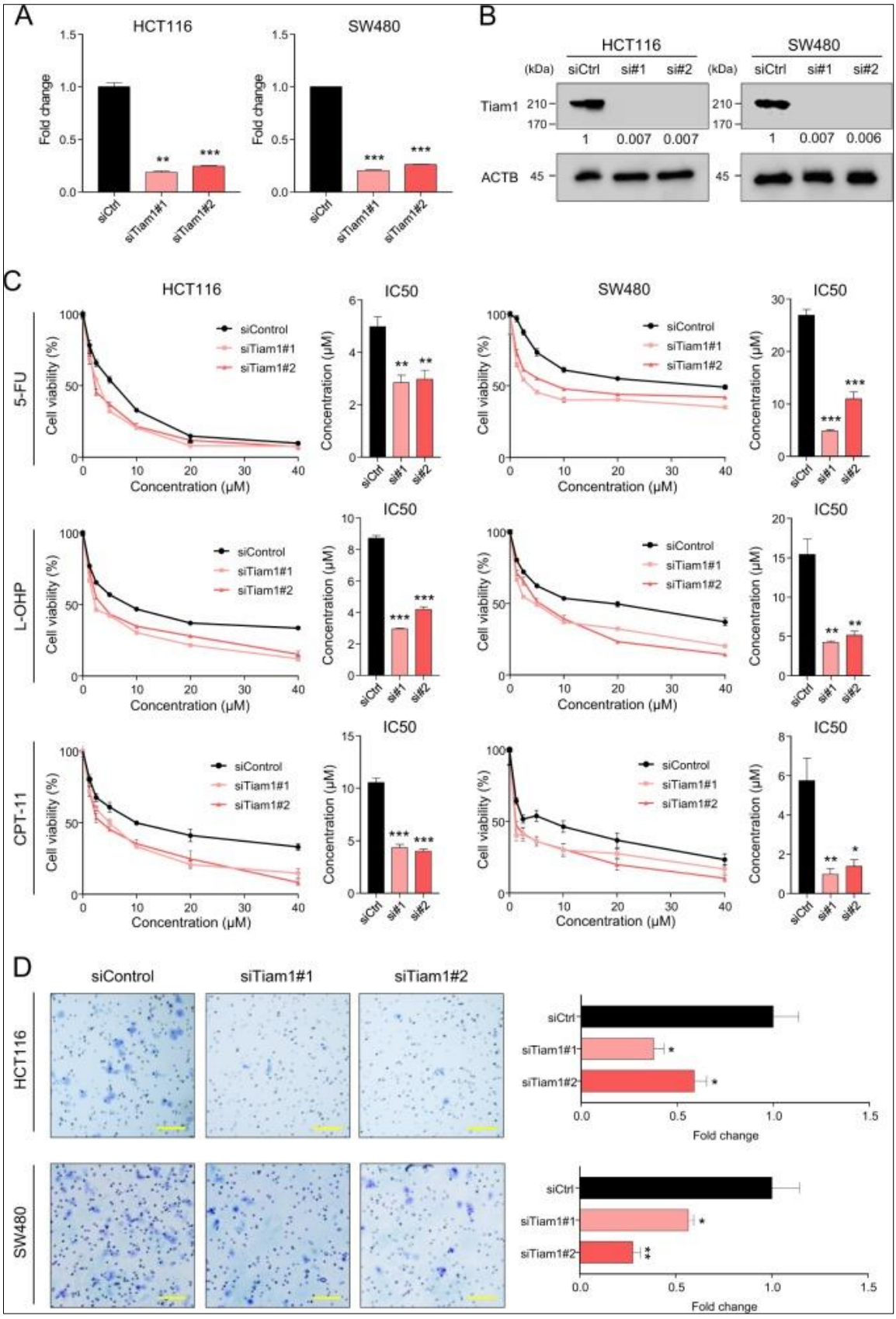

TIAM1 Chemoresistance Mechanism in Colon Tumor

The overexpression of TIAM1 is correlated with the chemoresistance of colon tumor during treatment and in the regulation of treatment repression in cancer cells. The examination of the expression of TIAM1 in different cells with high endogenous expression to undertake siRNA transfection indicated the

resistance of TIAM1 at both protein expression levels and mRNA. The application of cytotoxicity assays to investigate the regulation of TIAM1 towards phototherapeutic elements used in colon cancer patients indicated that TIAM1 resistance highly improved response to chemotherapeutic elements in colon cancer cycles.

Among of the main distinctions of cancer stem cells with advanced repression of chemotherapeutic factors is their high intrusion ability [[51]]. The examination of the invasion of colon cancer cells using or without using TIAM1 resistance by means of matrigel intrusion examinations indicated that the repression of TIAM1 highly reduced the invasiveness of colon cancer. Consequently, the formation of TIAM1 in colon tumor that have been made chemoresistance for more than a year by repeated treatment with L-OHP, 5-FU, and CPT11 indicates that TIAM1 is highly overexpressed in cell cycles that are immune against CPT-11, L-OHP, 5-FU equated to other parental cell cycles [[52]].

TIAM1 Modulated Chemoresistance through Stemness Control of Colon Cancer Cells

According to research, cancer stemness plays a significant function in modulating chemoresistance in different cancers [[53]]. With the fact that TIAM1 suppression leads to enhanced sensitivity towards colon cancer therapeutic drugs, it can be said that TIAM can modulate chemotherapy resistance via the modulation of cancer stemness. A cyclic experimental test using cancer tumor with the presence or without the presence of TIAM1 resistance to investigate the interaction between stemness and TIAM1 indicates that TIAM1 takes part in the regulation of cancer stemness. Among the most significant downstream phases of TIAM1 that modulate stemness is Rac 1 [[54]]. Rac1 induction acts as a key function in stemness repression by semaphorin-3F in colon cancer [[55]]. Consequently, the inhibition of TIAM1 leads to a reduction of the phosphorylation of Rac1. These outcomes confirm that repression of TIAM1 inhibits cancer stemness in sections via suppression of Rac1 phosphorylation.

Colon Cancer-Associated Cafs Intensify Drug Resistance through TAIM1 Overexpression

According to research, cancer microenvironment acts a significant agent in the acquisition of drug inhibition and the maintenance of stemness in different cancers, including colon cancer [[56]]. Cancer-mediated fibroblasts (CAFs) have the potential to facilitate invasiveness and stemness in colon cancer [[57]]. Therefore, it can be concluded that CAFs lead to over production of protein copies of TIAM1 in colon cancer, and that can afterward can be seen in heightened chemotherapeutic inhibition in colon cancer patients.

The Dormant State of Cancer Stem Cells

Their quiescent state is another factor leading to drug resistance in colon cancer [[58]]. A metabonomics study of colon cancer indicated a key suppression of the response to stimulus production of protein in colo205 CD133+ colon cancer cells in comparison with CD133 cells and the attenuated creation of nucleotides such as glucose and cholesterol-modulated lipids [[59]]. The unparalleled factors of CRCSC indicate a sluggish flow attribute that enhance chemotherapy inhibition. Since various chemotherapeutic treatments exterminate rapid-developing cells preferentially, cancer cells are dynamic in DNA reproduction and are more active in DNA impairment factors [[60]]. Furthermore, colon cancer has more time to fix DNA impairment and thrive. This,

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therefore, indicate that despite the fact that most circulation cancer cells can be alienated by chemotherapy, remaining colon cancer cells can join the cell series and lead to tumor return [61].

DISCUSSION

The review has indicated that much is known about resistance to targeted and cytotoxic therapies in the handling of colon cancer, though much need to be done. The aim of researching on the mechanisms of resistance is to come up with new ways of overcoming the resistance to enhance this treatment and achieve improved, long lasting treatment responses and lasting patient survival. The existence of multiple target therapy, customized treatments with available drugs is expected to present better outcomes. Previous examinations of customized therapy related to different anomaly conditions and expressions did not indicate any development in progression-free endurance. The basis of colon cancer treatment involves, targeted therapy, surgery, adjuvant chemotherapy, and neoadjuvant radiotherapy. Recent studies on the impact of the tumor microenvironment have gained attention, introducing the extensive analysis of clinical trials to examine immune-cell infiltration as predictive and prognosis markers.

CONCLUSION

Colon stem cells can be found in different cancers such as colon cancer, lung cancer, pancreatic cancer, and breast cancer. They are seen as an effective focus for cancer treatment. These cells cannot be completely alienated during chemotherapy leading to the growth of resistance to medical care, which is primarily the cause of poor prognosis, tumor reappearance, and metastasis. This study reviews the key pathways of colon cancer chemotherapy inhibition in colon cancer.

This review, provides a comprehensive assessment of the most relevant and significant study of the crucial 5-FU inhibition mechanism in colon. All proteins and their associated pathway in 5-FU hindrance of colon tumors, responsible for metastasis, tumor development, and recurrence have been discussed. Using a line of in vivo and in vitro experiments, research have been able to indicate that TIAM1 modulates the drug sensitivity of colon cancer chemotherapeutic factors. Consequently, cross-drug sensitization of TIAM1 resistance is in line with suppressed stemness.

The association between colon cancer cells and CAFs on drug inhibition via modulation of tumor stemness have been discussed [62]. According to research, the tissue environment is a complicated system of different cellular action regulated by physical connections, soluble molecules, and biochemical indicators [63]. This makes the study of signals traced from cancer microenvironment on tumor development a topic of interest. New findings have proven that CAFs are among the primary factors of tumor microenvironment which leads to drug resistance. The review has indicated that CAF-associated CM led to overexpression of TIAM1 in colon cancer cells. We also demonstrated that resistance of TIAM1 production of protein copies in CAFs hinders drug inhibition and indicates the significance of inhibiting TIAM1 expression in both CAFs and cancer cells.

The review has indicated that TIAM1 modulates hinderance to chemo-treatment factors via improvement of stemness affirming the significance of TIAM1 in colon cancer drug resistance.

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