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Editorial Board Member of *World Journal of Gastroenterology*, Sung-Chul Lim, MD, PhD, Professor, Department of Pathology, Chosun University Hospital, Gwangju 501-717, South Korea. sclim@chosun.ac.kr

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EDITORIAL

Colorectal cancer cell dormancy: An insight into pathways

Anil Kumar, Lekha Saha

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Anil Kumar, Lekha Saha, Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Lekha Saha, Doctor, MBBS, MD, Professor, Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. lekhasaha@rediffmail.com

Abstract

Cancer cell dormancy (CCD) in colorectal cancer (CRC) poses a significant challenge to effective treatment. In CRC, CCD contributes to tumour recurrence, drug resistance, and amplifying the disease's burden. The molecular mechanisms governing CCD and strategies for eliminating dormant cancer cells remain largely unexplored. Therefore, understanding the molecular mechanisms governing dormancy is crucial for improving patient outcomes and developing targeted therapies. This editorial highlights the complex interplay of signalling pathways and factors involved in colorectal CCD, emphasizing the roles of Hippo/YAP, pluripotent transcription factors such as NANOG, HIF-1α signalling, and Notch signalling pathways. Additionally, ERK/p38α/β/MAPK pathways, AKT signalling pathway, and Extracellular Matrix Metalloproteinase Inducer, along with some potential less explored pathways such as STAT/p53 switch and canonical and non-canonical Wnt and SMAD signalling, are also involved in promoting colorectal CCD. Highlighting their clinical significance, these findings may offer the potential for identifying key dormancy regulator pathways, improving treatment strategies, surmounting drug resistance, and advancing personalized medicine approaches. Moreover, insights into dormancy mechanisms could lead to the development of predictive biomarkers for identifying patients at risk of recurrence and the tailoring of targeted therapies based on individual dormancy profiles. It is essential to conduct further research into these pathways and their modulation to fully comprehend CRC dormancy mechanisms and enhance patient outcomes.

Key Words: Colorectal cancer; Colorectal cancer cell dormancy; Cancer cell dormancy; Pathways in colorectal cancer dormancy

Core Tip: Colorectal cancer (CRC) cell dormancy drives therapeutic resistance, recurrence, and metastasis. Key molecular pathways involved in CRC dormancy include Hippo/YAP, NANOG, HIF-1α, Notch, ERK/MAPK, AKT, Wnt, and SMAD. Dysregulation of these pathways promotes dormancy. After re-entering active tumor state following dormancy, these cancer cells become more aggressive and metastasize quickly. The mechanisms behind CRC dormancy are largely unexplored. This editorial summarizes these pathways and their interactions, highlighting the identification of predictive biomarkers crucial for developing targeted therapies, overcoming drug resistance, and enhancing personalized treatments and patient outcomes.

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INTRODUCTION

Colorectal cancer (CRC) is a significant health concern worldwide, ranking third in terms of global cancer incidence. It represents 6.1% of all cancer cases, following lung, breast, and prostate cancers[1]. What's particularly alarming is, CRC stands as the second leading cause of cancer-related deaths globally. Despite multiple treatment modalities, such as chemotherapy, radiotherapy, targeted therapy, and immunotherapy, some cases fail to eliminate chemotherapy-resistant quiescent tumour cells (tumour dormant cells), potentially leading to the generation of metastatic lesions in distant organs. Along with high occurrence, high death rate, and low survival, CRC also exhibits the phenomenon of cancer dormancy or tumour dormancy. Dormant cancer cells are responsible for fueling both the recurrence of CRC and the development of drug resistance, ultimately resulting in a poor prognosis[2]. Currently, there is no specific therapy designed for dormant CRC. However, *in vitro* studies have shown that dormant CRC cells were responding to itraconazole, a drug that inhibits the Wnt pathway *via* noncanonical hedgehog signalling. Through preclinical validation, it was observed that itraconazole treatment initially stimulated a burst of cell proliferation, prompting dormant cells to briefly enter the cell cycle before undergoing irreversible G1 arrest and senescence[3].

The clinical phenomenon of cancer dormancy exists in three patterns - primary, metastatic, and therapy-induced dormancy[4]. Primary cancer dormancy characterized by the prolonged period of temporary and reversible arrest of mitotic growth[5], is physiologically activated by cancer to avoid the stressful conditions during which patients remain asymptomatic before experiencing metastasis and relapse. Tumour dormancy presents itself in two distinct forms: Tumour mass dormancy and cancer cell dormancy (CCD). Tumour mass dormancy is not merely a halt in cell proliferation; rather, it arises from factors like insufficient vascularization (angiogenic dormancy)[6,7] and consequent hypoxia, or immune responses (immunogenic dormancy)[8,9] triggering apoptotic cell death. Consequently, the reduction in tumour mass is primarily due to increased cell death rather than reduced proliferation. On the other hand, CCD involves a unique mechanism where cells temporarily enter a reversible arrest in the G0 phase through activation of the quiescence programme[10], effectively halting their proliferation. Metastatic dormancy occurs when cancer cells disseminate from the primary tumour site and enter a state of dormancy in distant organs or tissues, preventing the formation of metastatic lesions, while therapy-induced dormancy is dormancy that occurs in response to any antitumour therapy especially chemotherapy. This study mainly focuses on CCD. CCD has gained significant attention in recent years, prompting researchers to dive deeper into its complexities and its implications for cancer progression.

Understanding CCD development is a challenge, as its induction mechanism is complex and multifaceted[11]. Dormancy can be induced by various factors such as cell type, nutrient availability, growth factors, extracellular matrix, oxygen levels, immune interactions, and genetic and epigenetic factors[12]. Each of these factors may contribute differently to the induction of dormancy, making it challenging to develop accurate models. Even if models are developed, the relapse and metastasis of cancer after a dormant period may not be accurately reflected in organoid cultures or rodent models. A promising approach lies in identifying markers associated with CCD, considering the diverse mechanisms involved. This attempt requires a comprehensive understanding of the possible cellular pathways implicated in dormancy.

Recent studies have revealed several key factors and signalling pathways involved in CRC dormancy. These pathways involve the Hippo/YAP pathway, pluripotent transcription factors (NANOG and ZEB2), hypoxia-induced signalling (HIF-1α, CSN8, and FBX8), Notch signalling, and the ERK/p38α/MAPK and AKT signalling pathways. Additionally, factors such as Extracellular Matrix Metalloproteinase Inducer (EMMPRIN), the STAT/p53 switch, and both canonical and non-canonical Wnt and SMAD signalling have been identified as critical regulators of CRC dormancy. Figure 1 details these pathways and their potential interactions with each other.

Considering the poor prognosis, drug resistance, cancer relapse, and metastasis driven by cancer dormancy, clinicians and researchers face significant hurdles. By highlighting the key molecules and their respective pathways involved in cell dormancy in CRC, this editorial aims to not only enhance treatment strategies but also advance the frontier of new dormancy-targeted potential therapeutic approaches in CRC. Furthermore, insights into dormancy mechanisms hold promise for the development of predictive biomarkers, enabling the identification of patients at high risk of recurrence and the tailored administration of targeted therapies based on individual dormancy profiles. This editorial aims to help researchers and clinicians better understand dormancy in CRC, leading to improved treatments and outcomes.

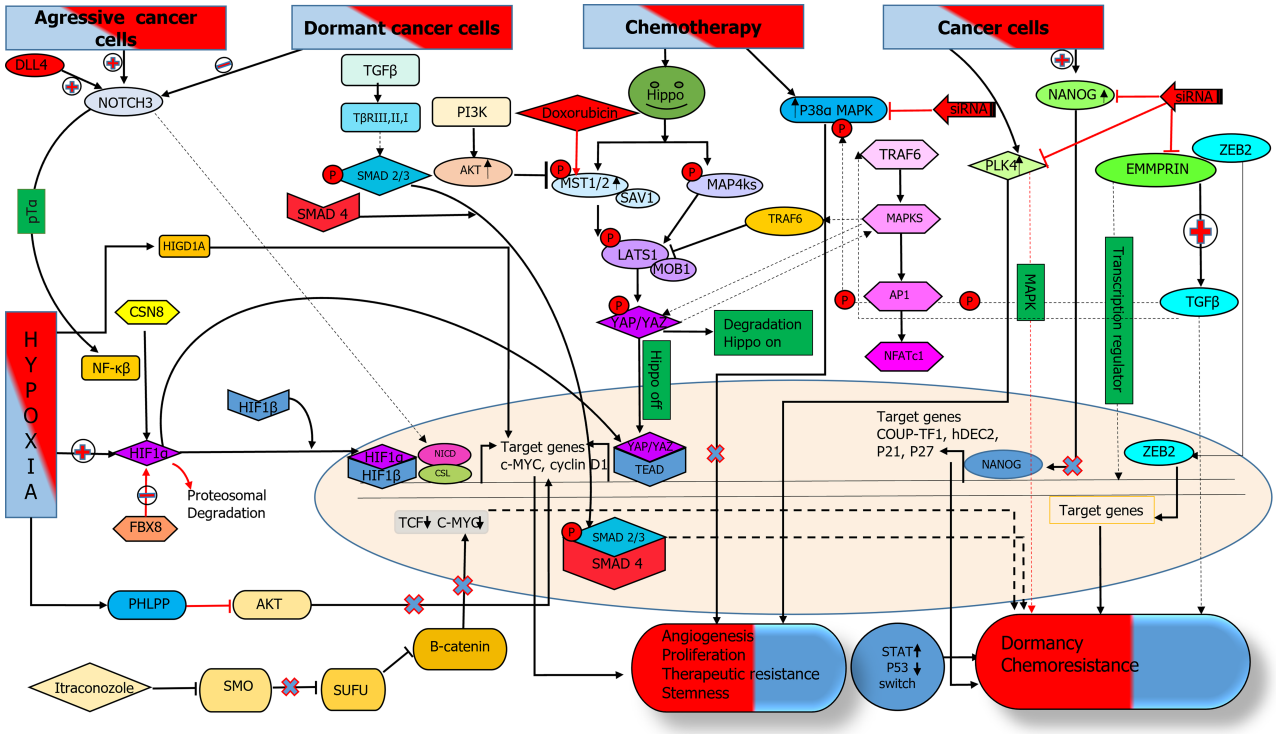

Figure 1 Various signaling pathways implicated in driving cancer cells into dormancy, along with interactions between these pathways and their associated molecules or markers. Notch signaling exhibits variable expression, being elevated in aggressive cancer cells and reduced in dormant ones. Notch 3, with CSN8, activates NF-κB signaling, increasing HIF1α expression under low oxygen or stress, which promotes proliferation and angiogenesis. HIF1α either partners with HIF1β to drive gene expression in the nucleus or enhances YAP/TAZ-TEAD interaction, both supporting growth and angiogenesis. This suggests that Hippo pathway activation induces dormancy, while HIF1α signaling is reduced during dormancy. Conversely, the FBX8 F-box protein degrades HIF1α, increasing dormancy marker expression. It is still a question of how HIF1α regulates both proliferation and dormancy concurrently. Hypoxic conditions increase PHLPP expression, blocking AKT signaling and boosting dormancy markers while reducing proliferation markers in dormant colorectal cancer (CRC) cells. AKT and MAPKs negatively regulate Hippo signaling and promote YAP/TAZ nuclear translocation by inhibiting MST1/2/SAV1 and LATS1/MOB1 complexes, respectively. Dormant CRC cells show decreased AKT and increased MAPK expression. HIGD1A, a hypoxia-induced factor, typically promotes cancer cell proliferation under stress but induces tumor dormancy in deeper cancer tissues. TGFβ/SMAD signaling drives cancer cell dormancy, while the MAPK pathway, *via* increased P38α expression, regulates the switch between proliferation and dormancy in CRC and cancer cell dormancy. Downregulation of P38α leads to growth arrest, and PLK4, a key proliferation regulator, decreases in dormant CRC cells driven by MAPK signaling. Itraconazole regulates the non-canonical WNT pathway in CRC dormancy by inhibiting smoothened, activating suppressor of fused, and ultimately inhibiting β-catenin, temporarily inducing a brief growth cycle before permanent arrest. EMMPRIN inhibition promotes dormancy, while NANOG and ZEB increase dormancy marker expression, making all three dormancy markers. SMO: Smoothened; SUFU: Suppressor of fused.

The mechanisms underlying the decades-long phenomenon of tumour dormancy, particularly CCD, remain poorly understood, despite their significant contribution to tumour relapse and poor prognosis in patients. Tumour dormancy may be influenced by various factors such as cellular processes, the tumour microenvironment (TME), as well as epigenetic and genetic changes. These factors essentially induce tumour dormancy by minimizing proliferation, reducing cell death, and promoting the reversibility of growth arrest, which can ultimately lead to cancer relapse with metastasis. The molecular pathways associated with CCD are currently under extensive exploration. These pathways can be categorized into two groups: Those whose upregulation leads to the development of CCD, and those whose downregulation results in the same. Various key molecules also involved in governing these pathways and driving cancer cells towards tumour dormancy and CCD are also discussed.

Hippo/YAP signalling

The Hippo signalling pathway is a crucial regulatory mechanism in animals that controls cell proliferation, apoptosis, and organ size. The pathway's core components include Hippo (MST1/2) and Warts (LATS1/2), which are serine/threonine kinases. When activated, Hippo phosphorylates and activates Warts. Active Warts then phosphorylate and inhibit Yorkie (YAP/TAZ in mammals). Inhibition of Yorkie prevents its entry into the nucleus, thereby blocking the activation of its target genes involved in cell proliferation and survival[13].

A recent study found that chemotherapy activates the YAP signalling in cancer cells, leading to their dormancy. However, by using a drug called Dox, the pathway prevents the cancer cells from breaking dormancy and regrowing after chemotherapy. Additionally, they found that another drug called TEADi (blocks the YAP-TEAD interaction), when used in combination with chemotherapy, also helped prevent cancer relapse[14]. These results highlight the potential of targeting the YAP pathway to prevent cancer recurrence and improve patient outcomes and suggest that targeting the YAP pathway could be a promising strategy to prevent cancer relapse in CRC patients by maintaining dormancy. In another study in CRC liver metastases, 5-fluorouracil induces quiescence by activating Yes tyrosine kinase (YES1) and

depleting Yes-associated protein (YAP) from the nucleus. YES1 activation and YAP nuclear depletion contribute to CCD [15,16]. Another protein which negatively regulates YAP by its degradation *via* proteasomal degradation is FBX8, a member of the ubiquitin protease family, which regulates dormancy in CRC liver metastasis cells. It upregulates dormancy-related markers such as CK, E-cadherin, and Sox-2, while downregulating markers like Vimentin, C-Myc, CDK4, and HIF-1α. FBX8 interacts with genes involved in hypoxia, cell cycle, and Myc-related pathways, promoting ubiquitination and degradation of HIF-1α, CDK4, and C-Myc[17]. This regulation inhibits angiogenesis, cell cycle progression, and cell proliferation and promotes dormancy, highlighting FBX8 as a potential therapeutic target for dormant CRC liver metastasis cells.

Pluripotent transcription factors

Pluripotent transcription factors also influence the dormancy of CRC cells[18]. In a recent study, one of these genes, *NANOG*, was significantly upregulated in dormant CRC cells (HT29 and HCT116) compared to active ones. When *NANOG* was silenced using a post-transcriptional gene silencing technique called small interfering RNA, several important changes were observed: The viability of the cancer cells decreased, fewer cells remained dormant, and more cells died (apoptosis increased). Additionally, silencing *NANOG* reduced the expression of certain genes (*COUP-TF1*, *hDEC2*, *P21*, and *P27*) involved in maintaining dormancy[2]. *NANOG* was regulated by the fatty acid oxidation/ATP citrate lyase-dependent pathway. *NANOG* upregulation increased the transcription of P21 and P27, which promoted the dormancy of CRC cells. These findings suggest that *NANOG* plays a crucial role in keeping CRC cells dormant and silencing *NANOG* can disrupt this dormancy, causing the cancer cells to undergo apoptosis when provided with chemotherapy again. *NANOG* also triggers a process where the cells use fatty acids for energy, which activates *NANOG*. Once activated, *NANOG* increases the production of two other proteins, P21 and P27, which push the cancer cells into a dormant state. In a recent study investigating CRC dormancy, researchers isolated and characterized quiescent CRC stem cells responsible for chemoresistance in colorectal tumours, revealing a rare cell population, PKH26+ /ZEB2+, responsible for chemoresistance. These cells exhibit stemness, chemoresistance, and epithelial-mesenchymal transition (EMT) features. ZEB2 overexpression induces a transition towards a slow-growing, chemoresistant, and dormant state, suggesting potential therapeutic targets to address dormancy and chemoresistance in CRC[19].

HIF-1α signalling

Another important factor responsible for cancer dormancy is hypoxia, a master regulator of cancer biology. Hypoxia is a persistent condition that arises due to increased oxygen consumption of fast-growing cancer cells combined with less oxygen supply due to defective cancerous vascularization[20]. In response to low oxygen levels, HIF-1α, a transcription factor, is activated. HIF-1α signalling is reported to be associated with hallmarks like stemness, dormancy, and resistance to anticancer therapies[21,22]. Substantial evidence indicates that hypoxia can trigger the expression of genes that inhibit or slow down apoptosis, thereby increasing the survival of dormant cells. However, the regulation of both proliferation and dormancy by hypoxia remains unclear. A study on CRC cells and mice involving a protein named CSN8, a key regulator of hypoxia-induced EMT and dormancy in CRC cells, found that overexpression of CSN8 arrested cell proliferation-upregulated key dormancy markers (NR2F1, DEC2, and p27) and hypoxia response genes (*HIF-1α* and *GLUT-1*), and dramatically enhanced survival under hypoxia. This suggests that CSN8 favours the upregulation of HIF-1α signalling, crucial for CRC cells' adaptation to the TME. CSN8 activates HIF-1α expression partially *via* the NF-κB pathway, increasing dormancy induction[23]. Conversely, another study showed that the F-box protein FBX8 promotes the ubiquitination and degradation of HIF-1α, CDK4, and C-Myc[17], suggesting that HIF-1α degradation may promote dormancy. Further studies are needed to resolve whether HIF-1α is upregulated, downregulated, or regulated by different molecular pathways to promote dormancy.

There is another hypoxia-inducible gene domain family member 1A[24,25], which in deep tumour tissues promotes dormancy. There are comparatively fewer studies of hypoxia-induced cell dormancy in CRC as it is difficult to establish hypoxic cell line models in CRC due to less cell viability in hypoxic conditions unlike some prostate cancer cell lines[22].

Notch signalling

Another important signalling pathway involved in cell proliferation, fate, differentiation, and lineage specification is Notch signalling, a crucial pathway in cell functions, involves interactions between Notch receptors (Notch 1-4) and ligands (Jagged1, Jagged2, DLL1, DLL3, and DLL4). These interactions trigger proteolytic cleavages, releasing the Notch intracellular domain, which then activates target genes[26]. A recent study on Notch3 revealed its role in CRC dormancy and identified factors that could be targeted to break dormancy without inducing cancer activity and metastasis. The findings showed that the Notch ligand DLL4 played a crucial role in regulating Notch3 signalling in tumour cells within the angiogenic TME. The study demonstrated that quiescent tumours lacked DLL4 expression, while aggressive tumours exhibited intense DLL4 expression[27]. Notably, neutralization of DLL4 *in vivo* significantly impaired Notch signalling in tumour cells. These results suggest that targeting Notch3 signalling and DLL4 could be a potential strategy to break CRC dormancy and prevent cancer metastasis.

ERK/ p38-MAPK pathway

The MAPK pathway is a very vital signalling pathway that controls important functions like growth, proliferation, apoptosis, resistance, and dormancy[28-31]. Here are four main MAPK cascades identified in eukaryotic cells: ERK, JNK, p38 MAPK, and ERK5 signal transduction pathways. The JNK and p38 MAPK pathways primarily govern cellular stress and apoptosis and the ERK/MAPK pathway, the most studied MAPK signalling pathway, is closely linked to cell proliferation and differentiation[32]. Understanding the dual role of the p38α MAPK pathway in CRC development and

chemoresistance or dormancy may offer insights into targeting this pathway for therapeutic intervention. However, some studies favour that ERK/p38α/MAPK can disrupt the dormant state, leading to reactivation and proliferation of cancer cells. Conversely, other research indicates that sustained activation of p38α MAPK may be necessary for maintaining dormancy and preventing the reactivation of dormant cancer cells. In addition to the core components of the MAPK pathway, other factors regulated by this pathway also play a significant role in inducing dormancy in CRC cells. One such factor is Polo-like kinase 4 (PLK4), a key regulator of cell division, which has been identified as a crucial factor in regulating CRC cell dormancy. Downregulation of PLK4 induces dormancy, inhibits migration and invasion of CRC cells, and is associated with late recurrence in CRC. Mechanistically, downregulation of PLK4 induces autophagy, leading to the restoration of aggressive tumour cells to a dormant state through the MAPK signalling pathway. Inhibition of autophagy triggers apoptosis of dormant CRC cells[33]. These findings highlight the role of PLK4 and MAPK signalling in CRC dormancy and suggest autophagy inhibitors as potential therapeutic targets for eliminating dormant cancer cells.

AKT signalling pathway

Another signalling pathway that showed its role in CRC dormancy is the AKT signalling pathway. The PI3K/AKT/mTOR signalling pathway is altered in various cancer types[34]. This pathway governs multiple cellular processes, such as survival, proliferation, growth, metabolism, angiogenesis, and metastasis. A recent study revealed the role of AKT signalling suppression in inducing dormancy in CRC cells under chronic hypoxic conditions. This dormancy induction was associated with increased levels of phosphatases such as PHLPP and downregulation of PTEN[22]. These findings suggest that targeting the downregulation of AKT activity by modulating PHLPP and PTEN levels could be a promising strategy to break CRC dormancy and eliminate dormant cancer cells without reactivating them. Such an approach could overcome therapeutic resistance and improve treatment outcomes in CRC patients.

EMMPRIN

Some inducer factors also regulate the dormancy in CRC, and EMMPRIN acts as a critical regulator preventing CRC cells from entering a dormant state. EMMPRIN is a protein involved in various cellular processes, including transcription regulation[35]. Research demonstrates that tumour cells can stimulate adjacent macrophages to become M2-activated, promoting tumour growth and angiogenesis. However, when EMMPRIN expression is reduced in tumour cells, they enter a dormant state. EMMPRIN also regulates the production of TGFβ, a key player in dormancy and EMT. While EMMPRIN knockdown induces dormancy, co-culturing with macrophages partially reverses this effect[36]. Thus, EMMPRIN emerges as a potential therapeutic target for preventing tumour dormancy and metastasis.

POTENTIAL PATHWAYS LIKELY INVOLVED IN CRC DORMANCY

STAT and p53 switch

In addition to known pathways associated with CRC dormancy, other potential pathways remain unexplored but might play a significant role in inducing dormancy. One such switch is STAT3 and p53, which have opposing roles in cellular regulation. While p53 acts as a tumour suppressor, triggering cell cycle arrest and apoptosis, STAT3 is constitutively activated in many cancers, promoting cell proliferation and survival. Mutations that result in the loss or gain of p53 function, along with constitutive STAT3 activation, are frequent events in numerous cancer types. Although not extensively studied in the context of CRC dormancy, the STAT3/p53 pathway has the potential to push cancer cells towards dormancy.

Canonical and non-canonical SMAD signalling

TGFβ signalling triggers both canonical and noncanonical SMAD signalling pathways. In the canonical pathway, TGFβ binds to TβRIII and presents it to TβRII. TβRII recruits and phosphorylates TβRI. Activated TβRI phosphorylates SMAD2/3, leading to the formation of heteromeric complexes with SMAD4. These complexes translocate into the nucleus, where they regulate the expression of target genes. One of the target genes induced by TGFβ/SMAD signalling is SMAD7, which participates in a negative feedback loop by recruiting the E3 ubiquitin ligase SMURF to TβRI[37]. During the early stages of tumourigenesis, TGFβ stimulates the expression of cyclin-dependent kinase inhibitors such as p15, p21, p57, and eukaryotic translation initiation factor 4E-BP1, leading to cell cycle arrest, possibly participating in giving cancer cell a dormant state. Thus, targeting these cyclin-dependent kinase inhibitors could be a promising potential therapeutic approach to break cell dormancy and move the cells to the apoptosis process[38-40].

Non-canonical and canonical WNT switch

Canonical WNT and non-canonical Wnt signalling cascades act as a switch to turn on proliferation and dormancy. Canonical WNT signalling utilizes Frizzled and LRP5/6 to activate the β-catenin-TCF/LEF complex, leading to the upregulation of target genes like *MYC*, *CCND1*, and *LGR5* responsible for proliferation. Conversely, noncanonical WNT signalling is transmitted through Frizzled or ROR1/2 to activate different branches such as PLC, Rac1, and RhoA. These branches, in turn, activate transcription factors like NFAT and AP-1 which promote dormancy-like characteristics in tumours[37]. Wnt signalling is also affected by paracrine non-canonical hedgehog signalling. A recent study of the suppressor of fused (SUFU) activator itraconazole, which is a potent inhibitor of smoothened (SMO), found that itraconazole inhibited SMO and released its inhibitory effect from SUFU. Subsequently, itraconazole-derived SUFU activation in WNT high epithelial tumour (CRC cells) prevents the nuclear localisation of beta-catenin, causing

diminished TCF expression and a phenotype of proliferation. This ultimately results in the temporary vulnerability of dormant tumours for chemotherapy before undergoing permanent growth arrest (senescence), affecting both dividing and dormant cancer cells[41].

Given the limited literature directly implicating signalling pathways in CRC dormancy, future studies should be designed to explore these pathways and their direct involvement in CCD (CRC cell dormancy). The focus should be on identifying specific biomarkers that are unique to CCD. These markers could be identified through genetic expression studies of proteins associated with CRC, and filtering them based on their specific expression patterns in dormant cancer cells and further tumour progression can be enhanced with artificial intelligence[42]. Alternatively, researchers could focus on common factors or proteins that play a central role in regulating the signalling pathways involved in CCD. Once these markers are identified, efforts should be directed towards developing new treatments that can either temporarily awake dormant cancer cells followed by apoptosis and prevent them being metastatic and further proliferative, or induce senescence (irreversible growth arrest and cell death). Combining these new treatments with existing therapies, such as chemotherapy and immunotherapy, should also be explored to enhance treatment efficacy and to explore whether new treatments sensitize dormant resistant cells to standard therapies. Additionally, the role of the TME in shaping dormancy and drug resistance should be investigated. Understanding the interactions between tumour cells and their surrounding environment in the context of dormancy could lead to the development of adjuvant therapies that target these interactions alongside standard therapies targeting cancer cells. In addition to known pathways associated with CCD, other potential pathways remain unexplored but might play a significant role in inducing dormancy. Investigating these pathways, such as the STAT3 and p53 switch, canonical and noncanonical SMAD signalling, and the canonical and noncanonical WNT switch, could provide valuable insights into CCD mechanisms and uncover new therapeutic targets/biomarkers for CRC treatment.

Translating basic research findings into clinical applications is crucial. Future studies should focus on translating preclinical findings into clinical trials to evaluate the efficacy of novel therapeutic strategies aimed at targeting CCD in CRC patients. Clinical trials exploring the safety and efficacy of targeted therapies, immunotherapies, and combination treatments specifically designed to disrupt dormancy and prevent cancer recurrence are warranted.

CONCLUSION

In summary, continued research into the mechanisms of CCD in CRC is essential for developing effective therapeutic strategies to prevent cancer from undergoing dormancy, resistance, recurrence, and metastasis. By identifying dormancy biomarkers, developing targeted therapies, investigating microenvironment factors, translating research into clinical applications, and exploring novel pathways, we can move closer to achieving fruitful outcomes in the treatment of dormant CRC.

FOOTNOTES

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Country of origin: India

ORCID number: Anil Kumar 0000-0003-0000-6448; Lekha Saha 0000-0001-5925-7159.

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