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**Colorectal carcinogenesis: Insights into the cell death and signal transduction pathways: A review**

Ashokkumar P *et al.* Cell death mechanisms in colon cancer

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**Abstract**

Colorectal carcinogenesis (CRC) imposes a major health burden in developing countries. It is the third major cause of cancer death. Despite several treatment strategies, novel drugs are warranted to reduce the severity of this disease. Adenomatous polyps in colon are the major culprit in CRC and relatively found in 45% of cancers, especially 60 years of age. Inflammatory polyps are currently gaining attention in CRC and growing body of evidences denotes the role of inflammation in CRC. Several experimental models are employed to investigate CRC in animals which include APCmin/+ mouse model, Azoxymethane, Dimethyl hydrazine and combination of Dextral sodium sulphate and dimethyl hydrazine. During the progression of CRC, several signal transduction pathways are activated. Among the major signal transduction pathways are p53, Transforming growth factor beta, Wnt/β-catenin, Delta Notch, Hippo signalling, nuclear factor erythroid 2-related factor 2 and Kelch-like ECH-associated protein 1 pathways. These signalling pathways collaborate with cell death mechanisms including apoptosis, necroptosis and autophagy to determine the fate of the cell. Extensive research has been carried out in our laboratory investigating these signal transduction and cell death mechanistic pathways in CRC. This review summarizes the pathogenesis of CRC and related cell death and signal transduction pathways.

**Key words:** Colorectal cancer; Cell death; Apoptosis; Autophagy; Inflammation; Hippo signalling; Nuclear factor erythroid 2-related factor 2; Wnt signaling

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**Core tip:** Colorectal carcinogenesis (CRC) imposes a major health burden. This review addresses the cell death mechanisms and major signal transduction pathways involved in CRC. Regulated cell death is important for maintaining normal homeostasis and dysregulation of cell death process leads to a spectrum disease including cancer. It is interesting to note that cell death pathways collaborate with each other and therefore understanding the various cell death mechanisms are essential. CRC is orchestrated by various signal transduction pathways and used as drug targets. This review highlights the key concepts of Cell death mechanisms and signal transduction in CRC.

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**INTRODUCTION**

Cancer is a dreadful disease due to an anomalous growth of cells leading to irregular balance of cell proliferation and death. Cell death is a physiological process where normal cells are regulated by “touch contact inhibition”. However, the proliferated cells invade other tissues and metastasize to distant sites causing morbidity[1,2]. In recent years, colorectal carcinogenesis (CRC) imposes a major health burden in developing countries[3,4]. It is the second most cause of cancer death in women and third most cancer death in men[5]. Due to the environmental factors, sedentary life style and diet, the risk of CRC has been growing over the few years. In many cases, the symptoms are not known to the individual. Though the awareness of cancer screening and knowledge of therapy modalities have increased, the burden of CRC is much more pronounced in developing countries. The mortality rate of CRC is high in Asian and African populations. Recently, mortality rates are found to be declining in Western countries because of early screening and better treatment procedures[6]. Increase in mortality has been reported in several countries in Latin America, the Caribbean and Asia, probably due to inadequate health infrastructure and lack of knowledge in cancer screening[7].It is well-known that dietary factors influence the incidences of CRC[8] Diet rich in fibers, low fat content tend to avoid CRC. Food stuffs we intake determine the quality of health. Fried foods, red meat, processed food, increases the risk of CRC[9,10].

**ROLE OF POLYPS IN COLON CANCER**

The cells in the lining of the colon change morphologically and proliferate uncontrollably. Polyps are benign (non-cancerous) involving the lining of the bowel. They occur in several areas of gastrointestinal tract but predominantly in the colon. They appear as small protrusion in the lumen. When ageing progress, number of polyp’s increase. Malignant polyps indicate an adenoma that seems to be benign. Adenomas are precursor lesion in CRC arising through the adenoma-carcinoma sequence. CRC develops due to the formation of a malignant neoplasm from the lining of the large intestine[11].The malignancy risk has been linked to the site, histological characteristics of polyps as well as its size. Polyps < 5 mm in diameter are harmless and exhibit insignificant risk of malignancy and diameter of above 25 mm show a significant risk[12]. Colonic polyps are aberrant growth which appears on the colon. Polys, in principle can be diagnosed by screening the colon through endoscopy or colonoscopy. Three types of colonic polyps are hyperplastic polyp, adenomatous polyp and malignant polyp[13]. These small colorectal polyps vary in size ranging from small (< 10 mm), diminutive (< 6 mm) and displays progression of cancer in 3%-5% cases[14].The larger size of the polyp has greater chances of developing into a tumor. Among the polyps, the common ones are adenomas - which have potential to become cancerous and can be detached during screening tests. Hyperplastic polyps must be recognized to differentiate it from adenomatous polyp, as they have less potential to be cancerous, unless they are localized in the proximal colon[15]. Inflammatory polyps are gaining attention and train to ulcerative colitis and therefore ulcerative colitis upsurges the overall risk of CRC[16,17]. A recent article highlights the importance of managing these complex polpys and resection in colonic tumors[18]. It is documented that 5% of all the CRC are attributed to two specific inherited syndromes. They are hereditary nonpolyposis colorectal cancer (HNCC) and familial adenomatous polyposis (FAP)[19,20].

**SYMPTOMS AND RISK FACTORS OF COLON CANCER**

The common symptoms of CRC are rectal bleeding, significant change in the colour of the stool, especially dark or black colored stools, irregular bowel habits, pain or discomfort in the lower abdomen, weakness or fatigue and certain types of anemias[21]. Huge quanta of risk factors are proposed to cause CRC. Age is a major risk factor. About 90% of CRC patients are of the age above 50. The median age where CRC is diagnosed for men is 68, and 72 in case of women. The risk due to environmental factors include consuming diet rich in red meat and fat, poor intake of dietary fibre, sedimentary life style, obesity, diabetes mellitus, smoking and consumption of alcohol[22,23]. Dietary consumption of fish oil rich in omega 3 - fatty acid (Omega 3 PUFA) reduced the risk of CRC and the production of heterocyclic amines during cooking of meat, higher levels of fecal bile acids have been identified as possible mechanisms[24]. Personal history of sporadic tumours is known to increase the risk of CRC. A previous history of colonic polyps, small bowel, endometrial, breast or ovarian cancers are factors contributing CRC[25,26]. In recent years, there has been an upsurge interest in evaluating the genetic pathways contributing CRC. The current research trend has been diverted towards chromosome instability pathway, which correlates the sporadic CRC through the mutations arising from K-ras, p53 and APC. The microsatellite instability pathway describes the hereditary non-polyposis through frequent mutations in genes of mismatch repair pathway[27,28].

**STAGES OF COLON CANCER**

CRC is horrendously, a disease that progresses gradually through multiple steps precisely connecting three stages: Initiation - a process which amends the molecular message of the normal cell, promotion - to carry the tumour in support with aberrant signal transduction cascades and progression that ends up with phenotypically altered transformed cell. CRC can be divided into fivestages namely stage 0 to IV (Figure 1). Depending upon the stages it increases the severity of the disease and their therapeutic option[29]. Stage 0 can be characterized by tumour at the region of mucosa or inner lining of the colonic region. When the cancer cells grown at the mucosa and has the invasive capacity only at the muscular region and not at the neighbouring tissue of the colon can be observed in the stage I of the CRC[30]. Stage II can be sub categorise into three types based on the invasive growth on the walls of the colon, muscular layer in to abdomen lining and the walls of the colon in to nearby tissues[31]. Depending upon the growth of the cancer the stage III can be further divided in to three types. During this stage the cancer grown at the inner lining of the colonic muscular layer and lymph nodule formation at the surrounding tissues. Based on the number of nodule formation the stage can be named as IIIA, III B and III C. Stage IV describe the end stage of the disease and spread at the distant part of the body namely liver, lungs and other parts of the body[32].

**MURINE MODELS OF COLORECTAL CANCER**

The basic research in the CRC has grown itself on the animal models[33,34]. Especially, in recent times animal models become the strength in understanding the pathogenesis and for developing novel chemotherapeutic drugs. In spite of that, murine models have become a key tool in well understanding the effects of genetic modifications occur in the process of the CRC formation[35,36]. The researchers developed and modified the murine models of CRC which is a resource of immense potential. The murine models were segregated into three different classifications namely genetically modified, western diet induced and as well as chemically induced models[37].

***APCmin/+ mouse model***

Studies involving the preclinical CRC research over the past few decades involve the APCmin/+ mouse[38]. The APCmin/+ mouse is genetically engineered model of mouse colon carcinogenesis. When these mice reach at the age of 4 wk they spontaneously develop tumors in the intestine and colon. It is a well-known phenomenon, about 80% of the CRC arise because of the mutations of APC gene. Researchers’ removed the one allele of *APC* gene and developed as APCmin/+mice model. APCmin/+model of intestinal/colorectal cancer was extensively studied in developing the chemotherapeutic drugs[39,40].

***Dimethyl hydrazine and azoxymethane***

Azoxymethane (AOM) and 1,2 dimethyl hydrazine (DMH) are the two notorious chemical carcinogens used to induce and study CRC in rat and mouse models[41,42]. AOM and DMH are alkylating agents that produce the free radicals that bind to DNA and causes mutations. The accumulated mutations will be developed as tumours. These agents are injected either intraperitoneally (*i.p.*) or subcutaneously (*s.c.*) in animals for several weeks to induce colonic tumors[43]. Detailed analysis of the colonic tumours from the chemically which induced rodents harbour mutations in the *β-catenin* gene, quite similar to Human Non Polyposis Colorectal Cancer (HNPCC)[44]. In our laboratory, we extensively used this model to develop many natural chemotherapeutic agents[45].

***DSS/DMH model of ulcerative colitis induced CRC***

Chronic inflammatory bowel disease (IBD), where colon is extensively injured over a prolonged time due to inflammation increases the risk of CRC. Most common forms of inflammatory bowel disease are ulcerative colitis and Crohn’s disease[46]. Dextran sodium sulfate (DSS) and DMH in combination are now used to induce CRC in Fisher rats[47]. Single dose of AOM and three cycles of 2% DSS in drinking water for seven days results the tumor formation in 8 wk of time. Largely used by the researchers to screen the drugs using this AOM/DSS or DMH/DSS model in mouse.

***N-methyl-N-nitro-N-nitrosoguanidine and N-methyl-N-nitrosourea***

These chemically induced N-methyl N-nitro-N-nitrosoguanidine (MNNG) and N-methyl-N-nitrosourea (MNU) are non-specific colon cancer models. These carcinogens when administered to rodents induce neoplasia in multiple organs[48-51]. MNU injection to rodents induce prostate and breast cancer as well[52]. When MNU is administered through the rectum, it not only causes a greater incidence of CRC, but also induce thymic lymphoma and lung cancers[53]. Since, it is considered as one of the non-specific colon cancer model, nowadays it was not used frequently to induce colorectal cancer.

***Western-diet induced rodent CRC model***

Epidemiologic studies indicated that diet play a vital role in the development of colorectal cancer risk in humans[54]. There are many studies performed to examine the influence of specially designed some typical western diets on the incidence of colorectal cancer. About 12 wk feeding of western diets to rats and mice develop hyperplasia of colonic crypts[55,56]. Approximately 70% of the mice fed with the Western diet exhibited nuclear atypia in colonic epithelia and 40% of the mice showed feautures of dysplastic crypts at the end of two years[57,58]. These reports suggest the involvement of Western diet in eliciting CRC.

**EPITHELIAL-MESENCHYMAL TRANSITION IN COLORECTAL CANCER**

***Epithelial cells: Targeted cells in colorectal cancer***

It is believed that CRC originates in the epithelial cells that lining the colon and rectum. The epithelium is highly vulnerable to mutation and carcinogenesis as the replication rate of cells in the epithelium of colon and rectum is relatively high with a replication rate of 1010 cells every day[59].The abnormal accumulation of epithelial cells can cause mutation in oncogenes and tumour suppressor genes that may lead to neoplastic growth. Thus, the formed abnormal change of cells in the colon and rectum, which is a benign lesion, have the potential to further develop into cancer and metastasize to other organs[60].

***Epithelial-mesenchymal transition: A complex mechanism in cancer metastasis***

Epithelial-mesenchymal transition (EMT) represents a well-organized mechanism in which epithelial cells alter its cellular characteristics and behaviour, and re-form into a mesenchymal like phenotype[61]. The polarized epithelial cells are tightly packed through tight junction molecules such as claudin, occludin, zonula occludens; adherens molecules such as E-cadherin and desmosomes to form a sheet-like structure in the normal epithelium[62]. In contrast to epithelial cells, mesenchymal cells do not possess cell-to-cell adhesion molecules which give migratory capacity and invasiveness to mesenchymal cells. The dissolution of cell adhesion molecules results in loss of apical to basolateral cell polarity in mesenchymal cells. Yet another important feature of these mesenchymal cells is resistance to cellular senescence and apoptosis. Mesenchymal cells are characterized by the enhanced expression of extracellular proteases, and transcription factors such as snail, slug, twist that activates the cells to produce collagen, fibronectin, vimentin, α-smooth muscle actin (α-SMA), *etc*[63]. Interestingly, the shift from epithelial to mesenchymal transition is complex. Upon trigger by mediators, the events starting with dissolution of cell to cell adhesion occur which results in loss of microvilli as well as cilia in the apical surface of epithelial cells. At this stage, cytoskeletal re-organization takes place which releases alpha smooth muscle actin and matrix metalloproteinases. These secreted MMPs degrade the extra cellular matrix which facilitate the dissolution of cells from the basement membrane and allow cells to move along the matrix[64].

EMT plays a key role in spreading of cancer over distant parts of the body. The newly produced cells by EMT display several properties associated with cancer metastasis. Reports suggest that EMT cells can avoid cellular senescence by inhibiting tumour suppressor proteins[65]. Further, research evidences show that high level of vimentin in EMT cells makes the cell more resistant to chemotherapeutic drugs[66]. The mechanism of EMT in colorectal cancer metastasis is depicted in Figure 2. The mechanism of EMT is considered as complex because of the heterogeneity of population. Interestingly, not all the epithelial cells in a mutated epithelium undergo EMT. Moreover, not all formed EMT cells facilitate metastasis. Several environmental factors as well as signalling cascades regulate these mechanisms of EMT[67]. A successful metastasis is achieved through the involvement another mechanism, *i.e.,* mesenchymal-epithelial transition (MET). The invasive mesenchymal cells produced by EMT travelled through systemic circulation and anchored themselves in other distant parts. For this, cells must regain their epithelial features and thereby undergo MET. The modulation of cells between EMT and MET facilitate cancer metastasis[68].

Interestingly, E-cadherin, a hallmark for EMT is reported as a biomarker for colorectal cancer[69]. Recently, a research group has reported that silencing of ubiquitin-specific protease 47 (USP47), a deubiquitinating enzyme, augmented the proteasomal degradation of Snail, the transcription factor involved in EMT to prevent the progression of colorectal cancer[70]. A molecular genetic approach towards the involvement of EMT in colorectal cancer revealed that the epithelial phenotype in colon cancer cells might be sensitive to several drugs such as Src, Notch, and epidermal growth factor receptors inhibitors[71]. Further studies are warranted to identify novel regulators of EMT in order to find out novel cellular target of colorectal cancer.

**CELL DEATH IN COLORECTAL CANCER: “CUTS TWO WAYS” PROCESS FROM WOMB TO TOMB**

Though Carl Vogt reported the incidence of cell death in metamorphic toads in 1842, the mechanisms of cell death was recognized in the middle of 19th century[72]. However, research attempts are yet to come out with a clear picture of the phenomena of cell death; and confusions are remaining still between the alternative forms of cell death. Being an essential physiological process to maintain tissue homeostasis, the different modalities of cell death are intensively being studied[73]. The decision of a cell whether to live or die is an important and even the determining factor in the progression of cancers[74]. Chemotherapies targeting cell death mechanisms are highly encouraged in order to prevent cancer progression and metastasis[75,76]. Dis-regulated cell death signalling cascade are considered as a fundamental process in the progression and worsening of CRC. In this notion, the conceptual understanding of the involvement of different modes of cell death in colon carcinogenesis and its progression shed light in finding out novel cellular target against colorectal cancer.

***Death triggering environmental cues in the colorectum***

It is considered that the urogenital system and hindgut which include colon and rectum begin to divide in the 4th week of human gestational period and would become separate units by 7th week[77]. Cell death, particularly apoptosis in the mesenchyme plays a predominant role in this process. Research evidence shows that, apoptotic cells are concentrated in the mesenchyme of the terminal rectum for the formation of anal canal during the 7th week of gestational period[78]. A number of developmental regulatory signalling molecules such as Wnt 5a, Cdx1, Hoxd-13, Tcf4 and Shh are actively participating in the up and down-regulation of apoptotic cell death for the formation of colorectum[79,80]. Interestingly, researchers have reported the decisive role of autophagy for the activation of cellular signals required for the phagocytic engulfment of apoptotic cell during embryonic development[81]. Yet another research group has reported that alternative cell death mechanisms such as autophagy, cornification, entosis, and necroptosis exist when apoptosis machinery fails during embryogenesis[82]. Previous reports clearly pointed out that, cell death mechanisms are not only important in shaping of embryo but also for maintaining adult tissue homeostasis and therefore can be considered as key machinery from womb to tomb.

**TYPES AND CHARACTERIZATION OF CELL DEATH**

According to the nomenclature committee on cell death 2018, the cell death proceses, all together, are classified based on the morphological characteristics, enzymological criteria, functional phases and immunological reactions into fourteen and more subgroup including apoptosis, necrosis, necroptosis[83], ferroptosis[84], pyroptosis[85], parthanatos[86], entosis[87], NETosis[88], autophagy[89], and mitotic catastrophe[90]. Genetically programmed mechanisms for the targeted eradication of permanently damaged and destructive cells or organs are collectively termed as regulated cell death (RCD) mechanisms. Major classifications of different cell death modalities with functional aspects are depicted in Figure 3.

***Targeting cell death in colon cancer: Implications for therapy***

An interesting finding about the cancer clues reveals that, several genes responsible for cancer development are very much active during embryogenesis and foetal development which particularly regulate growth of embryo and organ formation. These genetic programs remain silent in the rest of the life of the organism; however, tuned on during cancer formation in cells[91]. The genetic paradigm of colorectal cancer reveals that adenomatous polyposis coli (APC) or β-catenin is responsible for the initial changes in normal mucosa to form dysplastic aberrant crypt foci. *COX-2* mainly regulates the formation of early adenoma and *K-RAS* regulate the formation of intermediate adenoma. *CPC4/SMAD4* is responsible for late adenoma and *p53* is majorly responsible for carcinoma[92]. During these sequential events from benign polyp formation through adenomas and finally carcinomas, cell death plays an essential role.

A low rate apoptosis in the base of the crypt where stem cells are expected to be existing is fundamental for the function of normal intestine. It is interesting to note that the epithelial cells residing of the villi present in small intestine as well as colon are resistant to apoptosis[93]. The changes in the expression pattern of several apoptotic proteins during the transformation of adenoma to carcinoma reveal the importance of apoptosis during colon cancer progression[94]. Since, 70% of reported CRCs are associated with mutation in tumour suppressor *p53* gene, the transition from adenoma to carcinoma in colorectal region can be considered as a mechanism where apoptosis machinery fails in the organ[95]. Therefore, chemotherapies intended to stimulate apoptosis in colon cells would be central in controlling disease progression[96]. In this notion, our laboratory is interested to elucidate the apoptosis inducing effect of certain phytochemicals in order to eradicate cancer cells and providing protection against CRC progression. We have provided evidences that the bioflavonoid luteolin has strong anti-proliferative activity by inhibiting Wnt/β-catenin signalling cascade, inducing apoptosis and cell cycle growth arrest in G2/M phase in HCT-15 colon cancer cells[97] as well as azoxymethane-induced experimental colon carcinogenesis in BALB/c mice[98]. While our reports suggest that, apoptosis is an efficient parameter in preventing malignant transformation as it eradicates harmful cells. On the contrary, apoptosis can also promote cancer growth by preventing the removal of certain genetic variants that have a high potential to induce malignancy. Yet another interesting hypothesis about cancer is that, tumour tissues possess a high apoptotic index than normal tissues, *i.e.,* the higher apoptotic index in tissue indicates more malignant tumour[99]. Therefore, apoptosis can be considered as a double-edged sword in cancer progression. However, the mechanism that linking high rate of apoptosis with increased cancer cell proliferation and metastasis needs to be further elucidated.

Apart from apoptosis, other cell death modes are also gaining attention in cancer research in order find out better therapeutic targets. In this point of view, the pro-as well as anti-metastatic effect of autophagy has been studied in several cancers including brain, liver, pancreas, colon etc. Several signalling cascades are known to regulate autophagy. Among these, PI3K/Akt/mTOR is an important signalling pathway which is a checkpoint in autophagy that promotes cancer progression. Interestingly, PI3K/Akt hyper activation, PIK3CA mutations and PTEN mutations and deletions have been reported in the incidence of CRC[100]. Autophagy is reported as an anti-metastatic mechanism in the early stage of cancer metastasis by preventing infiltration of inflammatory cells and tumour cells necrosis that helps to reduce cancer cell invasion and metastasis. However, autophagy may tend to act as a promoter of metastasis during the advanced stage by enhancing epithelial -mesenchymal transition, cell survival and metastasis[101]. Moreover, high expression of LC3I/II, which is a key regulator for the nucleation of autophagosome and down regulation of Beclin 1 has been reported in the advanced stage of CRC[102]. These research evidences pointed out that autophagy machinery influences all stages of cancer progression such as initiation, proliferation and metastasis and its role in inhibiting or promoting cancer metastasis seems to be context dependant.

Recently, necroptosis-a caspase independent, receptor-interacting protein kinase mediated form of regulated cell death targeted therapy has been postulated as a novel strategy for cancer preventions. A very few reports are available for the role of necroptosis in regulating CRC progression. Moriwaki and colleagues have shown a significant down regulation in the expression of RIPK1 and RIPK3 in colon cancer tissues when compared with normal colon tissues[103]. Interestingly, dimethyl fumarate (DMF), an approved drug for the treatment of multiple sclerosis is reported to have the ability to induce necroptosis through the depletion of reduced glutathione in colon cancer cells[104]. The drug resistance towards 5-fluorouracil (5-FU) of colon cancer cells has reported to be sensitized by the usage of pan-caspase inhibitors which facilitate 5-FU induced necroptosis in CRC cells[105]. However, more research should be conducted to identify the possible regulatory role of necroptosis in the prevention of CRC. Altogether these reports open a lime light in colon cancer research with a promising therapeutic target against cancer progression.

**SIGNALLING PATHWAYS IN COLON CANCER**

The development of CRC involves various signalling pathways that regulates cellular proliferation, differentiation and immortalization. Among various cell proliferative signalling activation of Wnt/βcatenin, inactivation of TGF-β, EGFR, mutation in k-ras signalling play a vital role in the progression of CRC[106,107].

***Wnt/β-catenin signalling in colon cancer***

Wnt signaling plays a divergent role such as regulating cellular homeostasis and maintains self-renewal in embryonic and adulthood. Particularly, it promotes intestinal epithelial proliferation and differentiation of intestinal crypt[108]. In the presence of Wnt ligand, the receptor frizzled inhibits the phosphorylation of Glycogen synthase kinase-3 beta (GSK3-β) impeding the degradation of β-catenin through ubiquitin pathway. Accumulated β-catenin in the cytoplasm translocates to the nucleus and transcript the target genes (Figure 4). The activity of the signaling pathway depends on the cellular localization of the β-catenin. Among 90% of the colonic tumours have a mutation in the adenomatous polyposis coli (APC) and β-catenin gene[109]. Mutation in the cluster region of the APC leads to the generation of truncated protein which fails to prevent the complex formation. This mutational dis-regulation in the Wnt signalling stabilises cytoplasmic β-catenin and its nuclear translocation promotes β-catenin dependent transcription of Wnt target genes contributes to the progression of CRC[110]. Nuclear β-catenin favours the peripheral cellular changes for cell adhesion and migration. Interestingly, Wnt signaling is necessary for the initial activation of intestinal stem cells. It plays a crucial role not only for stem cell maintenance but also for crypt homeostasis. Research evidence shows that experimental abolition of Wnt signalling in cells leads to the specific loss of proliferative crypts[111,112].

***PI3k/Akt/mTOR signalling in colon cancer***

PI3k/Akt/mTOR is the second most frequently mutated oncogenic signalling network in human cancers. The dysregulation of PI3K is observed in almost 30% of human cancers making this signalling cascade as an important therapeutic target in controlling cancer progression[113]. The association of PI3K/Akt /mTOR signalling in colon carcinogenesis has been intensively studied. Over expression of p-Akt with impaired expression of PTEN, a tumor suppressor negative regulator of Akt has been reported in 70% of colorectal cancer patients[114]. Lycopene, a carotenoid has been reported to supress leptin-mediated cell invasion in CRC HT-29 cells through the inhibition of phosphorylation of Akt[115]. Yet another research group has reported that aspirin, an inhibitor of mammalian target of rapamycin (mTOR) and activator of AMP-activated protein kinase (AMPK) induces autophagy and protects against the progression of colorectal cancer[116].

***TGF-β / Smad signalling in colon cancer***

Transforming Growth Factor-(TGF)-β and related bone morphogenetic proteins (BMP) belong to the family of cytokines involved in the governing of various biological process including proliferation, differentiation, apoptosis, in wide spectrum of cells[117]. The TGF-β superfamily of cytokines contains many proteins, including TGF-β1, -β2 and -β3, and activins. TGF-β conducts its signals *via* numerous intracellular signalling molecules, including smad family of proteins, mainly Smads 2 and 3[118,119]. TGF-β enhances the expression of several fibrogenic as well as pro-inflammatory cytokines, such as platelet derived growth factor (PDGF), TNF-α or IL-1β, and promotes development and progression of the fibrotic reaction[120]. Three major isoforms of TGF-β have been identified namely, TGF-β 1,2, and -3 in mammals. In general, TGF-β is secreted as an inactivated form through its attachment to a latent TGF-β binding protein[121]. The downstream regulation of TGF-β signaling is activated upon when ligand binding to type II receptor which phosphorylates the type I receptor, which then further phosphorylates Smads 2 and 3. Phosphorylates receptor smad forms heterodimerize with Smad4 and translocated into the nucleus for its transcription gene expression (Figure 5)[122]. TGF-β plays a dual role in progression of cancer during the early stage of the cancer. TGF-β can perform as a tumor suppressor pathway in normal colon epithelial cells by regulation of cell proliferation and apoptosis. But in later stage of the cancer it promotes migration by increasing the EMT and supressing the immune response[123,124]. The involvement of TGF signalling in CRC has been described earlier[125-127].

***Epidermal growth factor receptor and Ras-Raf-MEK-ERK signalling***

Epidermal growth factor, a membrane bound receptor tyrosine kinase play a vibrant role in many cancers for its development and progression. Ligand activated receptor forms homo and heterodimerize with the other family members of the ErbB and autophosphorylates on their tyrosine residue[128].Once ligand binds to the receptor, it triggers the activation of downstream signalling such as Ras, MAPK, ERK, NF-κB and PI3K/Akt. These pathways are very critical in CRC. Overexpression of EGFR and its ligands correlates with the development of human cancer and its poor prognosis[129].

**p53 AND COLORECTAL CANCER**

p53 is well known gene for its tumor suppressor role and it, is one of the most mutated gene in all forms of human cancer. DNA damaged stress response activation of p53 induces DNA repair and regulate the cell cycle to prevent the oncogenic mutation[130]. Alteration of p53 signaling in colon cancer which resulting in the loss of apoptosis and cellular checkpoint and altered genetic integrity which lead to malignancy. Accumulation of mutations in cancer-related genes, such as K-ras, p53 and APC instigates the transition from normal epithelium through adenomatous to colorectal cancer[131].

**NOTCH SIGNALLING IN CRC**

In mammals, the major components of Notch signalling include five ligands: DLL1, DLL3 and DLL4 (Delta like ligands) and Jagged1, Jagged2 (Sterrate like ligands); four Notch receptors (Notch 1-4) and several downstream target genes[132].The signal transduction initiates by the interaction of notch ligand present in one cell with the transmembrane Notch receptor present in neighbouring cell. This binding interaction activates metalloproteases which cleaves the transmembrane domain of Notch receptor resulting the release of constitutively active Notch intracellular domain (NCID) of receptor. Translocation of NCID to the nucleus regulates transcriptional complexes to induce expression of target genes (Figure 6)[133].Though currently available reports provide little information about cell-specific function of Notch signalling in CRC when compared with other solid tumours, the aberrant activation of Notch signalling has been reported in CRC. In a recent study, the superior therapeutic effect of targeting both Notch and MAPK signalling on colon cancer growth and its role in regulating tumor cell plasticity has been reported[134]. Notch signalling has been reported to induce cellular resistance to chemotherapeutic drugs. It was demonstrated that Notch signalling significantly up-regulated in experimentally generated Regorafenib, a multi-kinase inhibitor-resistant SW480 cells. Interestingly, inhibition of Notch signalling in resistant cells restored the sensitivity of cells towards Regorafenib suggesting the important role of Notch in inducing resistance to chemotherapeutic drugs[135]. Dysregulation of Notch signalling in mediating colon cancer metastasis has been studied in detail[136]. These reports strongly suggest the importance of Notch signalling in the pathogenesis and progression of CRC.

***Nrf2/Keap signalling in colorectal cancer***

Oxidative stress is denoted as the imbalance of oxidant production and antioxidant defences, where oxidants dominate and lead to cellular dysfunction and tissue damage. Oxidative stress caused by harmful reactive oxygen species (ROS) are involved in colorectal cancer. ROS causes cellular damage leading to progression of many disease such as including cancers, fibrosis, neurodegenerative disorders etc. In turn, cell possesses detoxification genes (Phase II) and antioxidant genes to counterbalance the lethal effects of ROS[137]. In many disease settings, NF-E2-related factor 2 (Nrf2), which is a basic leucine zipper transcription factor, orchestrates a crucial role in protecting tissues against free radical mediated insults including carcinogens, drugs, inflammation, *etc*[138]. Nrf2 is a member of Cap-N-collar transcription factor family. It distinguishes the antioxidant response element (ARE) in the promoter of target genes[139,140]. Under basal conditions, Nrf2 is kept tightly with Keap1 (Kelch like ECH associated protein) in the cytoplasm. Keap 1 is very critical as it serves as a substrate linker protein for interface of the Cul3-based E3-ubiquitin ligase complex with Nrf2 leading to ubiquitination and proteosomal degradation of Nrf2[141]. Under certain conditions, such as inducers of ARE, enables the detatchment of Nrf2 from its partner Keap1, thereby facilitating the Nrf2 progression to the nucleus. Inside the nucleus, Nrf2 dimerizes and associates with small Maf proteins leading to binding of Nrf2 to AREs thereby leading to transcriptional activation of these genes. In colorectal cancer the chemopreventive effect of many drugs greatly depend on this signalling[142-144].

***Hippo signalling and colorectal cancer***

The origin of hippo pathway started with observations in Drosophila melanogaster flies with concomitant mutations leading to tissue overgrowth in the flies[145]. Hippo signalling has gained its attention in cancer biology because of its cross talks with oncogenic signalling pathways[146]. Yes associated protein 1 (YAP) is the key transcriptional regulator of Hippo pathway. This protein along with its partner PDZ-binding domain taffazin (TAZ) orchestrate the Hippo pathway[147].In principle, hippo signalling play an important role in regulation of tissue homeostasis, development, regeneration, cancer[148]. Three protein components in mammals are depicted: Mammalian Ste 2 like kinase 1 (MST1 and 2), large tumor suppressor kinases (LATS 1 and 2). These kinases phosphorylate YAP and TAZ which leads to nuclear exclusion and further undergoes ubiquitin mediated proteosomal degradation that takes place in the cytoplasmic origin which leads to suppression of YAP/TAZ targeted genes[149,150]. Recently, a huge body of evidences suggest the critical role of Hippo signalling in CRC[151,152]. Hippo signalling has cross talks with other signalling pathways has been reported[153,154].

**MiRNAs And Colorectal Cancer**

Over the years, several molecular mechanisms were identified to be involved in CRC[155]. In recent years, the discovery of microRNAs (miRNA) attracts considerable attention in different disease conditions. Understandings the roles of miRNAs in the development and disease, especially in cancer, have made miRNAs is one of the attractive tools and considered as a novel therapeutic target[156]. Generally, miRNAs are non-coding RNAs consist of 20-24 nucleotide in length and it was classified into Oncomirs and tumor suppressor miRNA with related to cancer. According the recent research in relating the miRNA and cancer, it impacts several vital processes such as cell cycle, proliferation, differentiation, metabolism and apoptosis[157]. It was reported that miRNAs such as miR-21, miR-181b1, miR-101, the let7 family, miR-133b, miR-126 were dysregulated in CRC[158,159]. Recently, MiR-760 suppressing human colorectal cancer growth by targeting BATF3/AP-1/cyclinD1 signaling has been reported[160]. MiR-422a act as a tumor suppressor in colorectal cancer and its expression was limited in tumor of CRC. Increasing the expression of miR-422a could inhibit CRC cell growth and promote cell apoptosis in colorectal cancer cells. It was also reported that miR-422a restricts colorectal cancer by inhibiting p38/MAPK pathway[161]. Therefore, miRNAs are emerging as potential targets in CRC.

**CONCLUSION**

Research attempts that targeting more effective therapies against CRC progression are of outstanding important as the effectiveness of mono-therapeutic approaches are very much limited in CRC treatment. However, combinational therapies are gaining attention with their ability to manipulate certain signalling cascades or inducing different modalities of cell death in order to prevent cancer metastasis. Regulation of such cellular signalling pathways and modulation of cell death represents a promising tool to augment better response to chemotherapy. When the normal orchestra of cellular signalling is dys-regulated, the cells turn itself into pathological condition and these events ultimately decide whether cells to die or survive. Certain novel signalling pathways and their association with CRC progression and metastasis has been discussed in this review. Better understanding of anticancer agents targeting these cellular pathways and inducing different modalities of cell death hopefully provide more insights in to the complicated molecular mechanisms underlying colorectal cancer to enhance the treatment efficacy.

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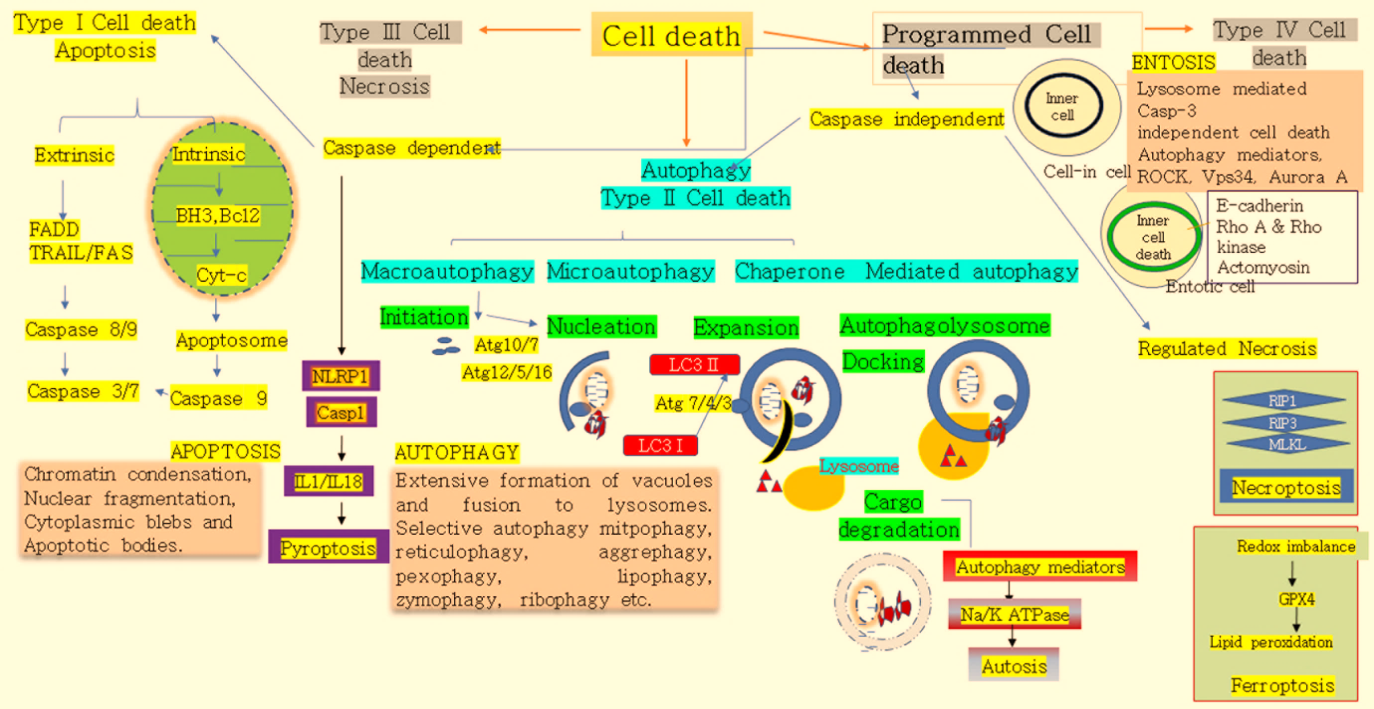
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**Figure 1 Different stages of progression of colorectal carcinogenesis.** Stage 0: The cancerous cells grow through the inner lining of mucosa; Stage I: The cancerous cells grow through the mucosa and submucosa. The growth invaded the muscular layer of colon; Stage II: The cancerous growth proliferates through the wall of the colon and not spread to neighbouring tissues or lymph nodes; Stage III: The cancer grows through the layers of the muscle to serosa, the layer of visceral peritoneum. Cancer starts to spread to lymph nodes; Stage IV: The cancer forms the nodule of tumour in tissue around the colon and appears in the lymph nodes and starts to metastasize.

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**Figure 2 Mechanism of epithelial mesenchymal transition in colorectal cancer.** External stimuli or mutation in cancerous cells induces Epithelial mesenchymal transition (EMT) in which epithelial cells undergo phenotypical changes and transit into more invasive mesenchymal cells. Mesenchymal cells invade systemic circulation and undergo mesenchymal-epithelial transition (MET) in distant organ; facilitates metastasis.



**Figure 3 Different modalities of cell death.** Unpredictable perturbations in the extracellular or intracellular microenvironment of a cell activate several signal transduction cascades that ultimately leads to various forms of cell death. Type I cell death apoptosis: Extrinsic pathway of apoptosis is mediated by Fas-associated death domain protein (FADD). Caspase 8, inturn triggers the caspases 3 and 7, which in turn activates caspase 9. Intrinsic or mitochondrial pathway of apoptosis is mediated through the inhibition of anti-apoptotic Bcl2 which in turn activates Bax/Bak that induce release of cytochrome c from the mitochondria. Activation of caspase 9 in the apoptosome induces apoptotic cell death; Type II cell death autophagy: Autophagy is an active lysosomal degradative flux which in turn divides into three types; macroautophagy, micro autophagy and chaperone mediated autophagy. Macroautophagy includes four different steps; initiation, autophagosome nucleation, phagosome expansion and completion, autolysosome docking. The tightly regulated autophagic machinery is mediated through several autophagy related (ATG) molecules; Regulated necrosis/ necroptosis: Regulated necrosis mediated through the interaction of receptor interacting protein 1 (RIP1) with RIP3 under conditions, when the activity of caspase-8 is inhibited. RIP3 and mixed lineage kinase domain-like (MLKL) are phosphorylated and assembled in complex IIb, translocates to the plasma membrane, where it mediates membrane permeabilization; Ferroptosis: This regulated form of cell death driven by loss of activity of glutathione peroxidase 4 (GPX4), the lipid repair enzyme followed by the accumulation of lipid hydroperoxides; Autosis: Plasma membrane Na+/K+ dependant autophagy form of cell death; Entosis: The internalized cells undergo entotic cell death through the formation of entotic vacuoles mediated by autophagy proteins Vps34, *etc*; Pyroptosis: Caspase dependant intermediate cell death mechanism between apoptosis and necrosis. Casapse-1 which is activated by NLRP3 inflammasome activates the inflammatory cytokines interleukin 1β and interleukin 18 that mediate the lytic mechanism.

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**Figure 4 Wnt/β catenin pathways.** In the absence of Wnt, β-catenin in the cytoplasm forms a complex with Axin (yellow), APC (blue), GSK3 (red), and CK1 (purple). The phosphorylated β-catenin undergoes ubiquitin mediated proteosomal degradation. In the presence of Wnt, the binding of Wnt with frizzled receptor induces the recruitment of Axin complex that disrupts Axin-mediated proteosomal degradation of β-catenin. Accumulated β-catenin in the cytoplasm travels to the nucleus and functions as a co-activator for TCF to activate genes subscribed by Wnt. GSK: Glycogen synthase kinase.

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**Figure 5 TGF/Smad pathway.** TGF-β signalling initiates by the binding of the TGF β1 ligand to the receptor II which promotes dimerization of receptor II with receptor I that results in transphosphorylation of TGF-β RI. The activated TGF-β RI activates receptor regulated-Smads (Smad2 and Smad3) *via* phosphorylation. Phosphorylated Smad along with co-Smad for trimerize complex and translocate to the nucleus and induces transcription of target genes to promote cell growth and survival. TGF: Transforming growth factor.

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**Figure 6 Delta/Notch Signaling**.Binding of Notchof one cell with the transmembrane ligands Delta or Jagged of the neighbouring cell initiates Notch signalling. This binding interaction cleaves the Notch receptor and releases NICD, where it travels to the nucleus and controls the transcription of Notch responsive genes. In the nucleus, NICD binds to transcriptional repressor CBF1 that recruits Mastermind-like (MAML) and other co-activators to initiate transcription of Notch regulated downstream genes.