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Mapping the Genetic Landscape of Colon Cancer: Innovations in Screening and Therapy

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ABSTRACT

Colon cancer originates from abnormal cell growth in the colon and is prevalent in adults greater than fifty years of age though it can develop at any age. Colon cancer often starts as benign polyps that may transform into cancer over time, emphasizing the importance of regular screenings for prevention. CRC (Colorectal cancer) is the second deadliest cancer and involves significant genetic and environmental risk factors. Genetic mutations due to genome instability in DNA repair genes like MSH2, MSH6, and MLH1, along with syndromes like Lynch syndrome, contribute to CRC's hereditary forms. CRC progression involves genomic instability, such as chromosomal and microsatellite instability, alongside DNA methylation changes that drive tumor development. Advancements in molecular diagnostics, such as next-generation sequencing (NGS) and PCR, have enhanced CRC detection, identifying key mutations in genes like KRAS and BRAF that inform treatment strategies. Circulating tumor DNA (ctDNA) also offers non-invasive screening options through "liquid biopsies." Innovations in gene therapy targeting p53 and KRAS genes present potential CRC treatments, although challenges remain regarding cost and accessibility. Early detection and gene-targeted therapies can improve CRC prognosis by minimizing side effects and enabling more precise treatments, though affordability remains a barrier to widespread implementation.

Keywords: Colon cancer; Gene therapy; MSH2; MSH6; MLH1; Chromosomal instability

INTRODUCTION:

Colon cancer originates in the colon and is a result of abnormal cell growth that typically begins in the inner most lining of the colon wall. This growth mostly starts as polyps, small clumps of cells that can be benign but sometimes evolve into cancer over years. Regular screenings are crucial because they allow doctors to find and remove polyps before they turn cancerous. Although most of the colon cancer cases are found in individuals over the age of 50, increasing numbers of diagnoses are occurring in younger populations. This shift may be influenced by factors, such as exercise and diet habits, as well as environmental influences.(1) There are also certain genetic mutations that raise the risk, making a person more susceptible to developing colon cancer. **Lynch syndrome**, for instance, is the most common hereditary risk factor, while **Familial Adenomatous Polyposis** (FAP) is a less common but significant genetic syndrome associated with the disease.

Colon cancer typically grows and spreads in stages. In the early stages, cancer is confined to the inner most layer of the colon. If it progresses, it can penetrate deeper layers and eventually spread into lymph nodes and other peripheral organs. Symptoms may not appear early on, which is why screening tests, like colonoscopies, are vital for early detection. There is also a notable link between inflammation and colon cancer. **Inflammatory Bowel Disease** can increase the risk of colon cancer, suggesting a close interaction between immune response and cancer development.(2) In recent years, research has shown that the gut microbiome plays a important role in colon health, with certain bacteria potentially increasing or decreasing cancer risk. Treatment for colon cancer depends on the stage of cancer and location of the tumor but often involves a chemotherapy, radiation therapy, surgery and immunotherapy. Advances in precision medicine and targeted gene therapy, which tailors treatment to the individual's genetic makeup and cancer profile, are beginning to improve outcomes for colon cancer patients.

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1. Colon and Rectum:

The **colon** and **rectum** are parts of the large intestine, which involves in the digestive process by absorbing water, electrolytes, and nutrients and storing waste before it leaves the body.

Colon: The colon is the first and largest portion of the large intestine, about 1.5 meters (5 feet) long. It connects to the later portion of the small intestine at the cecum consisting of four sections: the ascending colon, transverse colon, descending colon, and sigmoid colon. Its major functions are to absorb salts from partially digested intake, turning it into solid stool. The colon also houses gut bacteria that aid in digestion and vitamin production.(4)

Rectum: It is the final segment of the large intestine, approximately 15 to 20 centimetres (6 to 8 inches) long.(4) It connects the colon to the anus and acts as a temporary storage site for stool before it is excreted. The rectum has muscular walls that help move stool out of the body during a bowel movement, with nerves that signal the urge to defecate when the rectum fills.

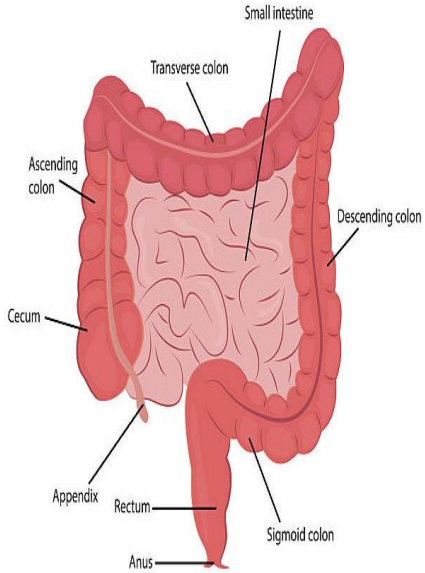

Fig 1: Anatomy of Colon and Rectum

2. The origin of colon cancer:

Generally, colorectal cancers initiate as growth within the innermost layer of the colon, developing into tumors over time. These growths, known as polyps, vary in their ability to become a tumor.(5) While not all polyps changes into tumor, certain types have a higher likelihood of eventually transforming into carcinoma. Polyps are classified into different types based on their structure and potential cancer risk. Adenomas, or adenomatous polyps, are the type most likely to become cancerous, which is why they are often referred to as precancerous lesions. There are three main types of adenomas, which are, tubular, villous, and tubulovillous. In contrast, there are non-cancerous polyps which are common, known as hyperplastic and inflammatory polyps. However, patients with larger hyperplastic polyps, typically those greater than 1 cm, may need more frequent screening due to a slightly elevated cancer risk.

SSPs and **TSAs** which are also known as **Sessile serrated polyps** and **Traditional serrated adenomas**, though less common, also carry a greater risk for developing into colorectal cancer which are managed similarly to adenomas.(6) If cancer begins in a polyp, it can grow deeper, extending through layers of the colon or rectal walls. These walls are composed of multiple layers, starting with the innermost mucosa, where most colorectal cancers originate, and extending outward.

Once embedded in the colon or rectal wall, cancer cells can invade small blood or lymph vessels, allowing them to travel to nearby lymph nodes or even distant body parts. The extent of a colorectal cancer's spread and how deeply it penetrates the wall's layers determine its stage or level of advancement, guiding treatment and prognosis.

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3. Genomic structure of colon cancer:

Colorectal cancer which is one of the most recognized inherited tumor conditions, often linked to specific genes involved in DNA repair. The specific genes **MSH2** and **MSH6** (positioned on chromosome 2), and **MLH1** (positioned on chromosome 3), play significant roles in preventing colorectal cancer. These genes typically produce proteins responsible for correcting gene errors that arise during DNA replication. If these genes are altered or mutated, the proteins they create may not function properly, resulting in uncorrected replication errors. This buildup of DNA damage can eventually lead to colorectal cancer.(1)

3.1. MSH2 and MSH6:

The **MSH2** and **MSH6** genes are essential for producing proteins that play a vital role in repairing DNA. These proteins correct errors made during DNA replication, a crucial process in cell division.(8) When the proteins created by the MSH2 and MSH6 genes, or sometimes MSH3, bind together, they form a two-protein structure known as a dimer. This dimer complex locates replication errors within the DNA. A separate protein complex, the **MLH1-PMS2 dimer**, attaches to the MSH2-MSH6 complex, removes mismatched DNA sequences, and replaces them with the correct ones. The MSH2 gene is part of a group known as mismatch repair (MMR) genes, which are critical in maintaining DNA integrity.

The **MSH6 gene**, spanning 23,806 base pairs on chromosome 2, includes 10 exons and untranslated regions and encodes a mismatch repair protein called **MutS homolog 6 (MSH6)**, which has a molecular weight of 153 kDa. In eukaryotic cells, MSH6, as the main mismatch-contacting unit of the **MSH2-MSH6 heterodimeric complex (MutSα)**,(8) is responsible for identifying simple mismatches and minor insertion-deletion errors. MSH6 forms a heterodimer with MSH2, a complex containing 1,358 amino acid residues. This dimer identifies both base substitutions and mismatches resulting from insertions or deletions. Mutations in the MSH6 gene can increase susceptibility to certain cancers, including gliomas and other malignancies. MSH6 mutations are linked to Lynch syndrome, with germline mutations in this gene contributing to 10–20% of cases associated with this hereditary condition.

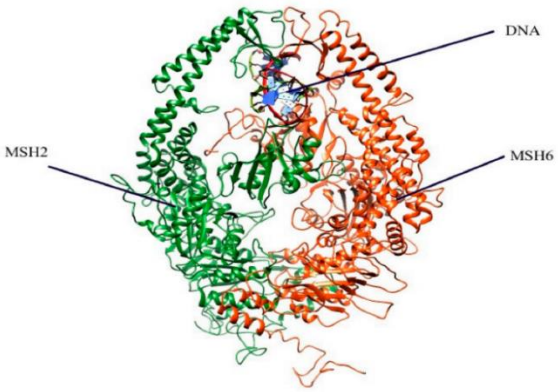

Fig 2: Structure of MSH2 and MSH6

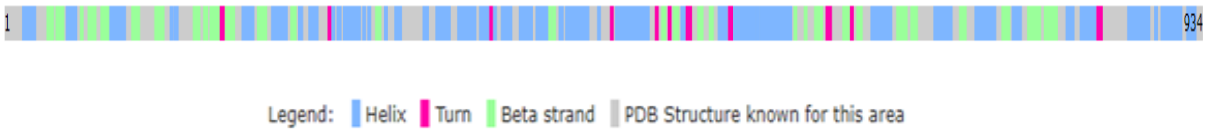

Fig 3: Secondary structure of MSH2 and MSH6

Table 1: Protein attributes for MSH2 and MSH6

Gene	Length	Mass	Sequence	Molecular weight	Theoretical pl
MSH2	80,000 base pairs	104743 Da	Human MSH2 protein sequence	104611.88 Da	5.58
MSH6	23,806 base pairs	153000 Da	Human MSH6 protein sequence	153000 Da	5.81

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3.2. MLH1:

A protein required for DNA repair is produced by the MLH1 gene. Cell division depends on the ability of this protein to correct mistakes that are generated during DNA replication. A two-protein complex known as a dimer is created when the MLH1 protein joins forces with PMS2, a protein that is generated by the PMS2 gene. The action of additional proteins that correct mistakes made during DNA replication is coordinated by this complex. A piece of damaged DNA is removed and replaced with a DNA sequence that has been repaired to complete the repairs. The mismatch repair (MMR) gene family includes the MLH1 gene.

3.2.1. Biochemistry:

The bacterial **mutL gene**, also known as the yeast mutator gene homolog, interacts with proteins such as **PMS2, MLH1**, and **NF1**, the latter being linked with a greater risk of early hematological cancers.(7) This gene plays a role in mismatch repair and is involved in several cancers, including sporadic cases of breast and endometrial cancer. MutL exists in multiple isoforms and contributes to DNA repair in non-small cell lung cancer (linked to TSG3B).(1) It is often absent in cases of sporadic colorectal cancer and can undergo mutations coupled with promoter hypermethylation in breast and colorectal cancers, leading to increased malignancy risk.

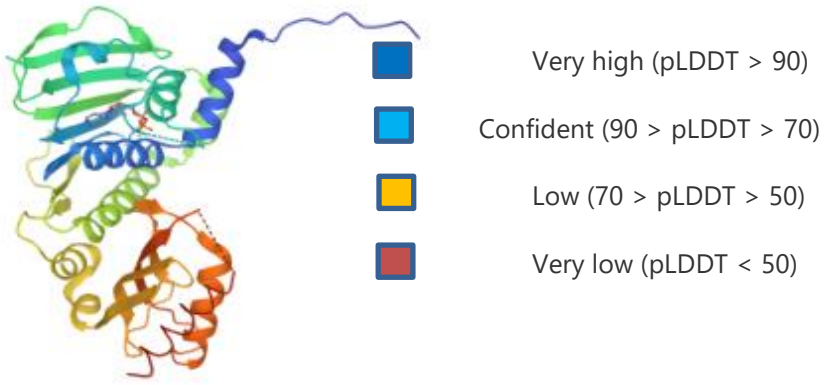

Fig 4: Structure of MLH1

Table 2: Protein attributes for MLH1

Length	Mass	Sequence	Molecular weight	Theoretical pl
348	84601 Da	Human MLH1 protein sequence	84469.78	5.51

4. Inheritance and Risk:

Several factors may indicate a genetic link to colorectal cancer, including:

- The presence of multiple primary tumors in one individual.
- A family history of various cancers, particularly those associated with inherited syndromes that elevate the potential risk of colorectal cancer, like endometrial cancer.
- A diagnosis of colon cancer in a younger patient.(9)
- A family history of colorectal cancer or polyps with a higher-than-average risk.

Certain conditions, like **MUTYH-associated polyposis** and **NTHL1-related disease**, are inherited in an autosomal recessive manner. However, autosomal dominant inheritance is the common pattern for hereditary colon cancer. (10)

To assess the likelihood of carrying a harmful mutation in the **mismatch repair (MMR) genes** related to **Lynch syndrome**, several predictive models can be used. These models, such as **MMRpredict**, **PREMM5** and **MMRpro**, can estimate the risk. Patients with

a risk score of 2.5% or higher on PREMM5 or 5% or higher on MMRpro or MMRpredict are advised to undergo genetic counseling and gene testing.

5. Associated Genes and Syndromes:

There are two types of inherited colorectal cancer which are well established:

- **Polyposis** is induced by harmful mutations in the **Adenomatous Polyposis Coli gene**, leading to conditions like **MUTYH-associated polyposis**, **AFAP**, and **FAP**.

- **Lynch syndrome**, results from mutations in genes responsible for DNA mismatch repair (MMR), including **MSH2**, **MSH6**, **MLH1, PMS2**, and **Epithelial Cellular Adhesion Molecule**.(11)

There are several other colorectal cancer syndromes that are linked to specific genes, such as **Cowden syndrome** (PTEN), **juvenile polyposis syndrome** (BMPR1A, SMAD4), **oligopolyposis** (POLE, POLD1), **Peutz-Jeghers syndrome** (STK11), and **NTHL1-associated polyposis**.(1) In addition, among other symptoms, several of these disorders manifest as extracolonic cancers. Hyperplastic polyps appear to be a hereditary feature of serrated polyposis syndrome, while the underlying genetic causes are still unknown. Some of these disorders still require the acquisition of their genetic histories in order to be completely characterized. The many additional families that have aggregation of CRC and/or adenomas without any obvious link to a known hereditary illness are referred to as "family-related CRC" families. Furthermore, most of the people with CRC who are diagnosed before the age of 45 and who do not have a hereditary history of the CRC do not have a pathogenic mutation linked to a hereditary cancer syndrome.(12)

Whereas the practical implication of these discoveries is still unclear, genome-wide studies are uncovering common, low-risk genetic variants that may contribute to a variety of complex diseases, including colorectal cancer (CRC).

6. Genetic diversity of colon cancer:

Advances in human genome sequencing have enabled the precise identification of genetic mutations linked to cancer. To systematically analyze these mutations, it was crucial to sequence human protein-coding genes with well-defined functions. However, determining the clinical relevance of individual mutations in colorectal cancer remains challenging due to the extensive genetic variability. Studies have shown that what was previously considered rare or unusual mutations in colon cancer are really more prevalent than previously thought, and these changes may potentially influence the development of other malignancies. This information opens up new possibilities for therapeutic strategies, diagnostic tools, and directions for tumor biology research. The genome's stability is crucial to sustaining cellular integrity,(13) and instability in genomics can result in mutations which lend rise to the malignant phenotype, accelerating the progression of colorectal cancer.(10) The role of genetics in cancer development is underscored by the identification of numerous genetic changes that affect genes regulating cell growth and maturation.

The types of instability in genome that are detailed here are:(10)

- Chromosomal-instability.
- Microsatellite-instability.
- Aberrant DNA-methylation.

6.1. Chromosomal-instability:

Baseline mutation rates by themselves cannot account for the wide variety of mutations required for cancer to develop. According to scientific theories, during a biological generation, a nucleotide base pair may experience as little as 10−9 changes. Loeb et al. state that the need for a "mutator phenotype" an intrinsic genomic instability that increases the rate of new mutations in cancer cells is necessary. Chondrosomal instability (CIN) is observed in 65–70% of instances of periodic colorectal cancer.(14) When entire or major chromosomal segments are gained or lost more frequently, it results in karyotypic variety between cells, a phenomenon known as CIN. Sub-chromosomal genomic amplifications, a high incidence of loss of heterozygosity (LOH), and aneuploidy are the underlying circumstances of CIN.(14)

6.2. Microsatellite-instability:

Microsatellite (MS), sometimes called SSRs (simple sequence repeats) or STRs (short tandem repeats), are repetitive sequences made up of one to six nucleoside phosphates. Tandem repeats, which have between 15 and 65 nucleotides, are distributed differently from small satellite DNA, which is mainly found on the ends of chromosomes. MS can be present in non-coding or intron regions, however they are mainly distributed and located in the coding area. The centre core and the outlying flanks are the two parts that comprise each MS specific location.

The quantity of core repeating units varies which is the main reason behind MS's peculiarities. The general consensus is that during DNA replication and repair, slippage of the strands between the fundamental group of complementary strands and slippage strands results in the absence or insertion of one or more repeating units. Mismatch repair (MMR)—a component of normal tissue DNA repair is able to correct errors in DNA replication. Tumor cells may not have MMR genes or may have issues with the replication repair process, which increases the risk of gene mutation [2]. The correlation between MSI and the development and occurrence of cancers is clearly apparent.

6.3. Aberrant DNA-methylation:

Colorectal malignancies exhibit traits such as promoter-specific DNA methylation and global hypomethylation. Significant and well-coordinated patterns of promoter methylation have also been identified in a subtype of CRCs called the CpG-island methylator phenotype. The genesis or advancement of colorectal cancer has not been connected to the majority of the genes, while several have been demonstrated to be tumor suppressors due to methylation.

In mammals, CpG sequences are often modified through the cytosine methylation at the pyrimidine ring (5^{th} position).(10) While CpG dinucleotides are randomly methylated throughout the genome, CpG islands typically remain unmethylated in normal cells. As individuals age, changes in the methylation pattern occur, with a gradual reversal that leads to the methylation of CpG islands and a decrease in overall methylation levels. This shift is particularly pronounced during the development of cancer. Colon cancer, for example, is marked by reduced cytosine methylation and abnormal, excessive CpG islands methylation linked to certain gene regulators. In sporadic colon cancer, the instability of satellite DNA contributes to somatic epigenetic changes, leading to the silencing of the **MLH1** gene.(10)

6.4. Tumor progression:

Colorectal cancer's inception and advancement is one of the most striking examples of cancer in stages. The transformation of an adenoma into a carcinoma is brought about by the accumulation of mutations that improve the tumor phenotype by favoring variations that have the best survival, growth, and colonization potential for cancer cells.(10)

7. Molecular diagnostic techniques of colon cancer:

Understanding how genetic variants in colorectal cancer (CRC) can improve clinical care with the use of technology advancements has advanced significantly. These developments lead to personalized medicine, which offers care that corresponds to each patient's individual medical needs and genetic profile. Compared with the more conventional strategy of alternating radiation and chemotherapy, it has been shown that this concept is effective in improving clinical outcomes. Many of the FDA-approved drugs target specific genetic disorders, and the number of drugs for the treatment of advanced-stage solid tumors is growing rapidly.(15) Since each person has a unique molecular profile that determines their best course of therapy, it is crucial to understand and appreciate the variety of molecular technologies that are accessible, both for diagnosing colorectal cancer (CRC) and for developing new molecular tools.

Before the development of polymerase chain reaction (PCR), identifying nucleic acid biomarkers was challenging due to tissue heterogeneity and the lack of sufficient nucleic acids in samples. With the advent of more precise methods like tumor-specific DNA, qPCR (quantitative PCR) can now be detected in measurable amounts. Additionally, miRNAs (RNA-based biomarkers) can be identified using RT-qPCR (quantitative reverse transcription PCR).(16) Advancements in technology have further enabled the detection of rare biomarkers, including tumor-specific circulating free DNA (cfDNA), through techniques like digital PCR, qPCR and NGS (next-generation sequencing). Digital PCR, the most recent advancement in PCR technology, has become an important tool for detection of gene variations or rare events in patient samples when traditional qPCR is not sensitive enough.(15) In contrast, NGS refers to high-throughput sequencing methods that analyze fragmented and amplified DNA. While NGS excels in large-scale genomic analysis, digital PCR is more effective for detecting rare events. The following sections will provide updates on how these cutting-edge molecular diagnostic techniques are being used to identify crucial biomarkers associated with colorectal cancer, including **KRAS**, **BRAF**, **MSI**, and others.

7.1. Detection of KRAS and BRAF mutations:(15)

The somatic KRAS mutational status is of particular importance since it might negatively affect the patient's response to anti-Epidermal Growth Factor Receptor (anti-EGFR) therapy, especially in patients with CRC, where somatic KRAS mutations are 40% prevalent.(15) A variety of molecular tests can be used to identify these mutations; the limits of detection for qPCR assays range from 1 to 5%, while the limits for Sanger DNA sequencing are between 10 and 20 percent. Pyrosequencing and high-resolution melt (HRM) curve analysis have detection limits of about 5%. Despite being the most successful technique for identifying KRAS and BRAF mutations, direct sequencing is not frequently employed because of its slow process and low sensitivity.

7.2. PCR based detections:

The KRAS and BRAF mutations can be detected using a number of FDA-approved assays,(17) including the cobas 4800 BRAF V600 mutation assay, Therascreen KRAS assay and cobas 4800 KRAS mutation assay. These assays are approved by the FDA for use with certain samples, however they should not be used with specimens that contain very little tissue, like core biopsies and micro needle aspirations.

Its NRAS–BRAF mutation test may identify V600 mutations for BRAF and codons 12, 13, 59, 61, 117, and 146 for NRAS; however, it cannot identify 21 mutations in clinically significant codons (12, 13, 59, 61, 117, and 146) from tissue samples that have been formalin-fixed paraffin embedded (FFPE) at the same time.(15)
The system is suitable for the majority of clinical settings because to its rapid turnaround time, low skill requirement, and ease of use.

7.3. Circulating Free DNA (cfDNA) Detection:

Circulating tumor DNA (ctDNA) is the term for tumor DNA fragments that are discharged into the bloodstream and are not associated with any specific cells.(15) It is common to confuse the term "ctDNA" with "cfDNA," which describes DNA that is not usually from tumors but instead floats freely in the circulation. Comprising all of the tumor's genetic material, ctDNA has garnered interest in medical circles for potential use as a "liquid biopsy." The range of ctDNA percentages is 0.01% to 90%.

To diagnose colorectal cancer (CRC), it is highly desirable to identify new biomarkers. Regarding minimal residual diseases, therapeutic response and prognosis assessment, and identification of resistance mechanisms, cell-free circulating DNA (cfDNA) is arguably the most promising liquid biopsy analytical approach. Assessing the quantity and kind of mutations present in body fluids is made possible by the preservation of the same genomic fingerprints observed in the matching tumor tissue in circulating cell-free tumor DNA (ctDNA). Therefore, a non-invasive method of detecting cancer is provided by ctDNA-based study.(18) Though it has many potential uses, the diagnostic, prognostic, and/or predictive usefulness of ctDNA in colorectal cancer (CRC) has attracted a lot of scholarly interest recently.

7.4. Detecting of Microsatellite Instability (MSI) Microsatellite Stable Status (MSS):

As mentioned earlier, microsatellite instability (MSI), which has substantial diagnostic, prognostic, and predictive relevance, is one of the most significant biomarkers for colorectal cancer (CRC). Testing for MMR-D (mismatch repair deficiency) and MSI (microsatellite instability) is recommended when screening for **Lynch syndrome**,(19) an autosomal-dominant genetic condition caused by inherited mutations in the MMR genes, which increases the risk of several types of cancer. Additionally, high microsatellite instability (MSI-H) is linked to a more favorable prognosis in early-stage colorectal cancer (CRC) and indicates that patients with stage II disease may not benefit from adjuvant 5-fluorouracil treatment.

7.5. miRNA Detection:

Many different physiological and molecular targets can be impacted by a class of tiny noncoding RNAs called microRNAs. Depending on the cell environment in which the information is expressed, miRNAs can either suppress or promote colorectal cancer (CRC) and are essential for a variety of biological functions.
MiRNAs have a major role in the unchecked growth of human colorectal cancer, which is the foundation for the development of cancer.

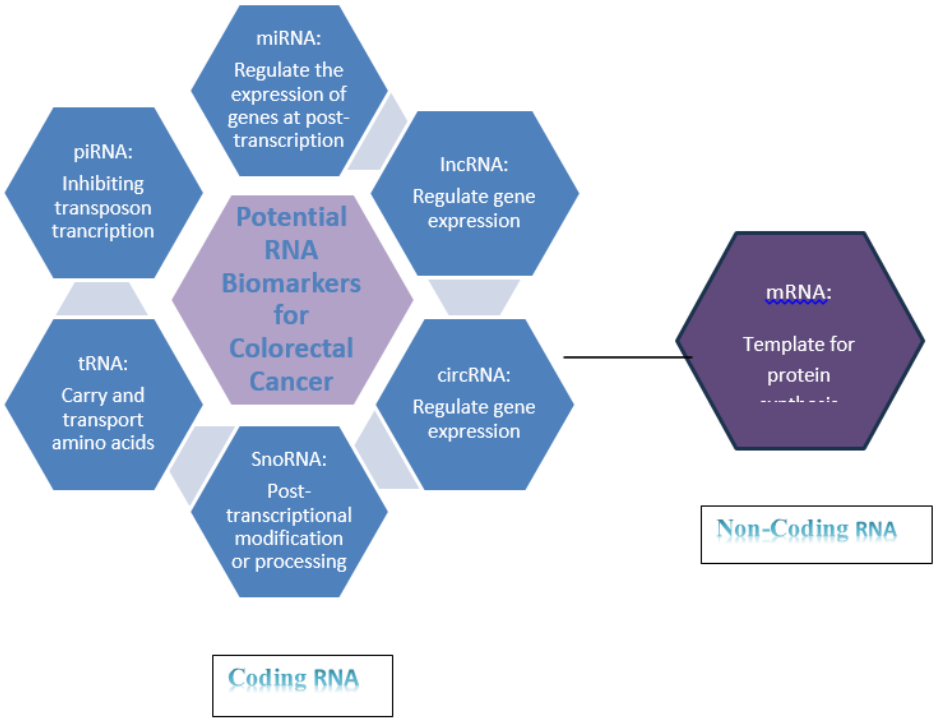

Fig 5: Potential RNA Biomarkers for Colorectal Cancer

7.6. Detection of other biomarkers:

Theoretically, with the exception of KRAS, BRAF, and MSI, most of the molecular biomarkers on the list should be detectable by comparable diagnostic techniques like NGS and qPCR. This is backed by numerous researches aimed at validating the application of additional biomarkers for diagnosing colorectal cancer.(15)

8. Gene therapy targeting p53 and KRAS:

The idea of treating CRC (colorectal cancer) by focusing on driver mutations has long piqued the community of scientist. Mutations like these are common in cancer cells and play an important role in their growth.(20) They are particular targets for cancer therapy. Gene therapy targeting p53 has been studied for a variety of solid cancers.(21) In oncology, p53-based therapeutic gene therapy is utilized to either reinstate wild-type p53 expression or block the production of mutant p53 in cancer cells lacking functional p53. Suppressing mutant p53 activity is an effective method for halting colorectal cancer development. The most prevalent genetic abnormalities linked to CRC are p53 and KRAS mutations.(22) Gene therapy that targets defective genes, such as the oncogene KRAS and TP53, which transcripts for p53, may offer an additional treatment option for colorectal cancer along with standard therapy.(21) Over the past ten years, there has been significant development in the application of gene therapy to treat a variety of cancers. This covers the creation of vectors for delivery methods.(21) Although targeted gene therapy has significant potential to treat cancer, there are certain disadvantages. These include the high cost of the required procedures, the absence of pertinent technology, and ethical difficulties.

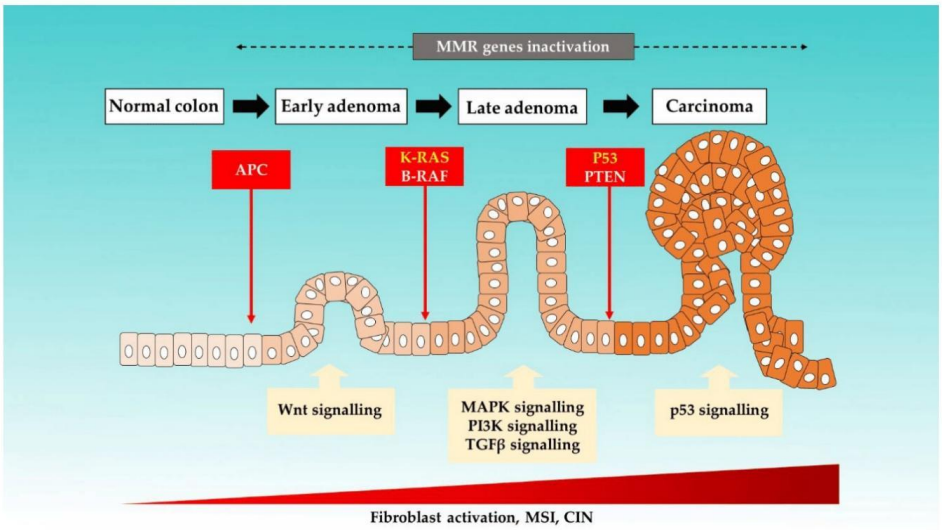

Fig 6: p53 and KRAS gene targeted therapy

9. Conclusion:

Colon cancer's genome has currently been thoroughly investigated. Undoubtedly, our comprehension in this area led to molecularly based diagnostics and certain specific treatments. By concentrating on employing immunoassay technology and miRNA detection (micro array) to target the colon cancer genome, safe and effective treatments may be developed, contributing to a reduction in the death rate associated with colon cancer. Despite a great deal of work being done to use genetics to understand the behaviour of MSH2 MSH6 MLH1, there is still some concern about new variations and mutations. These might have a big impact on focused treatments. Going forward, we have to acknowledge that early screening can reduce the death rate from colon cancer. Consequently, it highlights the significance of employing molecular diagnostic tools for an accurate and timely identification of colon cancer. Additionally, gene-targeted medicines help prevent unintended systemic toxicity, shield healthy cells from the negative effects of therapy, and enable the administration of greater doses of radiation and chemotherapy. However, not all CRC patients can currently afford this gene targeted therapeutic strategy due to its lack of economic efficiency. Therefore, improving the affordability of gene therapy can improve the quality of life for CRC patients.

Acknowledgement:

Not applicable

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