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Molecular Pathology of Colorectal Cancer is Something we Could Undertake Right Away

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ABSTRACT:-

The discovery of germ line mutations leading to these cancers and the study of relatively uncommon inherited tumours have been the main areas of molecular genetics' contribution to colorectal cancer. On the other hand, a lot is now understood about the somatic factors contributing to colorectal cancer in general. The relationship between genetic traits and prognosis has been investigated in several research. This article's goal is to review these studies and provide an overview of the present state of the field. It is evident that numerous distinct pathways exist for the development of this malignancy, and some molecular characteristics appear to correspond with clinicopathological features, despite the fact that many of the published studies are tiny and inconclusive. Studies are currently limited to analysing a small number of molecular markers, but with the development of techniques for the quick genetic profiling of large numbers of colorectal cancers, it will be possible to comprehensively analyse the therapeutic relevance of a range of colorectal cancer genotypes.

Keywords: colorectal cancer; prognosis; genes.

INTRODUCTION: -

More than 90% of the malignant tumours of the large colon are colorectal adenocarcinomas. Colorectal cancer is the third most prevalent cause of mortality from malignant disease in the West, after lung and breast cancer. About 30 000 new instances of the illness are diagnosed each year in England and Wales [1], resulting in about 17 000 deaths each year [2], and it has been calculated that there are at least 500,000 new cases of colorectal cancer each year worldwide [3]. In many nations, colorectal cancer incidence rates are rising. Sadly, despite advancements in medical and surgical care, death from colorectal cancer has changed relatively little over the past 40 years [4], and the overall five-year survival rate is just around 40%.

Natural history of colorectal cancer

About 60% of initial colorectal malignancies in Western nations are found in the rectum or sigmoid [5]. Half of the remaining cells emerge from the caecum. According to Dukes' approach, colorectal tumours are often classified into categories A, B, C, and D [5]. Grade can be categorised using the simpler Jass grouping or simply as the degree of differentiation

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(good, medium, or poorly differentiated) [6]. Stage and grade have excellent correlations with prognosis.

Molecular genetics of colorectal cancer

The idea that the majority of colorectal malignancies arise from normal epithelium through successively deteriorating degrees of adenomatous dysplasia was developed from histological data. 8 This idea of an adenoma to carcinoma sequence serves as the foundation for Fearon and Vogelstein's genetic pathway hypothesis for the development of sporadic colorectal [7].

The model proposed that the causative mutations in tumour suppressor genes and oncogenes occur in most colorectal cancers in a specific order (specifically, mutations in the adenomatous polyposis coli (APC) gene, global hypomethylation, mutations in the K-ras gene, mutations in the deleted in colon cancer (DCC) gene, and finally mutations in the p53 gene). Despite the fact that the total accumulation of mutations is the More than ten years ago, the Fearon and Vogelstein model of colorectal carcinogenesis was put forward. Since then, more mutations with a high frequency in colorectal cancer have been found, and the initial model can now be further expanded to account for sporadic malignancies [8]. The low prevalence of APC mutations in malignancies linked to inflammatory bowel illness shows that these mutations are not the primary cause of these tumour forms.

DISCUSSION :-

Given that there are likely multiple divergent genetic pathways underlying colorectal cancer, connections between the molecular and clinicopathological characteristics of tumors—features that are not readily visible using standard techniques like histology—may exist. These relationships could be used as prognostic indicators or to divide colorectal cancer patients into groups according to their response to various treatments. Numerous research have attempted to determine how genotypic variation in colorectal tumours and clinicopathological characteristics, particularly prognosis, are related [9]. The majority of research has taken the form of case control studies using genotype frequency as a proxy for survival by comparing primary and secondary tumour genotype frequencies [10]. The relationship between genotype and prognosis has only been studied in a restricted number of studies using the traditional survival analysis [21]. The evidence for genetic diversity in colorectal tumours as prognostic indicators is discussed in this section. This includes several studies of protein or mRNA expression that have been thought to be indicators of underlying mutations [11].

K-RAS

Vogelstein et al. shown in an early allelotyping study based on colorectal cancer patients that patients with more than the median percentage of allelic deletions had a worse prognosis. Later research looked at the relationship between particular chromosomal defects and tumour behaviour. Mutations that occur in genes involved in tumour progression rather than

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beginning are more likely to be prognostic relevant [18]. That allele loss at chromosome 5q, the location of the APC gene, has not been demonstrated to have predictive value, is therefore not surprising. The high rate of allele loss on other chromosomes, like 8p, 1p, and 11q, during the development of tumours raises the possibility that they may be the locations of additional tumour suppressor genes crucial to the development of colon tumours. One short research of 14 cancer patients found a link between 8p allele loss and microinvasion, a prognostic indicator unrelated to Dukes' stage. 97 In a study of 116 individuals who received curative treatment, a connection between tumour progression and chromosome 1 deletions was also discovered [12].

Less research has been done on the effects of allele loss at other chromosomes. 126 sporadic colorectal tumours were examined for allele loss at chromosome 11q22, but no correlation with the Dukes's grade or degree of diVerentiation was found. Allelic loss may be linked to a shorter disease-free life, according to a prospective study evaluating allelic loss at chromosome 4p14-16 in 181 patients [13, 14]. In a study of 194 consecutive primary, recurrent, and metastatic colorectal adenocarcinomas, Finkelstein et al. found that lymphogenous haematogenous metastatic disease had a considerably higher mutation rate of K-ras mutations. 101 When colorectal carcinomas were examined according to a particular K-ras mutation type, tumours with the codon 13 mutation did not spread locally or metastasize. Codon 12 valine-substituted tumours did not spread past pericolonic perirectal lymph nodes. In contrast, tumours with distant deposits frequently have codon 12 aspartic acid mutations. The majority of tumours with intraperitoneal deposits lacked mutations [15]. Based on these findings, Finkelstein et colleagues hypothesised that genotyping colorectal adenocarcinoma for K-ras status would distinguish subsets of patients likely to have slow-progressing or fast-progressing illness. The idea that having a K-ras mutation is independently connected with a shorter lifespan has received support from certain reports, but not all of them [16, 17].

DCC

The DCC gene must be a top candidate if chromosome 18q allele deletion predicts a bad prognosis in colorectal cancer. The origin of this connection. Expression of the DCC protein was found to be a highly positive survival predictor in a study of 132 patients with curatively removed stage II and III carcinomas. In comparison to patients with DCC-negative tumours, who had a survival rate of 62%, 114 patients with stage II disease had a five-year survival rate of 94%. Similar to this, the survival rates for people with stage III illness were 59% and 33% for those with and without detectable DCC expression, respectively. A new tiny 23 patient research that was released backs up this conclusion [18].

Mismatch Repair Genes and Microsatellite Instability

HNPCC has provided direct evidence linking molecular and clinicopathological information for colorectal cancer [19]. Colorectal tumours that occur in HNPCC mutation carriers are

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usually numerous and poorly differentiated. Contrarily, early data revealed that colorectal tumours in HNPCC conveyed a more favourable prognosis than in sporadic instances, despite the multiplicity and poor differentiation of malignancies. Studies from Finland and Japan give compelling evidence for enhanced survival in HNPCC.

p53 AND p27

In several tumour forms, it has been postulated that an elevated intracellular concentration of p53, which is frequently but not always connected to p53 mutation, is associated with a bad prognosis. Although p53 overexpression in tumours correlates with chromosome 17p deletion, hyperdiploid DNA content, and tumour site in colorectal cancer, research based on immunohistochemistry have shown inconsistent results regarding its function as a prognostic predictor [20-22]. This illustrates the fact that the strength of the relationship between p53 mutations and protein expression is partially dependent on the chosen antibody. The situation is clearer in research looking at the connection between p53 mutations and prognosis. According to studies, colorectal tumours with p53 mutations tend to be more aggressive, have a higher tendency to spread through the lymphatic system and blood, and have a worse prognosis. This isn't a universal truth, though [23].

CONCLUSIONS :-

Unfortunately, colorectal cancer is becoming more common, and the outlook for the majority of patients is still dismal. In order to choose the best course of action, it is critical to identify patients who have a high chance of developing both local and metastatic disease in the future. Pathological stage and grade, the kind of tumour growth, chromosomal aneuploidy, and the presence of microinvasion are prognostic factors that have been discovered to have a substantial effect on eVect. It has only lately become clearer how these indexes are molecularly based. Despite the fact that histology is still considered the "gold standard," the genetic characteristics of colorectal tumours will almost probably start to serve as helpful predictors of prognosis and the best course of action. One of the issues with clinicomolecular relationships that have been revealed thus far is that most research, for quite understandable reasons, have only examined a small number of tumours.

Accepting these limitations, there is evidence that colorectal tumours with abnormalities in the MMR genes have a better prognosis than those with chromosome anomalies, such as deletions of chromosomes 18q or 17, mutations in K-ras, or p53. Rapid genotyping techniques should make it possible to create mutation profiles for tumours and utilise multivariate analysis to identify the molecular characteristics that connect with the clinicopathological data.

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