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GENETIC ASPECTS IN THE COLORECTAL POLYPS CARCINOGENESIS

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Abstract: *Colorectal cancer, one of the most frequent cancers worldwide, is more prevalent in North America, Argentina, Australia, New Zealand, Western Europe, Japan and Israel and, for this reason, is commonly regarded as a Western lifestyle disease. The progressive introduction of Western dietary habits, especially increased fat intake and reduced carbohydrate and dietary fiber intake is associated with an increased incidence of colorectal cancer and related deaths. This is the reason of a marked interest in the understanding of cell and molecular mechanisms underlying the carcinogenetic processes. The advanced neoplasm, including colorectal cancer, contain a large number of genetic and molecular alterations that contribute to their neoplastic progression. It is well known that early detection of malignancies in different tissues is quite important for reducing the disease. Cancer that is of epithelial origin is caused by both external and internal factors. These causal factors may act together or in sequence to initiate and /or promote cancer. In spite of knowing more than ever about the genetic and cellular events that can accelerate or inhibit cancer induction, cancer is still the number one health concern in the world, especially in Western and Westernized countries.*

Key words: *carcinogenesis, colorectal cancer, alkilant carcinogenetic agents.*

1. Introduction

Demonstrating the causal relationship polyp-cancer which suggests the invasive and carcinogenic potential, as also the importance of a right attitude in front of polyps and rectocolonic polyposis, led to deepen the whole benign proliferation pathology- neoplastic or hamartomatous, of the glandular superficial epithelium or structures of the colonic wall.

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2. The colonic carcinogenesis- multistadial evolution

Multistadial carcinogenesis represents the main future of colonic neoplasia. There is an initial critical genetic event, which takes place in the normal colonic epithelial tissue, known to have a high rate of proliferation that remains still unclear. The result of this process is the genomic instability. This status leads to a higher susceptibility to new mutations. During successively mutagenesis and selection cycles, the affected cells proliferate clonally; It takes several genetic events before the normal cellular phenotype is replaced with a malignant one; the future genetic abnormalities are correlated with the grade of invasion and metastasis.

The colonic carcinogenesis involves scrolling to some mandatory steps, determined by mutational alterations of specific genes. Research in the molecular specific evolution of colorectal carcinogenesis revealed these characteristic features:

I. The mutational activation of specific oncogenes and inactivation of some Tumor Suppressor Genes (TSG or anti-oncogenes) lead to epithelial tumor proliferation.

II. Acquiring the malignant phenotype involves the inactivation of several TSG, a reasonable demanding by the fact that the proteic products of these genes participate to the regulation of multiple cellular processes that contributes to the normal action of vital functions.

III. The neoplastic phenotype (benign tumors) requires a smaller number of mutational events in comparison to the malignant phenotype, which is preceded by 4-5 mutational events [15], [40].

IV. Acquiring malignancy is conditioned by the accumulation of a critical number of mutations, but also by the chronological sequence of their acquisition. At the moment the order of the accumulation of genetic events is considered priority to their numbers [15], [40].

Specific mutations for the carcinogenic transformation of the colorectal polyps

The carcinogenic transformation of the polypoid adenomas begins with mutations in the nuclei of the epithelial colorectal cells. The diet of humans contains a large number of mutagens and substances that are metabolised in mutagens. The most of these are toxic chemical substances synthesized by plants, as an immediate response to the aggression of the bacteria, fungi, insects or other microorganisms. The presence of these toxic components is so obvious, that the colonic mucosa owns detoxifying protective and efficient mechanisms [38].

The metabolization of the precarcinogenic substances is very complex and can involve the following events: intestinal absorption, hepatic metabolization, biliary secretion, colonic oxidation [20], [27].

Various components of the diet were studied and described. These parts may play the role of the initiator for malignant transformation of the polypoid adenomas. Therefore, the following substances with mutagenic action are described in the literature [4]:

- the glycoside cicazina extracted from the nuts of the bread tree [3];
- quercetin and ptaquiloside extracted from ferns [28];
- fecapentene isolated from the human feces [18];
- mutagenic chindones extracted from beef [17], [30];

Cicazina is a glycoside which must be hydrolyzed by the intestinal bacterial flora in order to produce methilazoxymethanol (MAM), an unstable product, which is spontaneous decomposed resulting a reactive carbonium ion, capable of producing the methylation of the nuclei acids. Cicazina becomes carcinogenic for the colon only when it is administrated orally, requiring the presence of β-glucuronidaze formed by the intestinal bacterial flora.

In the study of carcinogenic transformation of colorectal polyps a much more stable substance –dimethylhidrazina (DMH) was used experimentally. After the intestinal absorption in the colon, this precarcinogen is oxidated and hydrolyzed in the liver, resulting a less stable substance: MAM (Figure 1).

The final response of these biochimical events represents the alteration of the methylation process of DNA [13], [11], [14], [16], [12], which, as it is proved, it is involved in the initial stages of the microadenomas and colorectal adenomas early formation.

After exposing to this alkilant carcinogenic agent, the host tends to repair the altered DNA or, finally the cells respond to the injury of DNA by proceeding to the programmed cellular death (apoptosis).

Dwan, Meier and Blackman proved that there are genetic differences in the induction of colorectal cancer under the influence of DMH in experimental animals; these scientists observed that not any kind of rats develops intestinal tumors as a response to DMH; the species which resisted to the colorectal carcinogenesis develop leukaemia as a response to this procarcinogen [10].

After the administration of DMH, the colonic epithelium develops tumors, although it is transplanted in small bowel. This situation is not suitable for the adenomatous development on small bowel islands that were transplanted in the colon [9].

The administration of a single dose of alkilant carcinogen (DMH) is sufficient to produce adenoma and carcinoma in experimental animals, after a 4 months latency period.

The characteristic G $\rightarrow$ A mutations, detected in the K-ras genes (66% proportion), begins in the 15th week of treatment with carcinogen, the final process of tumor genesis being closed after another 24 weeks. The G $\rightarrow$ A mutations produced by DMH in experimental animals involves the entire genome. When a mutation leads to the inactivation of a gene, which is vital for the surviving of the cell, the cell must be immediately eliminated. The mutational inactivation of the regulating area of the K-ras gene to 12,13 and 61 codon appears in a single cell after the carcinogenic exposure, because these cells will expand clonally, will invade the neighbouring cells and will create a large number of progens. This experimental model proves the sequentially nature of genetic lesions and demonstrates that the initial and specific mutations of colorectal human carcinogenesis are determined by the chemical carcinogens.

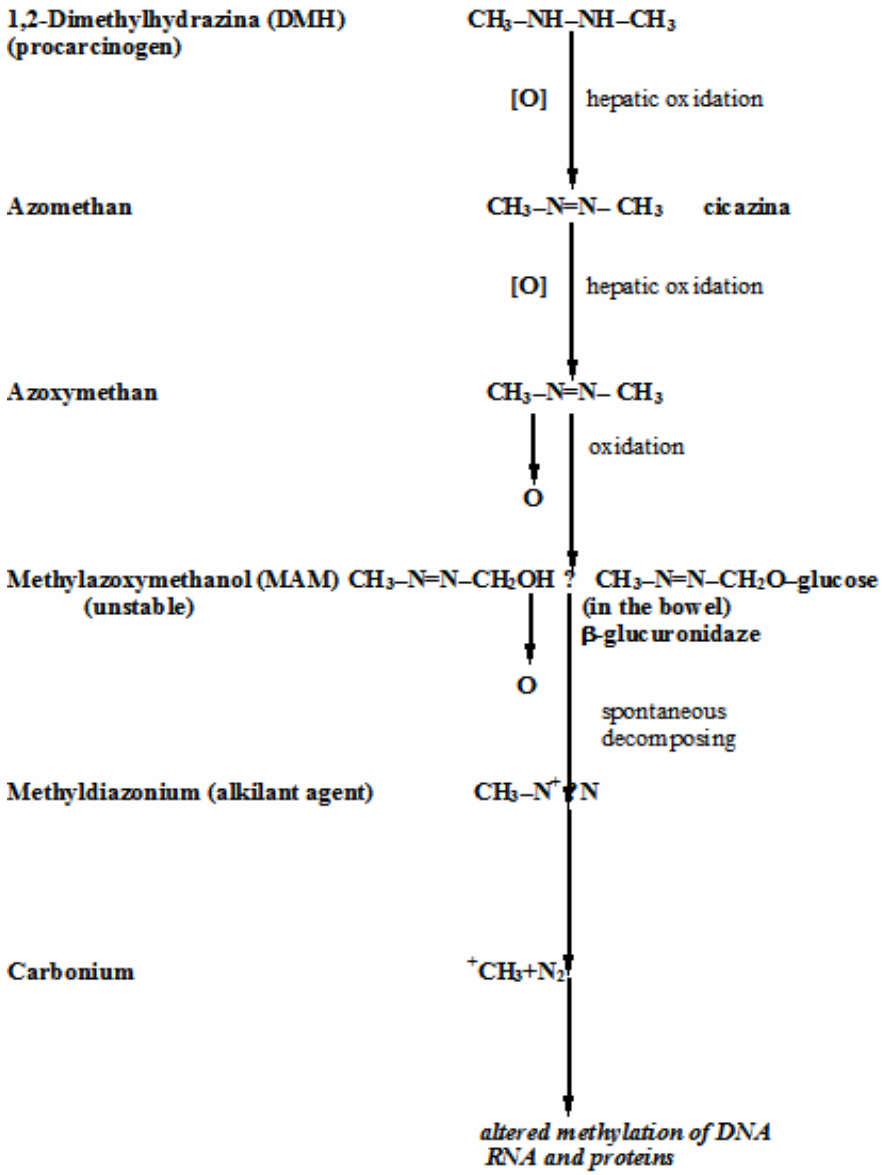

Fig. 1. *The metabolic activation of the dimethylhidrazina carcinogen (DMH)*

3. The role of mutagen agents in the appearance, recurrence and carcinogenic transformation of the colorectal adenomas

Analysing the structure of mutagenic substances is difficult due to their hyperactivity and to the tendency to decompose them spontaneously. Detecting the presence of mutagenic agents is possible using the Ames test, which consists of measuring the induction of in vitro produced mutations on Salmonella species [2], [29]. The limit of the test is that it appreciates only the presence of mutagens, without being able to isolate and analyse their structure.

Mover, Chinotsubo and Wang studied the presence of mutagens in faces of 2 groups subjects patients, comprised of high risk for adenomas and colorectal cancer persons and patients with polypoid adenomas without colorectal cancer risk.
The study revealed a direct proportional relationship between the presence of mutagens and high carcinogenic risk.

In contrast to the result of this study there is another study, realised by Shiffman, R.L. Van Tassell and Robinson, which states the fact that there is no correlation between the fecapentenes with mutagenic role isolated from feces and the colorectal cancer [35].

The fact that mutagens are disabled through different processes (intestinal absorption, hepatic metabolization, biliary secretion, colonic oxidation), and that the gastrointestinal flora is relatively stable, suggest that it would be difficult for all the mutagens to eliminate themselves through faces [36]. In spite of that fact, most prevention of carcinogenic polyps transformation strategies rely on the presence of mutagens in the colon and on the interference between carcinogens and the colonic epithelium [7].

Studies in the literature reveal an inversely proportional relationship between antioxidants- vitamin A, vitamin C, vitamin E-and the production of mutagens in the feces. This observation has implications in the primary prevention of polypoid adenomas and colorectal carcinomas. The protective role of calcium against carcinogenic development and transformation of the polypoid adenomas is justified by the binding of calcium to the biliary acids, to cholesterol and fecal fats [5], [22]. The calcium inhibits the aggression on colonic mucosa and hyperproliferation, induced by the biliary acids or carcinogens [33], [34]. The studies that used diets containing fats and calcium supplements reported a low incidence of tumors, while the administration of low fat and low calcium diets [26], [37] had a lower effect and even no effect in the reduction of the tumoral growth. The experimental studies suggest that the rich calcium diet selectively inhibits the tumors with K-ras mutations [23], a confirmed fact by an epidemiological study realised by Bautista, Obrador and Marenco [6]. Researches led to the hypothesis that the way calcium acts is by precipitating the biliary acids or the fat acids from the feces in calcium phosphate complexes [39]. Scientists like Van der Meer, Cats, Luptan or Alberts found that the calcium supplement in the diet reduces the fecal water cytotoxicity, the proportion of second biliary acids of all biliary acids and reduces also the concentration of biliary acids in feces [1], [8], [24], [39].

The supplementary amounts of calcium have a more obvious effect on the apparition risk of colorectal adenoma than on the polypoid carcinogenic progression [32]. The reduction of recurrence risk of adenoma is obvious after 9 months from starting supplementary calcium in the diet, effect that has no longer been observed after this interval.

The action of mutagens from the feces of patients with colorectal adenoma and carcinoma was also positively correlated with the acetylator status that allows the metabolisation of some elements of the diet. The heterocyclic amines resulted from broiled or fried aliments are metabolised by acetylation or oxidation in carcinogenic agents. The rapid oxidation phenotypes with NAT2 dependent metabolism play an important role in producing carcinogenic products and carcinogenesis.

In conclusion, the colonic mutagenesis is the result of certain substances derived from the interaction between aliments, microbial flora and colonic mucosa enzymes. Although revealing mutagens in feces, technically, is easy to perform, their unstable and hyperactive character makes structural description difficult.

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