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Digestive and Liver Disease xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

The molecular landscape of colitis-associated carcinogenesis

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ARTICLE INFO

Article history:
Received 17 November 2016
Accepted 9 December 2016
Available online xxx

Keywords:
Biomarkers
Colitis
Dysplasia
IBD
Molecular pathology

ABSTRACT

In spite of the well-established histopathological phenotyping of IBD-associated preneoplastic and neoplastic lesions, their molecular landscape remains to be fully elucidated. Several studies have pinpointed the initiating role of longstanding/relapsing inflammatory insult on the intestinal mucosa, with the activation of different pro-inflammatory cytokines (TNF-α, IL-6, IL-10, IFN-γ), chemokines and metabolites of arachidonic acid resulting in the activation of key transcription factors such as NF-κB. Longstanding inflammation may also modify the intestinal microbiota, prompting the overgrowth of genotoxic microorganisms, which may act as further cancer promoters. Most of the molecular dysregulation occurring in sporadic colorectal carcinogenesis is documented in colitis-associated adenocarcinoma too, but marked differences have been established in both their timing and prevalence. Unlike sporadic cancers, *TP53* alterations occur early in IBD-related carcinogenesis, while *APC* dysregulation emerges mainly in the most advanced stages of the oncogenic cascade. From the therapeutic standpoint, colitis-associated cancers are associated with a lower prevalence of *KRAS* mutations than the sporadic variant. Epigenetic changes, including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs, are significantly involved in colitis-associated cancer development and progression. The focus now is on identifying diagnostic and prognostic biomarkers, with a view to ultimately designing patient-tailored therapies.

1. Introduction

Sporadic colorectal carcinogenesis comprises a well-established sequence of phenotypic changes and molecular derangements [1]. Among non-syndromic colorectal cancers (CRC), on the other hand, colitis-associated cancer (CAC) is a particular entity with its own natural history, precancerous phenotypes, and molecular profile [2].

In both Crohn's disease (CD) and ulcerative colitis (UC), the cumulative risk of cancer ranges between 3% and 5% [3–5]. In single patients, the CAC risk increases along with the duration and severity of the inflammatory disease, and rises further in patients with familial CRC and/or concomitant primary sclerosing cholangitis [6–13].

The natural history of CAC prompts the recommendation for follow-up strategies that are consistently based on endoscopic surveillance coupled with appropriate (extensive) biopsy sampling [14,15]. The histological detection of precancerous lesions (*i.e.* dysplasia [synonym: intra-epithelial neoplasia; IEN]) is discriminatory in the choice of clinical strategy for the purpose of secondary cancer prevention [16,17]. Colitis-associated dysplasia frequently occurs in the form of patchy, flat lesions that may easily be overlooked, even with latest-generation high-definition endoscopy [2,18].

This clinical background means that priority goes to efforts to identify reliable biomarkers of a high cancer risk and/or early neoplastic transformation [19,20]. Such efforts come up against three main difficulties, however: (i) the complexity of the genetic background behind IBD-associated carcinogenesis; (ii) the confounding interference of the gut microbiota in colitis-associated carcinogenesis; and (iii) the characteristics of biopsy samples available for translational research purposes. In clinical practice, IBD biopsy samples are obtained mainly for diagnostic purposes, and tend to consist of formalin-fixed, paraffin-embedded (FFPE) specimens,

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http://dx.doi.org/10.1016/j.dld.2016.12.011
1590-8658/

which are considered sub-optimal for use in downstream molecular biology procedures [1].

This review aims to provide an up-to-date overview of the peculiar histology and molecular background of IBD-associated carcinogenesis.

2. Histology of dysplasia and colitis-associated cancer

In IBD patients, dysplasia is the most reliable marker of a higher risk of malignancy [2,21–23]. The accuracy of the endoscopic inspection and the appropriateness of the biopsy sampling protocol both significantly affect the likelihood of dysplasia being detected histologically, which also depends on the pathologist's experience [24–27].

Grossly, IBD-associated dysplasia may occur as flat or raised (polypoid) mucosal lesions [23,28–30]. While the latter are generally detectable on "traditional" endoscopy, the reliable assessment of flat lesions demands elective endoscopy experience and high-performance instruments. Even if such conditions are met, IBD-associated dysplasia is most frequently encountered in randomly obtained biopsy samples [2].

Depending on their histological phenotype, polypoid alterations can be divided into two sub-categories: (i) dysplasia-associated lesions or masses (DALM); and (ii) adenoma-like lesions [23]. The definition of DALM includes irregular bumps, plaques, velvety patches, nodules, wart-like thickenings, stricturing lesions and broad-based masses. These lesions can easily be masked by gross inflammatory abnormalities, and they are not usually amenable to removal using routine endoscopic methods [14,15]. On the other hand, adenoma-like lesions (both sessile, and pedunculated) are endoscopically indistinguishable from sporadic colorectal cancer, and are easy to remove endoscopically [2,31]. The distinction between DALM and adenoma-like dysplasia has far from negligible clinical consequences because polypoid lesions only require endoscopic resection, whereas the frequent concomitance of DALM with cancer warrants prophylactic proctocolectomy [27].

As for the histological assessment, the ECCO/ESP Consensus panel recommends that histological diagnoses be confirmed by a "GI-dedicated" pathologist [27]. Despite its well-established definition, the histological recognition and grading of dysplasia in this setting suffers from a significant inter-observer variability. Distinguishing between low-grade (LG) and high-grade (HG) lesions entails a different patient management due to the different prevalence of synchronous cancers detected in dysplasia patients undergoing proctocolectomy (LG and HG dysplasia are associated with synchronous cancer in 3% and 29% of cases, respectively) [32].

Invasive adenocarcinoma is identified from the "invasive" spreading of neoplastic cells beyond the native structure of the colonic glands. Compared with sporadic CRCs, IBD-associated cancers tend to be multifocal, more often mucinous, frequently including a signet ring cell component, and featuring a higher histological grade (Fig. 1) [18,29,33].

3. Molecular landscapes of colitis-associated cancers

3.1. The pathogenic role of the inflammatory insult

Colitis-related carcinogenesis is characterized by a cascade of molecular and phenotypic alterations initiated and sustained by (relapsing) inflammation [34,35]. As in other inflammation-related carcinogenic models, so too in the IBD setting, the pathogenic role of longstanding inflammation is supported by two main clinical factors: (i) the risk of CAC increases along with the duration/severity of the disease; and (ii) the introduction of anti-inflammatory treatment is associated with significant reduction in this cancer risk [25,36–38].

The molecular mechanisms linking longstanding IBD with cancer are gradually becoming less obscure. The long-term persistence of inflammation sustained by granulocytes, plasma cells, lymphocytes, and macrophages results in high levels of pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6], interleukin-10 [IL-10], interferon-gamma [IFN-γ]), chemokines and metabolites of arachidonic acid [39]. This "inflammatory background" leads to the activation of key transcription factors, such as nuclear transcription factor kappaB [NF-κB], that play a pivotal part in cancer development [29].

Among the pro-inflammatory cytokines, IL-6 in particular promotes proliferation and inhibits apoptosis by activating the JAK/STAT signaling pathway [40,41]. The IL-6-dependent enhancement of human colon cancer cell proliferation *in vitro* is largely mediated by hyperphosphorylation of the transcription factor STAT3 [42,43]. In biopsy samples obtained from active UC coexisting with neoplastic lesions, IL-6 and STAT3 expression in the gut epithelia is significantly higher than in either patients with inactive IBD or non-IBD controls [44]. Matsumoto et al. demonstrated that activation of the IL-6/STAT3 pathway is involved in both the experimental development of ileitis (SAMP1/Yit mice) and in cancer promotion [45].

In IBD, as in other carcinogenic models, several pro-inflammatory cytokines (particularly IL-1 and TNF-α) also significantly enhance the production of cyclo-oxygenase-2 (COX2), an inducible enzyme that interferes with cell proliferation, angiogenesis, and apoptosis. In the IBD setting, COX2 mRNA levels have been found increased in the inflamed mucosa, in dysplastic lesions, and in IBD-associated cancer [46].

Another important mechanism involved in the initiation and/or progression of CAC is oxidative stress of the colon mucosa due to the production and accumulation of reactive oxygen species (ROS), and reactive nitrogen intermediates (RNI) [47]. Stimulated by the pro-inflammatory cytokines, the inflammatory cells produce ROS and RNI, which in turn recruit additional inflammatory cells, generating to a self-promoting pathogenic loop. Oxidative stress is known to be involved in cancer biology because of its ability to damage DNA, and cell lipids and proteins [48,49]. For instance, the lipid peroxidation occurring when ROS and RNI interact with cell membranes gives rise to DNA adducts that frequently involve the *TP53* gene [48,49].

3.2. The intestinal microbiota in the carcinogenic cascade

Mounting evidence supports a role for both intestinal microbiota, and innate immune responses in initiating and maintaining colonic mucosa inflammation, and in eventually promoting colon cancer [29].

Gut microbiota imbalance (*i.e.* dysbiosis) is well documented in IBD patients, and dysbiosis is emerging as a key player in the pathogenesis of CAC. A higher prevalence of colon cancers has been documented in rodents colonized with feces obtained from CAC mice than in rodents treated with feces obtained from healthy mice. The demonstration that neither IL-10-deficient mice, nor TCRβ/p53 double knockout mice ever develop colon cancer under germfree environmental conditions further supports the interplay between colorectal cancer and gut microbiota [50].

IL-10 is a potent anti-inflammatory cytokine that inhibits NF-κB signaling [51–53]. IL-10-deficient mice have less diversity in their intestinal bacteria (a situation consistently demonstrated in both human and experimental cancers). In this murine model, gut colonization with either *Escherichia coli* or *Enterococcus faecalis* results in colonic inflammation, but it is noteworthy that only animal colonized by *E. coli* develop inflammation-related colon tumors [54,55].

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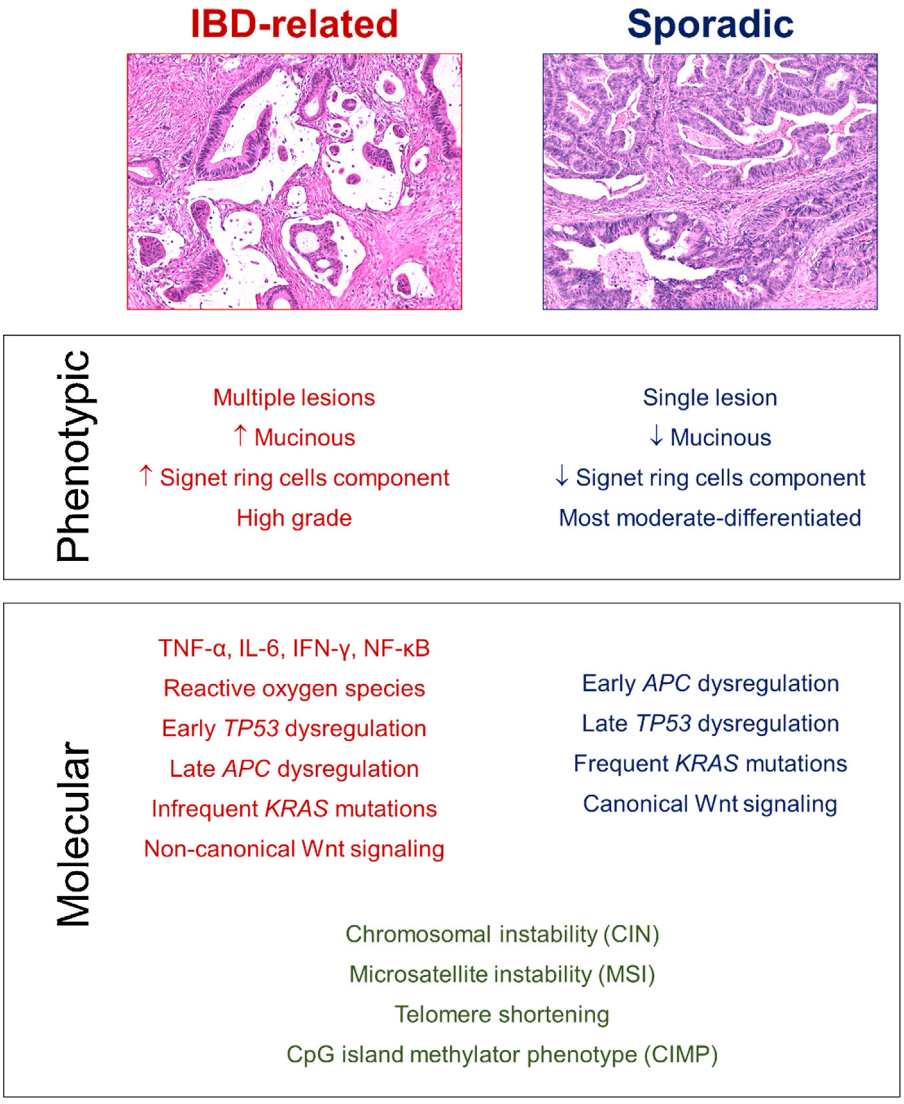

Fig. 1. Pathological and molecular features of IBD-related and sporadic adenocarcinomas.

3.3. Molecular pathways driving cancer initiation

The major molecular dysregulations involved in sporadic CRCs have been documented in colitis-associated neoplastic lesions too, though the timing and frequency of such molecular alterations in the latter reveal features peculiar to IBD [1]. In CAC, as in sporadic CRC, chromosomal instability (CIN), microsatellite instability (MSI), telomere shortening, and CpG island methylator phenotype (CIMP) are the main causative events behind genetic instability [29,56]. In UC patients, telomere shortening has been documented in mucosa adjacent to dysplasia and cancer, and it has been detected more frequently in patients who subsequently develop cancer [57,58].

In contrast with the late involvement of *TP53* dysregulation in sporadic colon carcinogenesis, seminal mutational profiling and LOH studies addressing IBD-associated oncogenesis have consistently pinpointed *TP53* mutations and *TP53* gene locus loss as early molecular changes already underway in intraepithelial neoplastic lesions [59–65]. *TP53* mutations have also been observed in non-dysplastic UC-affected mucosa, further supporting the early involvement of *TP53* [66]. It is worth adding that mice harboring a germline *TP53* mutation show a prolonged NF-κB activation and a rapid onset of flat dysplastic lesions that progress to invasive carcinoma in the dextran sulfate sodium (DSS) cancerization model [67].

The *adenomatous polyposis coli* (*APC*) gene is a driver of sporadic colorectal carcinogenesis, being involved in β-catenin regulation, cytoskeleton organization, apoptosis, and cell adhesion [1,68]. *APC* dysregulation is less frequent in IBD-related carcinogenesis, occurring only in advanced phases (if ever), and it has never been associated with non-dysplastic mucosa [63,69–71]. In the setting of IBD, it has been suggested that an enhanced β-catenin signaling could be promoted by the inflammatory micro-environment instead.

KRAS mutations are relatively less common in CAC than in sporadic carcinomas, and this may have therapeutic implications [72,73]. A recent whole-exome sequencing study on 31 IBD-related CRCs demonstrated a low *KRAS* mutation rate, further validating both the low prevalence of *APC* mutations and the high rate of *TP53* mutations [74]. The authors also demonstrated that alterations in *SOX9* and *EP300* (Wnt pathway), *NRG1* (ERBB pathway) and *IL16* (cytokine) genes are frequently involved. Their analysis identified recurrent mutations in the Rho and Rac GTPase network, pointing to a role for non-canonical Wnt signaling in the IBD setting.

3.4. Epigenetic modifications

Epigenetic changes – including DNA methylation, histone modifications, chromatin remodeling and small non-coding microRNAs

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– are involved in both the CRC's initiation and the progression [75–78]. Epigenetic silencing in DNA repair genes (such as *hMLH1*, *p16INK4a* and *MGMT*), which results in MSI, has been found in the CAC setting too [79]. MLH1 promoter hypermethylation is less frequent than in sporadic MSI cancers, however, because oxidative stress and ROS might cause MSI even in the absence of defects in the DNA mismatch repair pathway [29]. The CIMP pathway is also seen less often in CAC [80,81].

For the last three decades, microRNAs (miRNAs) have represented the most promising class of diagnostic and prognostic biomarkers. Their stability in biological samples, small size, ability to regulate hundreds of messenger RNAs (mRNAs), and relatively small total number (compared to mRNAs) make miRNAs plausible candidates for monitoring the cancer risk associated with IBD [82–84].

In 2008, a seminal study on miRNA expression in colonic mucosa samples from IBD patients identified a set of 11 miRNAs expressed differently in active UC vis-à-vis normal colonic mucosa [85]. This initial evidence was supported by further studies. Among others, miR-21 and miR-135b emerged as common key oncogenes in both sporadic and IBD-related carcinogenic processes [86,87]. Moreover, thanks to their intrinsic stability in body fluids, measuring circulating miRNA levels in the plasma and serum of IBD patients has shown potential as a tool for enabling an earlier diagnosis and prognosis, and for predicting response to therapy [83,88,89].

4. Conclusions

In spite of our thorough understanding of the phenotypic events occurring in IBD-related carcinogenesis, its molecular profiling has only been partially clarified. No reliable biomarkers are available as yet for prognosticating the cancer risk associated with colitis. The picture is further complicated by the recent acknowledgment of the influence of intestinal dysbiosis, which represents an additional variable in an already puzzling landscape.

There is growing evidence to support the reliability of some IBD-specific molecular markers of cancer risk, but none of them have been validated as yet, and their therapeutic implications (if any) are by no means well established. So is it time to test the reliability of (at least) some of these biomarkers in clinical diagnostic practice? Some of the available evidence seems to suggest that the time has come.

Conflict of interest

None declared.

Financial support

This work was partly supported by a grant from the Italian Association for Cancer Research (AIRC Regional grant 2008 N. 6421).

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Please cite this article in press as: Saraggi D, et al. The molecular landscape of colitis-associated carcinogenesis. Dig Liver Dis (2016), http://dx.doi.org/10.1016/j.dld.2016.12.011