Immunobiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Immunobiology

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

Review

Changes of immunocytic phenotypes and functions from human colorectal adenomatous stage to cancerous stage: Update

Yanhong Shi[a], Zhenfeng Li[b], Wei Zheng[b], Xia Liu[b], Chenyi Sun[b], Jann-Birger Laugsand[c], Zhanju Liu[a,**], Guanglin Cui[b,c,*]

[a] Department of Gastroenterology, The Shanghai Tenth People's Hospital of Tongji University, Shanghai 200072, China
[b] Research Group of Gastrointestinal Diseases, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[c] Faculty of Heath, University College of Nord-Trøndelag, Levanger, Norway

ARTICLE INFO

Article history:
Received 6 March 2015
Received in revised form 27 May 2015
Accepted 1 June 2015
Available online xxx

Keywords:
Adenoma
Carcinogenesis
Colorectum
Immunosurveillance
Immunosuppressive

ABSTRACT

It is believed that chronic inflammation as seen in patients with ulcerative colitis significantly increases the colorectal cancer (CRC) risk and functions as the main driving force for the development of colitis associated CRC. Recently, increasing evidences suggest that inflammation is also involved in the processing of sporadic CRCs that mostly develop from the preformed adenomas through a long-term progression. Within the adenoma/CRC tumor microenvironment, high dense immunocytes with significant phenotypic and functional changes have been observed. These cells might produce high level of inflammatory mediators and then affect the adenoma-cancer transition. In this review, we summarize the update on altered phenotypes and inflammatory mediators within the tumor microenvironment from the adenomatous stage to the cancerous stage, and discuss the significance of inflammatory mediators as biomarkers in predicating the progression from the premalignant adenoma lesion to the sporadic CRC lesion and the potential as therapeutic targets.

Contents

1. Background 00
2. Significant phenotypic changes of immunocytes within the tumor microenvironment from human adenomatous stage to CRC stage 00
   2.1. Phenotypic features of T lymphocytic subtypes in tumor tissues 00
   2.2. regulatory (Treg) cells 00
   2.3. Th17 cells 00
   2.4. M1/M2 phenotypes of macrophages 00
   2.5. Mature/immature dendritic cells (DCs) 00
3. Inflammatory mediators contribute to the immune functional shift within the tumor microenvironment along the adenoma-carcinoma sequence 00
   3.1. NF-$_k$ pathway 00
   3.2. COX-2 00
   3.3. Th17 related cytokines 00
   3.4. IL-17A/F 00
   3.5. The IL-33/ST2 axis 00
   3.6. The IL-8/IL-8 receptor axis 00
4. The potential of inflammatory mediators as biomarkers in predicting the risk of CRC in premalignant adenomatous 00
5. The potential of inflammatory mediators as the therapeutic target in preventing the transformation from the adenoma to the CRC 00

Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor α; IFN-γ, interferon γ; CRC, colorectal carcinoma.

* Corresponding author at: Faculty of Heath, University College of Nord-Trøndelag, Levanger, Norway.
** Corresponding author.
E-mail addresses: liuzhanju88@126.com (Z. Liu), guanglin.cui@hint.no (G. Cui).

http://dx.doi.org/10.1016/j.imbio.2015.06.003
0171-2985/

5.1. Inhibitory effect of COX-2 pathway 00
5.2. Anti-cytokine antibodies 00
5.2.1. Anti-TNF-α 00
5.2.2. Anti-IL-6 00
5.2.3. Anti-IL-8/IL-8 receptor 00
5.2.4. Anti-IL-17A 00
6. Conclusion marker 00
Conflict of interest 00
Acknowledgment 00
References 00

1. Background

The role of chronic inflammation in the development of colorectal cancer (CRC) has been recognized. It is believed that chronic inflammation as seen in patients with ulcerative colitis (UC) significantly increases the CRC risk and functions as the main driving force for the development of colitis associated CRC (CAC). However, CAC only accounts for ~15% CRCs, most sporadic CRCs are processed from the preexisted adenomas and named as the adenoma-carcinoma sequence (Fearon and Vogelstein, 1990). The appearing time of inflammation in the course of CAC development is different to that in the course of sporadic CRC development. In CAC, inflammation is already existed in colitis tissues before the formation of CAC, inflammation results in the strong activation of diverse immunocytes like T lymphocytes, macrophages and mast cells and produce masse inflammatory mediators to be involved in the formation of premalignant lesion; whereas most peoples believe that inflammation and the activation of immunocytes in sporadic CRC usually appear after the formation of premalignant stage (adenomas) and become more seriously when CRC developed (Rhodes and Campbell, 2002).

Recently, increasing evidences suggest that inflammation is also involved in the processing of sporadic neoplastic lesions from the adenomatous stage to the CRC stage. The formation of a sporadic CRC appears to be through a long-term premalignant adenomatous stage, in which multistep genetic and molecular changes are accompanied with the progression of histological features (Fearon and Vogelstein, 1990). The primary genetic mutation is occurred in *Adenomatous polyposis coli* (*APC*) gene that is the critical event in premalignant lesion (adenoma) formation, while *Kras* activation and p53 mutations are important subsequent genetic events during the transition from a premalignant adenoma to a CRC (Fearon and Vogelstein, 1990). The emerging evidence has also revealed that genetic alterations will certainly induce a strong inflammatory response (Abdullah et al., 2013; Chung and Chang, 2003; Galamb et al., 2008; Gunter et al., 2006; Heijmans et al., 2012). Within the tumor microenvironment, dense infiltrating immunocytes are found in the adenomatous/cancerous tissues and increased expression level of inflammatory mediators i.e., cytokines is shown in all stages of the adenoma-carcinoma sequence (Abdullah et al., 2013; Chung and Chang, 2003; Galamb et al., 2008; Gunter et al., 2006; Heijmans et al., 2012). For example, macrophage is one of common immunocytes that produces many important pro-inflammatory cytokines and involved in the pathogenesis of tumor initiation, progression and metastasis (Lewis and Pollard, 2006; Galdiero et al., 2013; Porta et al., 2009). The density of macrophages present in the pretumor/tumor tissue is significantly increased (Lewis and Pollard, 2006). In addition, the function of macrophages in the tumor inflammatory microenvironment is altered from an anti-tumor (M1) to a pro-tumor (M2) character; those macrophages are named as tumor associated macrophages (TAMs) (Edin et al., 2012) and increased density of TAM infiltrated in the adenomatous/cancerous tissues is the important histological feature (Banner et al., 1993a,b). CRC cells can secrete many factors to educate the macrophage phenotypes from M1 to M2 (Edin et al., 2013), and then M2 TAMs produce masse pro-inflammatory mediators and pro-tumor factors to affect the adenoma-cancer transition (Adegboyega et al., 2004; Nakanishi et al., 2011).

In view of the importance of immunocytes and inflammatory mediators in the establishment of sporadic CRC, we have previously reviewed the altered inflammatory micrenvironmental components along the adenoma – carcinoma sequence (Cui et al., 2012a,b). Recent progression in this research field is very fast and a lot of new findings have been reported. Here, we review certain update data, with an emphasis on the phenotypic and functional changes of immunocytic subsets within the adenomatous/cancerous tumor microenvironment, and discuss the significance of inflammatory mediators as biomarkers in predicating the progression of adenoma to CRC and the potential as biotherapeutic target in the prophylaxis of sporadic CRCs.

2. Significant phenotypic changes of immunocytes within the tumor microenvironment from human adenomatous stage to CRC stage

2.1. Phenotypic features of T lymphocytic subtypes in tumor tissues

The existence and importance of immunocytes in colitis associated CRC have been well characterized. Recently, the role of immunocytes in the development of sporadic CRC has also attracted much attention (Banner et al., 1993a,b; Cui et al., 2009a,b; Funada et al., 2003; Forssell et al., 2007; Nagorsen et al., 2007). Accumulating evidence has suggested that the appearance of inflammation in the formation of sporadic CRC starts from the early adenomatous stage and throughout the whole adenoma-carcinoma sequence. Phonotypical studies have revealed that cellular inflammatory microenvironment is composited by a variety of inflammation-related immunocytes i.e., lymphocytes, macrophages, dendritic cells and mast cells (Funada et al., 2003; Deschoolmeester et al., 2010; Bateman et al., 1995). These cells produce high level of inflammatory mediators and interact with premalignant/malignant epithelial cells and stromal cells in a complex manner to regulate the processing of tumor cell growth and tumor evoked inflammation (Banner et al., 1993a,b; Cui et al., 2009a,b; Funada et al., 2003; Forssell et al., 2007; Nagorsen et al., 2007).

T lymphocyte is one the most important immunocytes, and high density of T lymphocytes has been frequently observed in the tumor tissues. Regarding the infiltration pattern of T lymphocytes in the adenomatous tissues, ours and others results have revealed that T lymphocytes are observed in both the tumor stroma and adenomatous epithelium (Banner et al., 1993a,b; Cui et al., 2009a,b). In the adenoma tumor stroma, T lymphocytes are located at the subepithelial area and have a close anatomic contacting with the adenomatous epithelium (Cui et al., 2009a,b). Some of T lympho-

Please cite this article in press as: Shi, Y., et al., Changes of immunocytic phenotypes and functions from human colorectal adenomatous stage to cancerous stage: Update. Immunobiology (2015), http://dx.doi.org/10.1016/j.imbio.2015.06.003