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Cytokine Gene Polymorphisms in Colorectal Cancer

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1. Introduction

Colorectal cancer is the second-leading cause of cancer-related deaths in Europe and the United States (Parkin DM, 2001). Although the primary therapy of CRC is surgical, the elucidation of different novel prognostic markers may prove to serve as future therapeutic options and contribute to the overall understanding of this cancer entity, as well as to improve disease outcome. Inflammation has been known to be a key factor of development and progression of cancer, and this is particularly notable in colorectal. At the cellular level, the colonic epithelium is exposed to a range of toxic and pathogenic challenges, including the balance between intestinal microflora. In turn, a shift can result in a change in immune response, leading to the induction of inflammation. Interactions between tumor and immune cells at the site of inflammation either enhance or inhibit cancer progression. The epidemiological data available are very impressive and show a clear association between chronic inflammatory conditions and subsequent malignant transformation in the inflamed tissue (Macarthur et al., 2004). New evidence suggests that up to 25% of all cancers are due to chronic infection or other types of chronic inflammation (Hussain SP, et al., 2007). Inflammation is mediated by an array of cytokines, which are synthesized by activated immune cells and exert their biological activities upon binding to specific receptors and activate the NF- κ B transcription factor signal pathway in the epithelial cells. The ubiquitous transcription factor family NF- κ B is a central regulator of the transcriptional activation of a number of genes involved in cell adhesion, immune and proinflammatory responses, apoptosis, differentiation, and growth. Induction of these genes in intestinal epithelial cells by activated NF- κ B profoundly influences mucosal inflammation and repair (Jobin and Sartor, 2000).

There is strong evidence to suggest that cytokines are involved in the control of cancer development and also promote tumorigenesis, invasion, propagation, and metastasis of tumors, and that they may be relevant for gastrointestinal tumors. More recently, the molecular mechanism whereby the inflammation regulates the antitumor immune responses has been elucidated. In many tumors, signal transducers and activator of transcription (STAT)3 are activated, and thereby antitumor immune surveillance is suppressed (H. Yu and R. Jove, 2004).

In general the genes that encode cytokines involved in regulation of inflammatory conditions are genetically polymorphic and different genotypes are responsible for level of protein expression.

Genetic polymorphisms have emerged in recent years as important determinants of disease susceptibility and severity. Polymorphisms are naturally occurring DNA sequence variations, which differ from gene mutations in that they occur in the normal healthy population and have a frequency of at least 1%. Approximately 90% of DNA polymorphisms are single nucleotide polymorphisms (SNPs) due to single base substitutions. Others include insertion/deletion polymorphisms, minisatellite and microsatellite polymorphisms. Although most polymorphisms are functionally neutral, some have effects on regulation of gene expression or on the function of the coded protein. These functional polymorphisms, despite being of low penetrance, could contribute to the differences between individuals in susceptibility to and severity of disease. Many studies have examined the relationship between certain cytokine gene polymorphism, cytokine gene expression in vitro, and the susceptibility to and clinical severity of diseases (Bidwell et al., 1999; Hollegaard and Bidwell, 2006). SNPs are the most common sources of human genetic variation, and they may contribute to an individual's susceptibility to cancer. Cytokine gene polymorphisms have emerged in recent years as important determinants of susceptibility and severity of colorectal cancer. Cytokine polymorphisms directly influence interindividual variation in the magnitude of cytokine response, and this clearly contributes to an individual's ultimate clinical outcome. Dysregulation of cytokine production strongly influenced both tumor progression and host anti-tumor immunity. Cytokines secreted by activated immune and inflammatory cells can either promote tumor cell survival and growth or exert antitumor effects. In addition, some tumor cells may evade the immune system by secreting cytokines which may induce regulatory cells particularly the immunosuppressive CD4+CD25+ FoxP3+ T regulatory cells. In this chapter the polymorphisms of selected candidate genes for susceptibility to and/or severity of CRC are reviewed. Special attention is paid to studies concerning the genes of inflammatory related cytokines.

2. Cytokine gene polymorphisms of proinflammatory cytokines: IL-1; TNF- α and IL-6

The most compelling evidence for the role of inflammation in CRC comes from studies showing that proinflammatory cytokine gene polymorphisms increase the risk of cancer and its precursors.

IL-1 β is a prominent proinflammatory cytokine, which together with tumor necrosis factor- α (TNF- α) serve as primary initiators of the complex inflammatory response and they are classical activators of NF κ B signaling pathway. IL-1 β and TNF- α genes have a number of functional polymorphisms. The IL-1B-31T/C and TNF-A-308G/A SNPs have been shown to be functionally significant with the C allele of IL-1B-31T/C and A allele of TNF-A-308G/A being associated with increased production of their respective cytokines (Hwang et al., 2002; Abraham and Kroeger, 1999). IL-1 gene cluster polymorphisms suspected of enhancing production of IL-1 β have been shown to be relevant in the development of H. pylori-associated gastric adenocarcinoma. A study published in Nature showed for the first time that polymorphisms in interleukin-1B (IL-1B) were associated with gastric cancer risk (El Omar et al, 2000). Two of these polymorphisms are in near-complete linkage disequilibrium and one is a TATA-box polymorphism that markedly affects DNA-protein interactions in vitro. These linked IL-1B single nucleotide polymorphisms that increase IL-1 β expression

(-511 C>T and -31 T>C) were associated with a 2- to 3-fold increased risk of gastric cancer. Heterozygosity at the IL1B -31T/C locus has also been associated with colorectal adenoma, a precursor of colorectal cancer (Gunter et al., 2006). However, Macarthur et al., 2005 did not reveal significant associations between the cytokine polymorphisms of IL-1B-31T/C and risk of colorectal cancer. In the same directions are results obtained by Ito et al., 2007 for the same SNP in IL-1B. Simultaneously they found that IL-1B-511 heterozygotes and T carriers had a significantly low risk for gastric and colorectal carcinoma in the Japanese population.

The TNF cytokines are well known for their cytotoxic and antitumor activity. TNF- α is a proinflammatory cytokine secreted mainly by activated monocytes/ macrophages. TNF- α mediates the early inflammatory response and regulates the production of other cytokines, including IL-1 and IL-6. TNF- α gene is transcriptionally silent in unstimulated monocytes and is rapidly transcribed in response to a variety of signals, such as bacterial endotoxin (LPS) and other stimuli. The signaling cascades leading to TNF- α production bifurcates to control both transcription of TNF- α gene and translation of TNF- α mRNA (Swantek et al., 1997). Transcriptional control of the TNF- α gene is mediated primarily by NF- κ B binding sites present within the TNF- α gene promoter (Sweet and Hume, 1996; Yao et al., 1997). One microsatellite polymorphism in the vicinity of the TNF- α gene (TNF-A) has 14 different alleles (a1-a14). The a6 allele was associated with lower TNF- α secretion from activated monocytes (Pociot et al., 1993). For this TNF- α polymorphism, one allele was associated with an increased risk (a2 allele) and two other TNF-A alleles with decreased risks (a5 and a13 allele) of CRC (Gallagher, G et al., 1997; De Jong et al., 2002).

Among the other investigated polymorphisms of the TNF- α gene, the promoter -308G/A SNP was intensively studied. The presence of TNF- α -308A allele involved in gene transcription is associated with higher levels of TNF- α . Park et al., investigated TNF-A and NcoI RFLP of TNF-B genes and the risk of CRC (Park et al., 1998). The first intron of TNFB and the -308 promoter region of TNFA SNP polymorphisms were determined in 136 colorectal cancer patients and 325 healthy controls in an Asian population. Their results indicated that homozygous TNF-B*1/TNF-B*1 genotypes showed an increased risk for colorectal cancer, although no association in tumor susceptibility was found for the -308 G/A polymorphism of the TNF- α gene when comparing colorectal cancer patients and healthy controls. Landi et al., 2003 found a trend of reduced risk for CRC in TNF -308A allele carriers, but Theodoropoulos et al., 2006 found no effect of this SNP and the risk of CRC in Greek population.

For another SNP in TNF- α gene promoter, the -238 G > A site, has been reported that the A allele decreases the risk of developing colorectal cancer (Jang et al., 2001). Up to now, however, most studies have focused more on other cancer entities, such as melanoma and breast cancer, than on colorectal cancer.

The TNF- α pro-cancerous effect has recently been established. It's binding to specific receptors sets up signal transduction pathways, leading to cell apoptosis and gene regulation, via the MAPKinase and NF- κ B pathways (Waterston A, and Bower, 2004).

Interleukin-6 (IL-6) is a pleiotropic cytokine that participates in physiological and pathological processes for a variety of human malignancies including colorectal cancer. In particular, a preoperative IL-6 level is correlated with tumor stage, survival rate, and liver metastasis in CRC (Nakagoe et al., 2003). A significant association between serum IL-6 level and staging of the tumor ($P < 0.001$), tumoral tissue IL-6 level ($r = 0.95$, $P < 0.001$) in the patients was founded (Esfandi F et al, 2006). IL-6 amount of the serum and tumoral tissue in the

patients with colorectal cancer correlate significantly with the staging of the tumor and with each other. It has been demonstrated that IL-6 acts as a colorectal growth factor and as an autocrine growth factor for colorectal cancer cells (Chung and Chang, 2003).

A common G/C polymorphism located within the IL-6 gene promoter (chromosome 7p21) at position 174 bp, upstream from the start site of transcription (−174 G/C locus), has been reported (Fishman D et al, 1998). This promoter SNP affects the transcription of the gene, and altering the final levels of IL-6 released (Terry et al., 2000, Bonafe et al., 2001). The G allele increases IL-6 expression, both in stimulated and non stimulated conditions, the highest IL-6 levels being found in subjects homozygous for the G allele. In the same line are data of Belluco et al., 2003 for increased serum levels of IL-6 in colorectal cancer patients with genotype GG, regardless of the tumor stage, grade and location. Moreover, they also found a close correlation between high levels of circulating IL-6 and the presence of hepatic metastasis. The association between IL-6 serum level and CRC hepatic metastasis may depend on IL-6 properties to up-regulating the expression of adhesion receptors on endothelial cells and inducing the production of growth factors, such as hepatocyte growth factor and vascular endothelial growth factor, both of which may stimulate tumor metastasis. IL-6 promoter activation involves synergism between the transcription factors NF-IL-6 and NF-κB (Huang et al, 2000), and this may explain increased IL-6 serum levels in the CRC patients with hepatic metastasis. The first report, for investigation the promoter polymorphism in IL-6 gene with sporadic colorectal cancer risk has been the study of Landi et al., 2003. They found that the allele IL6 −174C is associated with increased risk of CRC. This association was seen both under a codominant model as well as when genotypes were grouped for both cancer of the colon and cancer of the rectum. A possible explanation of this effect is that the −174C allele could cause increased inflammation for colorectal cells in response to activated neutrophils (Nusrat et al., 2001). Slattery and colleagues reported that the GG genotype of the −174 G/C IL-6 polymorphism was associated with a significantly reduced risk of colon, but not rectal, cancers (Slattery et al., 2007). The IL6 −174C allele's role in CRC risk could not be replicated in the studies of others collectives (Theodopoulos et al., 2006; Cacev et al., 2010).

A possible cause for the conflicts and mismatches, like those observed here and the earlier study in allele and genotype distributions, may be the differences in racial or ethnical backgrounds. Duch et al. analyzed 52 patients with multiple myeloma and found that the G allele frequency was higher in the Brazilian population than in the European population (Duch C et al., 2007). Nowadays Yeh et al. observations on the allele and genotype distribution of the IL-6 −174 G/C polymorphism demonstrated that there are low frequencies of the G allele and GG genotype in the Taiwanese CRC population compared to the Western counterpart (Yeh et al., 2009).

Experimental data suggest that IL-6 plays an important role not only in developed but also in the progression of metastasis from colorectal cancer. In CRC patients, high expression of IL-6 has been correlated with poor survival and IL-6 −174 genotype CC was also significantly associated with shorter survival time when compared with the heterozygous genotype CG (Chung YC et al., 2006; Wilkening et al., 2008). Also, Belluco and colleagues analyzed 62 CRC patients and observed that patients with the C allele had lower serum IL-6 levels than those without the C allele, particularly in the presence of hepatic metastasis (Belluco C et al., 2003).

Specifically, IL-6/IL-6R complexes initiate homodimerization of gp 130, activate a cytoplasmic tyrosine kinase, and trigger signaling cascades through the JAK/STAT, Ras/MAPK and PI3-K/AKT pathways (Su et al., 2005; Chung YC et al., 2006). It has been shown that activation of signal transducers and activators of transcription 3 (STAT3) a member of a family of six different transcription factors is constitutively active in CRC cells (Corvinus et al., 2005). One of the main activators of these signal transducers are proinflammatory cytokines such as IL-6, TNF- α and growth factors. STAT3 activity in CRC cells triggered through interleukins was found to be abundant in dedifferentiated cancer cells and infiltrating lymphocytes of CRC samples. These actions regulate inflammatory reactions, immune responses, and several other pathophysiological processes of malignancy including cell growth and survival, differentiation, cell mobility and angiogenesis. Thus, the presence of proinflammatory cytokine polymorphisms in colorectal cancer development remains a pertinent question and one that we are not aware of other investigators having considered.

3. Cytokine gene polymorphisms of antiinflammatory cytokines: TGF- β and IL-10

Anti-inflammatory cytokines play an important role in downregulation of inflammation and the prevention of neoplastic disorders. Genetic variations of anti-inflammatory cytokines are assumed to influence such responses. Typical anti-inflammatory cytokines (TGF- β and IL-10) with immunosuppressive effect are secreted mainly from T regulatory cells (Tregs).

Transforming growth factor-beta (TGF- β or TGFB) is an immunoregulatory cytokine that plays an important role in tumor immune response within the gastrointestinal tract and this is shown in TGFB gene knockout mice, which proceed to develop uncontrolled inflammatory response and early death (Kulkarni et al., 1993). In mammalian cells, there are three isoforms described TGFB1, TGFB2, and TGFB3. Among them TGFB1 is the most abundant subtype.

TGF β 1 is involved in many critical cellular processes, including cell growth, extracellular matrix formation, cell motility, angiogenesis, hematopoiesis, apoptosis, and immune function (Moustakas et al., 2002; Schuster & Kriegstein, 2002). All immune cell lineages, including B, T and dendritic cells as well as macrophages, secrete TGF- β , which negatively regulates their proliferation, differentiation and activation by other cytokines.

The TGF- β signaling pathway plays an important role in controlling cell proliferation and differentiation involved in colorectal carcinogenesis. Binding of cytokine to the TGF- β receptor complex leads to phosphorylation of Smad proteins and triggers Smads intracellular signaling mediators to modulate gene transcription, mainly by transcription factor Sp1. Xu and Pasche, 2007 shown that TGF- β signaling alterations have been implicated in susceptibility to colorectal cancer.

In normal intestinal epithelium TGF- β 1 acts as a growth inhibitor, however loss of TGF- β 1 - mediated growth restraint has been shown to be associated with the transformation of colorectal adenoma to cancer. In addition, there is evidence that excess production and/or activation of TGF- β by cancer cells can contribute to the tumor progression by paracrine mechanisms involving neoangiogenesis, production of stroma and proteases, and subversion of immune surveillance mechanisms in tumor hosts (Muraoka-Cook et al., 2005). Moreover, TGF- β is the most frequently up-regulated in tumor cells (Elliott and Blobe, 2005).

TGF- β 1 is also a potent effector within the tumor microenvironment. It exerts a predominantly immunosuppressive effect on CD8⁺ cytotoxic T-lymphocytes and has been shown an active player in tumor immune evasion (Li et al., 2006). Friedman et al. reported that high levels of transforming growth factor β 1 correlate with disease progression in human colon cancer (Friedman et al. 1995). In light of these finding TGF- β 1 gene is a functional candidate gene for genetic predisposition in CRC.

The TGF- β 1 gene is located on chromosome 19 and several SNPs were described in promoter region, in the non-translated region (introns), in the coding region (exons), and in the 3'-UTR region of the gene (Watanabe et al., 2002). Certain inherited variants in the promoter region of the TGF- β gene (-800G/A and -509C/T) have been associated with higher cytokine circulating concentrations. The -800G/A SNP is located in a consensus cyclic AMP response element binding protein (CREB) half site and may cause reduced affinity for CREB transcription factors whose binding is important for transcription control (Grainger D et al., 1999). The -509C/T is located within a YY1 consensus binding site and -509T allele has been associated with increased TGF- β 1 plasma level (Grainger D et al., 1999) and reduced T-cell proliferation (Meng et al., 2005). Moreover these two SNPs of the TGF- β gene are in linkage disequilibrium. The 509 C/T polymorphism has been implicated in both colorectal adenoma and cancer risk. However, published data remains conflicting.

In the study of Macarthur et al., 2005 no association was found between -509C/T SNP in TGF- β 1 promoter and colorectal cancer. Authors investigated also association between cytokine polymorphisms of IL-1, IL-10 and TNF- α genes in a population based case-control study of 264 CRC patients and 408 controls in the Northeast of Scotland and analyzed their interaction with regular aspirin use. The beneficial association between nonsteroidal anti-inflammatory drugs use, such as aspirin and decreased risk of colorectal cancer provided further evidence to suggest a role for chronic inflammation in the pathogenesis of sporadic colorectal cancer. Whereas a statistically significant association was not found between any of the SNPs and CRC alone, the authors observed a significant interaction between the IL-10-592 genotype and aspirin use. The effect of aspirin on CRC risk was limited to carriers of low producing A allele (AA and AC) compared with CC genotype. The authors postulated that individuals who are genetically prone to producing reduced levels of the anti-inflammatory IL-10 (i.e., carriers of the variant A allele) are more likely to benefit from the anti-inflammatory properties of aspirin in decreasing risk of CRC development.

Berndt et al., 2007 examined two SNPs in the promoter region of the TGF β 1 (-800G/A; -509C/T) and two in exon 1 (Leu10Pro; Arg25Pro) and one in exon 5 (Thr263Ile) in association with advanced colorectal adenoma in population consisted primarily of Caucasians, living in the USA. The Leu10Pro and Arg25Pro SNPs encoded non synonymous amino acid substitution located in signal peptide sequence of the TGF- β 1 pro-peptide.

Dunning et al., 2003 revealed that the 10Pro variant lead to increased TGF- β secretion compared with the 10Leu allele. Similarly, the 25Arg allele has been associated with increased TGF- β production upon stimulation in vitro (Awad MR et al., 1998).

Berndt et al., reported that the high TGF- β produced genotypes, -509TT and 10Pro/Pro genotypes were associated with an increased risk of advanced colorectal adenoma compared with other genotypes. These increased risks, particularly for -509TT association were greater for the subsets of participant with multiple adenomas and those with rectal adenomas. Risk factors for hyperplastic and adenomatous polyps were generally similar to those for colorectal cancer. Another study investigated the same Leu10Pro polymorphism in

association with colorectal adenoma and hyperplastic polyps. In this study no association was found with this SNP and adenoma, but a lower risk of hyperplastic polyps was suggested for Pro allele carriers who were current or past smokers (Sparks et al, 2004).

Together these studies give support to the possible role of TGFB1 in the adenoma-carcinoma sequence and suggest that high TGFB1 produced genotypes may modulate the risk in this transformation.

To characterize association of genetic variation at the TGFB1 gene with circulating cytokine levels of TGF- β and risk of colorectal adenoma and adenocarcinoma, Saltzman et al., 2008 conducted two case-control studies (including 271 colorectal adenoma cases and 544 controls, and 535 colorectal adenocarcinoma cases and 656 controls) among Japanese Americans, Caucasians, and Native Hawaiians in Hawaii. The authors investigated 26 SNPs, spanning 39.8 kb region of the TGFB1 gene, distributed in two haplotype blocks of linkage disequilibrium named as tagSNPs, including all previously commented SNPs. They found that the variant A allele for tagSNP in 3'UTR A/G (rs6957) was associated with an increased serum level of TGF- β , and no association with promoter -509C/T and Leu10Pro polymorphisms was found. However, published data remains conflicting. In the recent study the association between -509 C/T and -800 G/A SNPs of the TGFB1 gene, and susceptibility to colorectal cancer in Iranian patients was investigated (Amighofran Z et al., 2009). They found a statistically significant lower frequency of 509T allele and TT genotype in patients than in control subjects. At position 800, no significant differences in genotype distribution and allele frequencies between the patients and healthy controls were found. The authors concluded that the genotype distributions and allele frequencies of the TGFB1 gene polymorphism at -509 C/T were significantly related to colorectal carcinoma in Iranian subjects. In the same directions are the results of Chung et al., 2007, that -509T variant allele reduced risk of colorectal cancer, but not adenoma in Koreans. A possible explanation for discrepancy in above commented results for involvement of -509 C/T SNP in colorectal cancer susceptibility occurs in the investigation of Fang et al., 2010. To derive a more precise estimation of the relationship, a meta-analysis of 994 colorectal cases and 2,335 controls from five published paper was performed. Overall, significantly increased colorectal cancer risks were found for CC versus TT in the subgroup analysis by ethnicity. Fang et al., 2010 concluded that TGFB1 -509 C/T substitution has a role in genetic predisposition for developing colorectal cancer in Asians, but no significant associations were found among Europeans.

Thus far, TGF- β 1 -509 T/C gene polymorphisms have been also relevant to Crohn's disease development (Schulte et al., 2001). In the same time patients with Crohn's disease are at increased risk for developing colorectal cancer. Several lines of evidence implicate chronic inflammation in inflammatory bowel disease (ulcerative colitis and Crohn's disease) as a key predisposing factor to distinct subset of colorectal tumors. (Itzkowitz and Yio, 2004).

IL-10 is an immuno-regulatory cytokine that plays a crucial role in modulating gastrointestinal tract inflammation (Moore et al, 2001; Lin and Karin, 2007). IL-10 is produced mainly by regulatory T cell and antigen presenting cells. It is pivotal in inhibiting inflammation and interrupting carcinogenesis. In cancer patients, the production of immune suppressive cytokines: IL-10 and TGF is accelerated, and IL-10-producing type I T-regulatory (Tr1) cells are highly infiltrated in tumor microenvironment. Thus, tumor cells might escape from the immune surveillance. That is the way the IL-10 gene might be involved in genetically predisposition and severity of CRC.

Large interindividual differences in the IL-10 inducibility have been observed, which has shown to have a genetic component of over 70%. The IL-10 gene comprises 5 exons, and it has been mapped to chromosome 1q31-32. To date, at least 49 *IL10*-associated polymorphisms have been reported, and an even larger number of polymorphisms are recorded in SNP databases (Ensembl Genome Browser, 2006). Promoter polymorphisms have been subject to the most studies, particularly with regard to possible influences on gene transcription and protein production. Three SNPs at -1082(A/G), -819(C/T), -592(C/A) upstream from the transcription start site (D'Alfonso S et al., 1995; Turner D et al., 1997) have been described as well as additional two microsatellite (CA)_n repeats, termed IL-10G and IL-10R and located at -1151 and -3978 respectively (Eskdale J and Galager G, 1995; Eskdale J et al., 1997). In particular, SNP at position -1082A/G of IL-10 gene was associated with IL-10 production alone or in haplotypes with other distal SNPs. Turner et al., 1997 have shown that -1082A allele is associated with lower in vitro IL-10 production by Con A-stimulated PBMC from normal subjects. Crawley et al., 1999 have reported that GCC haplotype was associated with higher IL-10 level compared to ATA in whole blood cultures after LPS stimulation. In our studies, the functional effect of -1082 A/G polymorphism was demonstrated among the Bulgarian population in both healthy volunteers and in patients with sepsis (Stanilova et al., 2006).

Positive associations between IL-10 genotype or haplotype and cancer susceptibility, progression, or both were reported (Howell and Rose-Zerilli, 2007). The IL-10-1082/-819/-592 genotype status was associated with an increased risk for gastric cancer in Japan. The presence of the ATA/GCC haplotype of IL-10-1082/-819/-592 polymorphisms significantly increased the risk of gastric cancer development compared with presence of the ATA/ATA haplotype. (Sugimoto et al, 2007). The AA genotype of the -1082 A/G polymorphism in the interleukin-10 gene promoter was associated with lower IL-10 production in LPS, PHA or PWM stimulated healthy PBMC (Stanilova et al, 2006). This cytokine possess anti-inflammatory and immunoregulatory role and it is no wonder that IL-10 play a dual role in tumor development and progression (Mocellin et al., 2003; Mocellin et al, 2004; Dranoff 2004; Lin and Karin, 2007). Contradictory results are present in the literature concerning IL-10 systemic or tissue levels and survival of cancer patients. For instance, Mocellin et al. found that IL-10 overexpression within the tumour microenvironment was implicated in cancer immune rejection.

Although IL-10 suppression of pro-inflammatory cytokines synthesis favors its anti-tumor immunity, it might also promote tumor growth by stimulating cell proliferation and inhibiting cell apoptosis. A high systemic level of IL-10 has been reported for advanced colorectal cancer patients (O'Hara et al., 1998; Galizia et al., 2002). Increased level of IL-10 might better control inflammatory responses and cancer development. Results from our study demonstrated a stage dependent association between IL-10 serum level and severity of CRC (Stanilov et al., 2010). The highest IL-10 serum level was found in stage-IV CRC patients, suggesting a pro-tumorigenic activity of systemic IL-10 in CRC progression and play a role in tumor-induced immunosuppression in CRC patients. In addition, we determined a significantly increased mRNA in tumor tissue compared to normal mucosa (Stanilov et al., 2009). Moreover expression of IL-10 mRNA correlated positively with increased Foxp3 mRNA expression detected in tumor tissue. These results confirm the role of Foxp3 transcription factor in induction of IL-10 production and differentiation of Treg-1 cells in tumor microenvironment.

Cacev et al, 2008 reported a statistically significant decrease in IL-10 mRNA expression in tumor tissue then normal mucous depending on IL-10 SNPs. IL-10 promoter genotypes -819 TT and -592 AA associated with low IL-10 mRNA expression in tumor and corresponding normal mucosa. The 'low-producer genotypes' were present more frequently in colon cancer patients and this difference in genotype distribution was statistically significant. In the same study IL-10 -1082AA genotype was associated with lower IL-10 mRNA expression, whereas -1082GG genotype was associated with higher IL-10 mRNA expression in tumor tissue. In a group of colon cancer patients, an increased frequency of the -1082AA genotype compared with control group was observed without statistical significance. The authors conclude that IL-10-1082G/A SNP did not influence sporadic colon cancer susceptibility.

No associations were observed among colorectal cancer patients and controls for IL-10 -1082G/A and -592C/A genotype frequencies in a case-control study of 62 patients and 124 matched controls (Crivello et al., 2006). A possible reason for these contradictory results might be a small number of patients.

A recent study of Tsilidis K et al., 2009 investigated the association of 17 candidate SNPs in IL-10 with colorectal cancer in 208 patients. The authors established that -1082 promoter SNP is implicated. Compared with the AA genotype at the candidate IL10-1082 locus (rs1800896), carrying one or two G alleles, a known higher producer of the anti-inflammatory cytokine IL-10 was associated with lower risk of colorectal cancer ($p = 0.03$). Statistically significant associations with colorectal cancer were observed for three tagSNPs in IL10 (rs1800890, rs3024496, rs3024498) and one common haplotype, but these associations were due to high linkage disequilibrium with IL10-1082.

Associations between IL-10 genotypes and cancer chemopreventive strategies and survival were also published. Results of Macarthur et al. suggest that IL-10 SNPs may play a role in predicting response to chemopreventive strategies. Carriers of the *IL-10-592A* allele, had a statistically significant 50% reduced risk of colorectal cancer when taking regular aspirin, whereas risk was not reduced in carriers of the A allele who did not use aspirin, or among aspirin users with the CC genotype. It is possible that carriers of the *IL-10-592C* allele are more likely to derive chemopreventive benefits from aspirin in the presence of a lower production of their own endogenous anti-inflammatory interleukin-10 (Macarthur et al, 2005).

In particular proinflammatory genotypes characterized by a low IL-10 producer seem to be associated with a worse clinical outcome. Sharma et al. investigated the prognostic value of an inflammation-based Glasgow Prognostic Score in advanced colorectal cancer to explore a predictive pattern of cytokine gene polymorphisms for clinical outcome (Sharma et al., 2008). They found that IL-10-592A/C and IL-10 -1082A/G were predictive for overall survival. Patients homozygous for IL-10-592 CC had improved overall survival compared with those patients with ≥ 1 A allele (median survival, 12.2 ± 0.7 months vs. 8.6 ± 1.6 months). In contrast, patients homozygous for IL-10-1082 AA had poorer overall survival compared with patients with ≥ 1 G allele (median survival, 8.8 months ± 3.2 months vs. 11.2 ± 2.1 months).

Although the functional effects of polymorphisms in immunosuppressive genes TGFB and IL-10 have not yet been elucidated, obviously that they may play a significant role in modulating susceptibility, development and survival of colorectal cancer (Fig.1). The observation of increased circulating levels of IL-10 in colorectal cancer patients may have important implications for future investigations, immunological monitoring and therapeutic intervention on neoplastic patients, and suggests a mechanism for tumour cells escaping from immune surveillance.

Gene/ polymorphism	Genotype or allele associated with			
	Succeptibility - increased risk of CRC	Protection – decreased risk of CRC	Survival rate - Shorter survival	References
PROINFLAMMATORY				
IL-1B -511 C>T		TT ; CT		Ito et al., 2007
TNF-B	TNF-B*1/TNF-B*1			Park et al.,1998
TNF-A microsatellite	a2 allele	a5 and a13 allele		Gallager et al., 1997 ; DeJong et al, 2002
TNF-A- 238 G >A		AA and AG		Jang et al., 2001
IL6 -174G>C	C allele			Landi et al., 2003
			CC	Chung YC et al., 2006
		GG		Slattery M et al., 2007
ANTIINFLAMMATORY				
TGFB1 -509C>T	-509TT			Berndt et al., 2007
TGFB1 Leu10Pro	10Pro/Pro			Berndt et al., 2007
TGFB1 -509C>T		-509TT		Amighofran Z et al., 2009
TGFB1 -509C>T		-509T allele		Chung et al., 2007
TGFB1 -509C>T		-509TT		Fang et al., 2010
IL-10 -1082 A>G		G allele		Tsilidis K et al., 2009
IL-10 -592 C> A	-592 AA			Cacev et al, 2008
IL-10 -819 C>T	-819 TT			Cacev et al, 2008
IL-10 -1082 A>G ; -592 C> A			IL-10 – 1082AA IL-10 – 592 AA	Sharma et al., 2008

Table 1. Involvement of IL-1; TNF, IL-6, IL-10 and TGF-β gene polymorphisms into colorectal cancer.

4. Role of IL-12-related cytokines

Human interleukin (IL)-12 (IL-12p70) is a disulfide-linked heterodimer composed of two subunits p40 and p35. IL-12p40 subunit can be secreted as monomer, which can also form IL-23, a heterodimeric pro-inflammatory cytokine composed of p40 and p19 subunits, and a homodimer, IL-12p80, which can act as an IL-12 and IL-23 antagonist by competing at their receptors (Hoelscher, 2004). The IL-12 family cytokines are produced by antigen-presenting cells such as macrophages and dendritic cells and play critical roles in the regulation of Th cell differentiation. IL-12 induces IFN- γ production by NK and T cells and differentiation to Th1 cells. IL-23 induces IL-17 production by memory T cells and expands and maintains inflammatory Th17 cells. IL-27 induces the early Th1 differentiation and generation of IL-10-producing regulatory T cells. Although IL-12p70 is one of the most powerful antitumor cytokine (Colombo and Trinchieri, 2002), accumulating evidence revealed that the individual members of the IL-12 family play distinct roles in the regulation of antitumor immune responses.

Several polymorphisms have been described in the IL12B gene, encoding IL-12p40 subunit, including a single-nucleotide polymorphism in 3'-untranslated region (UTR) of IL12B with number rs3212227 and a complex polymorphism in promoter region of the IL12B (IL12Bpro), resulting from 4bp microinsertion combined with an AA/GC transition (rs17860508). Moreover, several studies have demonstrated that these two polymorphisms affect gene expression and IL-12 production (Morahan et al., 2001; Seegers et al., 2002; Muller-Berghaus et al., 2004; Stanilova and Miteva, 2005; Stanilova et al., 2008; Dobрева et al., 2009) and consequently could influence the pathogenesis of CRC. To test this hypothesis, we performed a case-control study to investigate the association between these gene polymorphisms and the risk of colorectal cancer. The paper of Miteva et al., 2009 was the first study which investigated the distribution of *IL12Bpro* polymorphism and the +16974A/C SNP in 3'UTR of *IL12B* among 85 Bulgarian patients with colorectal cancer. No differences in genotype and allelic frequencies of the *IL12B* polymorphisms in the promoter and 3'UTR regions between patients with CRC and controls were found, either when patients were analyzed as a whole group or when they were separated according to the TNM classification or clinical characteristics such as tumor location, differentiation degree, lymph node and metastases status. These data are in principal agreement with other studies, where no association with SNP in 3'UTR of *IL12B* was found in pathogenesis of other related gastrointestinal diseases. Navaglia et al. have reported that none of the studied *IL12B* gene polymorphisms, including SNP in 3'UTR, was correlated with *Helicobacter pylori* infection and intestinal metaplasia (Navaglia et al., 2005). There was no statistically significant association between the SNPs investigated in IL-12A gene ((+7506 A>T, +8707 A>G, +9177 T>A, +9508 G>A) and colorectal cancer risk in the study of Landi et al., 2006. The lack of association suggests that the role of both investigated polymorphisms in IL12B in susceptibility of sporadic colorectal cancer can be excluded. However, these findings do not exclude a key role for IL-12p40 in development and progression of the CRC. In our investigations, we have demonstrated that serum levels for IL-12p40 and IL-23 were significantly higher in patients compared to healthy donors. Additionally, we found the highest level of IL-12p40 in sera from patients with I stage of CRC and significantly lower in patients with more advanced stages. (Miteva et al., 2009; Stanilov et al., 2009; Stanilov et al., 2010). In respect to recent findings regarding different proteins in IL-12 related family which share the p40 subunit, we could attribute the relationship of decreased serum level of IL-

12p40 and severity of CRC to the action of Th1-promoting form of IL-12, such as IL-12p70, or free IL-12p40 in monomeric and homodimeric form.

In a recent study there were significant differences in the genotype and allele frequencies of the IL-12 gene 16974 A/C polymorphism between the group of patients with glioma and the control group (Zhao et al., 2009). Moreover, genotypes carrying the IL-12 16974 C variant allele were associated with decreased serum IL-12p40 and IL-27p28 levels compared to the homozygous wild-type genotype in patients with glioma.

The promoter polymorphisms in the human IL12B gene could influence JNK and p38 MAPKs control of IL-12p40 expression in human PBMC in response to mitogens and proinflammatory stimuli. The study of Dobrev et al., revealed that JNK and p38 MAPK inhibition in PBMC stimulated with C3b and LPS, significantly upregulated the IL-12p40 production from IL12Bpro-1 homozygotes and did not influence the IL-12p40 production from 1.2/2.2 genotypes (Dobrev et al., 2009). Also, the p38 inhibition led to significant increase of IL-12p40 production in IL12Bpro-1 homozygous PBMC stimulated with PHA. IL-12p40 is secreted at a 50-fold excess compared with IL-12p70 in a murine shock model (Wysocka et al., 1995) and at a 10-20-fold excess by stimulated human peripheral blood mononuclear cells (D'Andrea et al., 1992). IL-12p40 chain may form also a homodimer IL-12p80 that serves as an IL-12p70 and IL-23 antagonist by competing for binding at the receptor complexes of both cytokines (Cooper & Khader, 2006). The proper balance between IL-12p40-related cytokines play a key immunoregulatory role and control the appearance of protective Th1-mediated immune response. Current results demonstrated an opposite effect of JNK and p38 MAPKs inhibition on the IL-12p70 and IL-23 production in LPS and C3b-stimulated PBMC (Dobrev et al., 2008). Our results demonstrated that p38 MAPK inhibition down regulates IL-23 and up regulates IL-12p40/p70 inducible expression suggesting the benefit of p38 control in the treatment of inflammatory conditions.

IL-12 related cytokines (IL-12p70; IL-12p40 and IL-23) produced locally or systemic exhibit a significant role in progression of CRC. Accumulating evidence revealed that the individual members of the IL-12 family play distinct roles in progression of CRC. Studies have defined IL-12p70 as an important factor for the differentiation of naive T cells into IFN- γ producing Th1 cells and exhibits anti-tumor activity (Brunda et al., 1995; Gri et al., 2002). Although the antitumor activities of IL-12p70 are well characterized, studies of the role of IL-23 in development of CRC in humans are contradictory. Some authors reported that IL-23, as well as IL-12p70, have anti-tumor activity in murine tumor models (Wang et al., 2003; Lo et al., 2003; Shan et al., 2006). Contradictory results have been reported in studies of Langowski et al., 2006 which showed data that IL-23 promotes tumor incidence and growth in various human cancers. In this respect our results for enhanced serum levels of IL-23 in cancer patients regardless of severity supported the hypothesis that IL-23 promotes tumor development unlike IL-12p70 (Stanilov et al., 2010). Besides, the highest increase in transcriptional activity in tumor samples for IL-23p19 mRNA has been also reported in our study (Stanilov et al., 2009). IL-23p19 mRNA was approximately 29 fold upregulated ($p=0.0009$), whereas IL-12p35 mRNA was not significantly upregulated, when compared to their adjacent normal tissue. This difference indicated that IL-23 could be synthesized many times more than IL-12p70 in tumor tissue. Based on our and others data, we could assume that increased serum and locally produced IL-23 indicates impaired anti-tumor immune response and could be associated with poor prognosis of CRC. A molecular mechanism involved in IL-23 activities includes STAT3 activation. STAT3 signaling within the tumor microenvironment was recently elucidated to induce a protumor cytokine, IL-17 and IL-22,

while inhibiting a central antitumor cytokine, IL-12p70, thereby shifting the balance of tumor immunity toward tumorigenesis. Interestingly, unlike spleen Treg cells, tumor-associated Treg cells express IL-23R and activate STAT3 in response to IL-23, leading to upregulation of the Treg-specific transcription factor Foxp3 and the immunosuppressive cytokine IL-10 (Xu M et al., 2010). Collectively, IL-12 and IL-23 play critical roles in the regulation of antitumor or protumor response in respective situation.

5. Conclusion

In recent years, efforts have been made to identify genes involved in the genetic predisposition or progression of colorectal cancer. During the last two decades, many of the 'candidate' cytokine genes implicated in colorectal tumorigenesis have been identified and were summarized in this review. As cancer is a complex genetic disease, it is probable that besides oncogenes and tumor suppressor genes a number of cytokine genes also contribute to cancer susceptibility and development. Moreover cytokines are a key-player in inflammation, which have protumoral effect and mediated anti-tumor immune response. Cytokines present in tumor microenvironment have gained much attention due to their influence on cell activation, growth, differentiation or cell migration and they are increasingly recognized as potential cancer modifying genes. While numerous factors influence the inflammatory response in cancer, the role of an individual's genetic background has recently received increasing attention.

Cytokines and their receptors are often encoded by highly polymorphic genes. Single-nucleotide polymorphisms in cytokine genes potentially affect their production by either creating or eliminating key binding motifs within promoter and other regulatory sequences. In investigating disease-gene associations, there is a strong argument for focusing on polymorphisms of functional significance. Up to date contradictory results from case-control study have been published concerning cytokine gene polymorphisms and colorectal cancer development. Obviously reasons for such results included different numbers of patients; their ethnicity and differences in clinical and pathological data. In any case-control study, there are potential limitations. Despite the limitations of most published studies, the preliminary literature indicates that selected cytokine polymorphisms, particularly in IL-10; TGF- β ; IL-6 and TNF- α are required in colorectal cancer. Data included in this review summarized in table1 suggest that functional cytokine polymorphisms participate more in the onset of colorectal cancer progression rather than in its initial development. Due to the strong evidence concerning the biological significance of these SNPs further studies and meta analysis are needed to evaluate the significance in the clinic. Careful selection of SNPs to cover the whole length of a candidate gene sequence so that areas of association can be defined and informative haplotypes constructed. Emerging genotyping technologies will facilitate such definitive, comprehensive studies.

The preliminary data indicate that larger studies are required to confirm or reject existing results, extend studies to include more detailed genotype and haplotype analysis, and combine genotype and gene expression studies in the same subjects. Even larger numbers of cases and controls would be required to demonstrate more modest odds ratios with higher statistical power. Collection of definitive clinical and pathological data for all cases must be an integral part of such an approach.

Such studies will contribute significantly to our understanding of the biological role of cytokine polymorphisms in colorectal cancer development.

6. References

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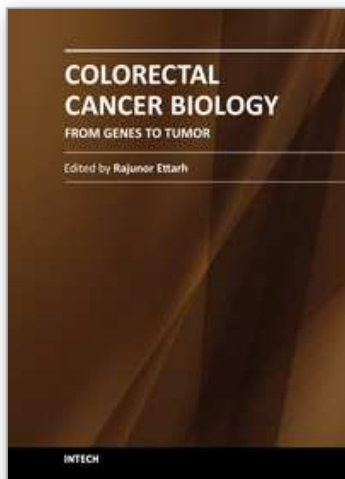
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Colorectal cancer is a common disease, affecting millions worldwide and represents a global health problem. Effective therapeutic solutions and control measures for the disease will come from the collective research efforts of clinicians and scientists worldwide. This book presents the current status of the strides being made to understand the fundamental scientific basis of colorectal cancer. It provides contributions from scientists, clinicians and investigators from 20 different countries. The four sections of this volume examine the evidence and data in relation to genes and various polymorphisms, tumor microenvironment and infections associated with colorectal cancer. An increasingly better appreciation of the complex inter-connected basic biology of colorectal cancer will translate into effective measures for management and treatment of the disease. Research scientists and investigators as well as clinicians searching for a good understanding of the disease will find this book useful.

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