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Chapter

IL10 as Cancer Biomarker

Maria Teresa Gonzalez-Garza, Delia Elva Cruz-Vega and Carmen Maldonado-Bernal

Abstract

Chronic inflammation can trigger events that would induce the malignant transformation of cells and carcinogenesis. Cytokines play a crucial role and can control the development and multiplication of cancerous cells. However, clinical data present controversy about the participation of these proteins in the establishment and development of cancer. Interleukin 10 (IL-10), a potent anti-inflammatory cytokine, has been the subject of multiple studies. Several studies have reported that IL-10 has pro- and antitumor effects. Elevated levels of IL-10 are associated with increased tumor growth with poor prognosis and drug resistance. However, this cytokine has both tumor-promoting and tumor-inhibiting properties. *In vitro* and *in vivo* studies report mechanisms by which IL-10 expression downregulates class I, which results in the control of the metastatic disease. IL-10 also inhibits tumorigenesis via downregulation of other cytokines. The variation observed could be the result of concentration ranges of this protein, genetic polymorphism, or both. The value obtained may serve as a biomarker indicative of tumor development and its prognosis.

Keywords: interleukin 10, IL-10, IL10 polymorphism, cancer biomarker

1. Introduction

The immune system is responsible for monitoring and getting rid of molecules or cells outside the body that can be potentially malignant. This system is constituted by cells that can act by themselves or the synthesis of molecules capable of inducing the destruction of strange agents or invading cells. In addition, these cells synthesize proteins called cytokines, which are not only capable of destroying invading cells; they activate other cells of the same immune system, which makes the system efficient. In a coordinated way, the synthesis of anti-inflammatory cytokines begins that will stop the inflammatory process and prevent the damage from spreading in healthy tissue. In the case of cancer, the cells will have nonnormal characteristics due to the changes they undergo during their transformation. The immune system works to eliminate these cells; however, for reasons not well established yet, at some point, the immune system fails, and the malignant cells survive and establish [1]. Even when the production of anti-inflammatory cytokines is present, the levels of pro- and anti-inflammatory cytokines have an imbalance that prevents completing the final objective. An increase of anti-inflammatory cytokines, such as interleukin 10 (IL-10), has been associated with a poor prognosis and considered as a biomarker for cancer disease. This chapter presents evidence that shows alterations in the serum levels of IL-10 in cancer patients, the participation of the cancerous tumor in the synthesis of this cytokine, and its possible relationship with polymorphisms in the gene promoter, the gene of this protein.

2. Interleukin 10 (IL-10)

IL-10 is an important regulatory cytokine with a potent anti-inflammatory effect. In humans, it is encoded by the IL10 gene [2]. It presents polymorphisms (SNPs), most of them within the promoter regions, and has been proposed as responsible for the altered function, by dysregulating their expression. Several groups report associations between polymorphism and cancer risk [3–7]. It is a helical cytokine and exists in solution predominantly as a homodimer, composed of two polypeptide chains of 160 amino acids, each with a molecular weight of 20,6419 kD [8].

IL-10 was initially thought to be produced only by T helper (Th2) cells but is now known to be made by a variety of cell types [9]. It is primarily produced by monocytes upon PD-1 triggering in these cells and, to a lesser extent, lymphocytes type 2 T helper cells (TH2), mast cells, CD4+CD25+Foxp3+ regulatory T cells, and in a specific subset of activated T cells and B cells (**Figure 1**) [10]. IL-10 expression is minimal in unstimulated tissues and seems to require triggering [11].

Cytokine signals are generated through a receptor complex consisting of two IL-10 receptor-1 and two IL-10 receptor-2 proteins. After IL-10 binding, it induces STAT3 signaling via the phosphorylation of the cytoplasmic tails of IL-10 receptor 1 + IL-10 receptor 2 by JAK1 and Tyk2, respectively (**Figure 2**) [12, 13].

IL-10 expression is regulated at the transcriptional and posttranscriptional levels. Extensive IL-10 locus remodeling in monocytes upon the stimulation of Toll-like receptor (TLR) or Fc receptor pathways was described. Induction involves ERK1/2, p38, and NF-κB signaling and transcriptional activation via promoter binding of

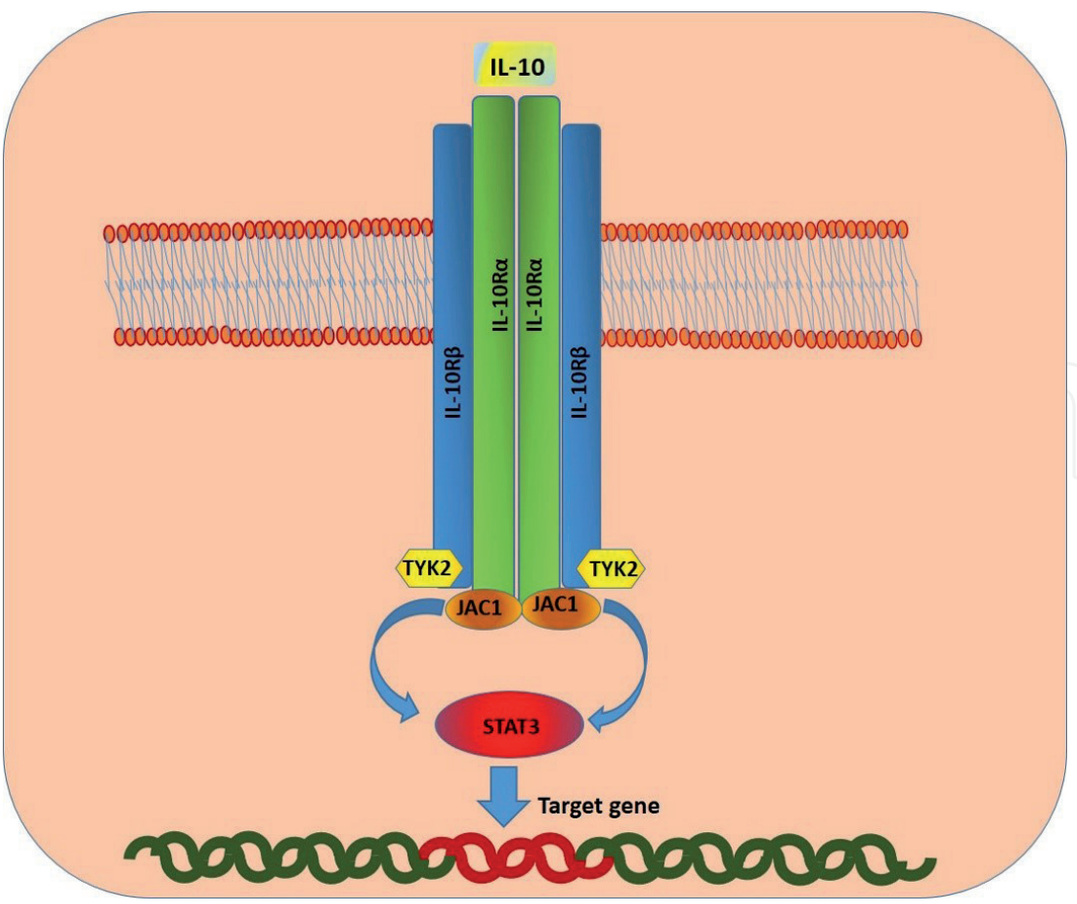

Figure 1.
IL-10R homodimers bind to form in a tetrameric heterodimer after IL-10 binds to its receptor α. It downstream signaling through STAT3 until target genes.

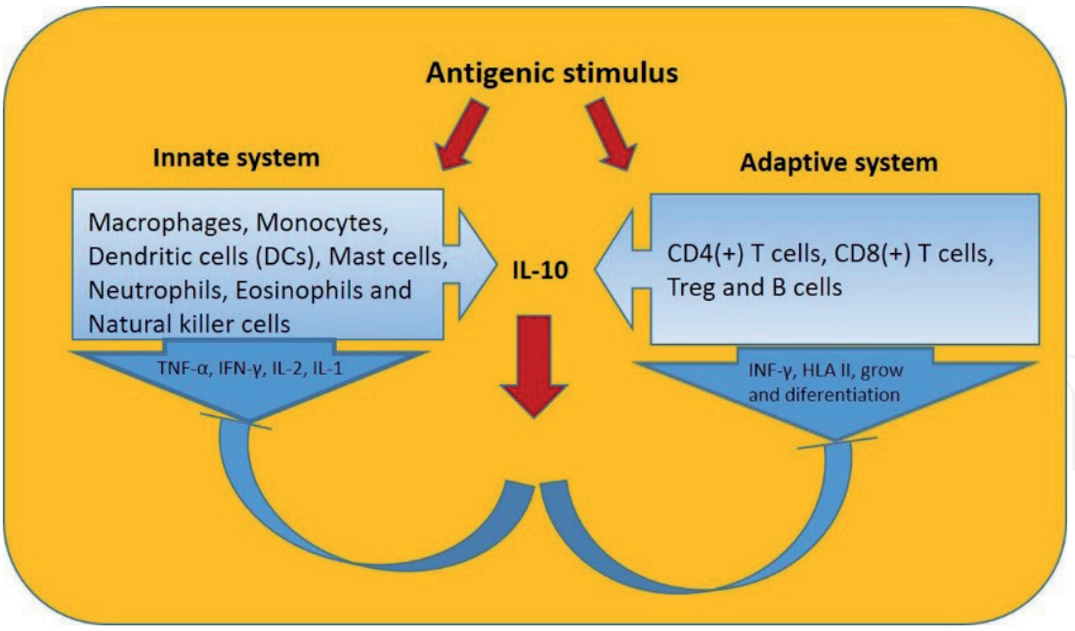

Figure 2.
After antigenic stimulus on cells from innate and adaptive system, the IL-10 is expressed from these cells. To avoid severe danger from pro-inflammatory cytokines and reactive radicals, IL-10 acts as anti-inflammatory cytokine by blocking its expression.

the transcription factors NF-κB and AP-1; other regulation as a complex of multiple transcriptional factors has been described, such as GATA-3, E4BP4, MAF, and Blimp [14, 15]. These reports are allowing the possibility that transcriptional regulatory machinery could be specific to certain cell types [16, 17]. In addition, the regulation of IL-10 production depending on the TLR2 or TLR4-stimulated in BM-derived macrophages presents different stability profiles for the IL10 mRNA [18].

It has the ability to inhibit activation and effector function of T cells, monocytes, and macrophages. It regulates the growth and differentiation of several cells such as B cells, NK cells, cytotoxic, and helper T cells, as well as mast cells, granulocytes, dendritic cells, keratinocytes, and endothelial cells (**Figure 1**).

Discovered in 1991, IL-10 was initially reported to suppress cytokine secretion, antigen presentation, and CD4+ T cell activation. IL-10 is crucial for controlling these T-cell responses, as IFNγ [19–22]. Further investigations have shown that IL-10 predominantly inhibits the synthesis of the pro-inflammatory cytokines IL-1, IL12, tumor necrosis factor (TNFα), and gamma Interferon (IFNγ) by stimulated monocytes/macrophages [23–25]. IL-10 is crucial for controlling these T-cell responses, as IFNγ-secreting and blocking proliferation [22, 26–28].

The pivotal role of autocrine IL-10 and the interaction with CD28 in the induction of T cell are to initiate peripheral tolerance as an immunoregulatory mechanism controlling antigen-specific T cell responses [21].

In addition, several effects have been reported: it downregulates the expression of Th1 cytokines, MHC class II antigens, dendritic cells, and co-stimulatory molecules on macrophages [29].

Biphasic effects have been reported on B cells. It prevents apoptosis in germinal B cells but induces apoptosis on B-chronic lymphocytic leukemia cells, enhances proliferation induced by CD40L, and promotes differentiation of B cells to become plasma cells secreting IgM, IgG, and IgA immunoglobulins [30–34].

IL-10 appears to have considerable importance in the development of human cancer and its immune escape. These have suggested that it could serve as a biomarker for prognostic diseases or as a target for treatment. Two factors should be considered: high levels of this cytokine in the system, and genetic polymorphisms.

3. IL-10 serum levels on cancer patients

Considering their possible role in the development and establishment of malignant cells, the first studies conducted to detect serum IL-10 levels in cancer patients, reported a higher concentration than in healthy subjects. In melanoma patients with lymph node metastases, stages III and IV showed significantly high concentration with respect to a healthy subject. *In vitro* determination performed on the supernatant of primary malignant melanoma cultures, IL-I0 mRNA, and protein was expressed. Later, in a meta-analysis that included melanoma patients, high expression of serous IL-10 leads to an adverse survival and correlated with worse outcomes in cancer patients [35–39].

On serum samples of 90 patients with gastric cancer, high IL-10 levels were associated with a worse prognosis independent of the gastric-stage patients and pancreatic cancer [40]. Similar observations were reported on another group of patients with a pancreatic and gastric cancer stage (IV). In the same study, patients with colon and renal carcinoma IL-10 levels did not significantly differ from controls [41]. *In vitro* study, supernatants of pancreatic tumors primary cultures, high concentration of IL-10 was detected [42].

Similar clinical findings on sera and tissues samples from lung cancer patients were report; samples with high levels were found on patients in stages III and IV, and less in stages II and I. The increased IL-10 levels correlate with a poor prognosis. On lung tumor tissues samples from those patients, IL10 concentration showed than the higher expression, presented lower survival rates [43].

Samples from breast cancer from patients, who underwent surgery as well as peritumoral normal breast tissue, were analyzed. Correlation between the IL-10 expressions of breast cancer tissue showed poor prognosis. No IL-10 was detected on normal tissue samples [44]. Determination of IL-10 on patients with breast cancer and early breast cancer showed that it could be usefully associated with other cytokines as biomarkers to discriminating advanced cancer, reported that IL-10 is significantly upregulated. These data could be used discerning between the two stages. [45].

Hodgkin's disease presented sera elevated IL-10 levels on range 4.5–225.6 pg/ml, suggesting that IL-10 could be an independent prognostic factor and correlates to poor survival [46]. Lymph nodes from pediatric patients with Hodgkin's disease express high levels of IL-10 mRNA where there were associated with an unfavorable prognosis [47, 48]. For the study of sera levels in 153 patients with Non-Hodgkin's disease, IL-10 was detectable with a similar frequency in all subtypes and all clinical stages. Nevertheless, high levels correlate with poor prognosis. Patients with stage IV disease and detectable serum IL-10 had a particularly poor prognosis [49, 50]. Additional information on sera levels of IL-10 is shown in **Table 1**.

IL-10 protein or mRNA appears to be an important component of the tumor micro-environment in a range of human cancer types, as renal cell carcinoma [68]. The role of macrophages in the regulation of tumor cell proliferation, invasion, angiogenesis, or immune control does not always have a positive effect; in fact, it has shown a negative effect. The secretion of IL-10 inhibits the inflammatory response [69–72] and also has been suggested that the detection of IL-10 into and surrounding the tumor may be derived directly from the tumor cells; *in vitro* studies reveal that melanoma cells themselves are the primary origin of IL-10 in tumor specimens *in vivo* [35]. Nevertheless, Mocellin *et al*. report evidence about immunostimulating anticancer properties, suggesting IL-10 over-expression within the tumor micro-environment and it may catalyze cancer immune rejection [73].

IL-10 and IL10R were quantified in sera and surgical specimens, although no significant serum IL-10 elevation was found. On surgical lung tumor cells, IL-10

Disease	Patients IL-10 levels	Healthy donor	References
Melanoma	15–480 pg/ml	<3.0 pg/ml	[35]
	8.75 pg/ml	<3.0 pg/ml	[39]
	24.3 ng/ml	3.4 ng/ml	[41]
Gastric cancer	6.3 ng/ml	3.4 ng/ml	[41]
	12.5 pg/ml	4.0 pg/ml	[40]
	27.52 pg/ml	<12 np/ml	[51]
	19.6 pg/ml	9.2 pg/ml	[52]
	>21.0 pg/ml	<3.0 pg/ml	[53]
Pancreatic cancer	6.8 ng/ml	3.4 ng/ml	[41]
	>10.0 pg/ml	ND	[54]
	>9.8 pg/ml	3.0 pg/ml	[55]
Colorectal cancer	97.36 ng/l	24.53 ng/l	[56]
	16.09 pg/ml	5.1 pg/ml	[57]
Hepatic cancer	12 pg/ml	6.3 pg/ml	[58]
Hodgkin lymphoma	61.5 pg/ml	No detectable	[46]
	>10 pg/ml	7.1 pg/ml	[59]
	>10 pg/ml	ND	[60]
	>10 pg/ml	ND	[61]
	26.79 pg/ml	ND	[62]
Non-Hodgkin lymphoma	>7.98 pg/ml	<5.0 pg/ml	[50]
Lung cancer	>38.16 pg/ml	32.55 pg/ml	[43]
	21.4 pg/ml	9.2 pg/ml	[63]
Multiple myeloma	201.96 pg/ml	ND	[64]
	2.39 ± 0.82 ng/ml	(0.34 ± 0.15 ng/ml)	[65]
B-cell lymphoma	26.0 pg/ml	18.0 pg/ml	[66]
Chronic lymphocytic leukemia	74 pg/ml	<13.68 pg/ml	[67]

Table 1.
Determination of IL-10 levels in serum from cancer patients.

expression was considered as a prognostic factor on nonsmall-cell lung cancer surgical specimens. In addition to an immunohistochemistry study on human lung surgery, a positive correlation between IL-10 and IL-10 receptor expressions was related to the lung tumor diameter. Interestingly, IL-10R was mainly expressed on the surface of Foxp-3þ T-regulatory lymphocytes infiltrating the tumor [74, 75].

4. IL10 polymorphims related to the development and prognosis of cancer

Single nucleotide polymorphisms (SNPs) has been described on IL10 promoter, where adenine was substituted by guanine at −1082 bp (rs1800896). Thymine was replaced by cytosine at −819 bp (rs1800871) and adenine by cytosine at −592 bp (rs1800872). All of those contribute to the variation in protein expression [76]. The IL10 production have a hereditary component estimated in 75%, suggesting that

clinical outcome imparted by IL10 genetic variants may be mediated by effects on the tumor micro-environment composition or modulation [47]. The possibility that SNPs participate in the development, establishment, and the prognosis of cancer has been investigated by numerous research groups and includes several group malignances.

Eastern European patients with breast cancer, IL10 −1082A > G, −819 T > C, −592A > C polymorphisms, and phased haplotypes have not revealed a prognostic value [77]. Nevertheless, another study report 592C > A polymorphisms could modify disease-free and overall survival in women with lymph node-positive breast cancer [78]. In a Chinese Han population study, the −1082AA genotype was associated with a significantly increase risk of lymph node involvement and larger tumor size at the time of diagnosis [79]. After meta-analysis, it showed that IL10 rs1800896 and rs1800871 polymorphisms had no association with breast cancer risk, while rs1800872 polymorphism had a decreased risk of breast cancer in Caucasians [3]. However, another meta-analysis suggests that IL10 rs1800871 and rs1800872 polymorphisms might contribute to breast cancer susceptibility in the overall population, but not by ethnicity [6].

Chinese men, diagnostic with prostate cancer, do not show significant differences in (−1082A/G, −819 T/C, and −592A/C) SNPs between patients and control subjects [80]. Meta-analysis performed with a Caucasian and Asiatic population suggests that there is no association between IL10 gene rs1800896, rs1800871, and rs1800872 polymorphisms and prostate cancer [81]. A study looking for the participation of variant alleles at both −819 and −592 polymorphisms was modestly associated with the advanced stages of prostate cancer [82, 83]. Other meta-analysis reports that rs1800896 polymorphism is associated with a decreased risk of prostate cancer [84].

In a meta-analysis including 26 studies designed to search the risk of skin cancer and IL10 polymorphism, the results show that there is not a significant association of −1082G > A or −592C > A and risk to skin cancer. Nevertheless, it suggested a potential association between −819C > T polymorphism and decreased risk of skin cancer [38]. A meta-analysis carried out for possible association between polymorphism and melanoma did not find an association between skin cancer risk and the −592A/C or IL-10-1082G/A. However, there was a correlation between IL10 −819T/C polymorphisms and skin cancer [85].

Association between IL10 −1082A/G, −592C/A, and −819T/C gene polymorphisms and risk of lung cancer was also investigated by meta-analysis, but until now, there are inconsistent results: on Asian populations, IL10 −1082A/G and −819T/C polymorphisms might have a significant association with the risk of lung cancer [86]. Another meta-analysis suggests that the polymorphism associated with a risk factor for lung cancer was IL10 −592A > C polymorphism, especially among Asians and Caucasians. In contrast, the IL10 −819 T > C and −1082A > G polymorphisms are not significantly associated with an increased risk of lung cancer [87].

Cervical cancer associated with a polymorphism at this time is not conclusive: −1082 polymorphism was suggested as a marker of genetic susceptibility to cervical cancer among Japanese women but was not significantly increased in Zimbabwean women or Korean women [88]. In a meta-analysis, including 17 publications of Asian, African, and Caucasian populations, it did not find a significant association between the polymorphism and cervical cancer risk [89]. Other meta-analysis looking for association between −1082 G/A polymorphism and cervical cancer risk, including the same population, report as well that there is no association [90].

Association between rs1800896 polymorphism and head and neck cancer risk and its clinical stages in Caucasian and Asiatic evaluated by meta-analysis gave a significant association with head and neck cancer risk but not with the clinical

Disease	Population	Polymorphism	Association	Reference
Breast cancer	Eastern European	IL10 −1082A/G, IL10 −592A, IL10 −819C	No prognostic value	[77]
	Eastern European	IL10 −592C > A	Associated with survival	[78]
	Chinese Han	IL10 −1082AA	Associated with cancer risk	[79]
	Chinese Han	rs1800896, rs1800871	No associated with cancer risk	[3]
	Caucasian	rs1800872	Associated with cancer risk	[3]
Prostate	Chinese men study	IL10 −1082A/G, IL10 −592A/C, IL10 −819 T/C	No associated with cancer risk	[80]
	Caucasian, African-Americans, and Asiatic	rs1800896	Associated with reduced cancer risk	[84]
	Caucasian and Asiatic	rs1800896, rs1800871, rs1800872	No association with risk cancer	[81]
	Caucasian, African-Americans, and Asiatic	IL10-1082 A4G, IL10-819 C4, IL10-592 C4A	No association with cancer risk	[82]
	Caucasian and Asiatic	IL10--592A > C	No association with cancer risk	[83]
Skin cancer	Caucasian, African-Americans, and Asiatic	IL10 −1082A/G, IL10-592A, IL10-819C	No associated with cancer skin risk	[82]
	Caucasian, African-Americans, and Asiatic	IL10 −592A/C, IL10 −1082G/A	No associated with cancer risk	[85]
Lung cancer	Asiatic	IL10 −1082A/G, IL10-592A, IL10-819C	Associated with cancer risk	[86]
	Caucasian	IL10 −1082A/G, IL10-592A, IL10-819C	No association with cancer risk	[86]
	Caucasian	IL10 −592A > C	Associated with cancer risk	[87]
	Caucasian and Asiatic	IL10 −819 T > C, IL10 −1082A > G	No associated with cancer risk	[87]
Cervix cancer	Japanese women	IL10 −1081	Associated with cancer risk	[88]
	Zimbabwean women and Korean women	IL10 −1082	No associated with risk	[88]
	Caucasian, African-Americans, and Asiatic	IL10 −1082A > G	No associated with risk	[89]
	Caucasian, African-Americans, and Asiatic	IL10 −1082 G/A	No associated with cancer risk	[90]
Head and neck cancer	Caucasian and Asiatic	rs1800896	Associated with cancer risk	[91]
	Caucasian, and Asiatic	IL10 −1082A > G, IL10 −819 T > C	Associated with cancer risk	[92]

Disease	Population	Polymorphism	Association	Reference
Gastric cancer	Mexican population	IL10 −819	Associated with risk	[93]
	Mexican population	IL10 −592C/A, IL10 −1082A/G	No associated with risk	[93]
Oral mucosa cancer	Indian population	IL10-592 A/C	Associated with cancer risk	[94]
Colorectal cancer	Caucasian and Asiatic	IL10819T > C	Associated with cancer risk	[95]
	Caucasian and Asiatic	rs1800871 rs1800872	No associated with cancer risk	[95]
	Caucasian and Asiatic	IL10 −1082A > G, IL10 −592C > A	No associated with cancer risk	[95]
Pediatric Hodgkin's disease	Caucasian	IL10-592AA	Pronostic marker	[96]
	Brazilian	IL10 −1082GG	Unfavorable prognosis	[47]
Acute myeloid leukemia	Egyptian	IL10-819	Associated with risk	[97]
	Chinese Han	IL-10-819, −592	Associated with risk	[98]
	Sudanese	IL10 −1082G/A	Associated with risk	[7]

Table 2.
Relationship of IL10 polymorphism and cancer risk.

stages [91]. Other analysis reports significant associations between the IL10 −1082A > G and IL10 −819 T > C polymorphism and increased risks of head and neck cancer similar population [92].

Other studies on the relation between risk or prognosis polymorphisms in cancer have been performed. In there, a possible association with gastric cancer showed a significant association with IL10-819 on the Mexican population. Nevertheless, no significant association was found for IL10 −592C/A (rs1800872) and IL10 −1082A/G (rs1800896) [93]. Looking for a possible predispose to oral squamous cell carcinoma (−592), A/C polymorphism was significantly associated with reduced risk [94]. In colorectal cancer IL10 −819 T > C, polymorphism was associated with significantly increased risk [95].

In a clinical study with child Hokdkin disease, −1082GG genotype was associated with lower IL10 mRNA expression. Nevertheless, genotypes of the −592 SNP showed no association with IL10 mRNA expression. However, −1082AACAG genotypes, ATA haplotype, and the presence of the −592AA genotype were associated with unfavorable prognosis [47, 96].

Genotypic variants of IL10 (−1082G/A) polymorphism in adult Sudanese patients with acute myeloid leukemia were investigated as a possible risk factor. In there, no association between IL10 (−1082G/A) and acute myeloid leukemia was detected [7]. Nevertheless, in the Egyptian population, −819 polymorphism was associated with enhanced risk [97]. In the Chinese population, the −819A allele frequencies in the AML group were higher than in the controls [98]. In pediatric patients, Classical Hodgkin lymphoma −1082AA/AG, −592CC genotypes, and ATA haplotype were associated with unfavorable prognosis; interestingly, −1082 was associated with low IL10 mRNA expression [46].

Unfortunately, to date, the results are controversial; the relationship of polymorphism with the presence of cancer and/or the possible risk of developing cancer is shown in **Table 2**.

5. Conclusions

High concentrations of IL-10 in the serum of cancer patients seem to correspond not only to the expression of this protein by immune cells. The evidence shows that the cancer cell is capable of synthesizing it, which would cause an imbalance in the homeostasis of the immune system.

Besides, the presence of polymorphisms suggested the possibility that some of them could be involved in the regulation of the activity of IL10; this gave rise to numerous studies seeking opportunities to explore for cancer risks or implications in the development, establishment, and survival of the cancer cell. The relationship between polymorphisms and the risk and prevalence of different types of cancer had evaluated by meta-analysis. Unfortunately, until now, the results are not conclusive.

Nevertheless, the fact is that IL-10 can exert the antitumor effect by mechanisms such as the activation of natural killer cells (NK), lymphocytes T, macrophages, and nitric oxide; its high concentration shows the deregulation of the immune system, where a high level of IL10 allows the tumor to escape. Nevertheless, the fact that IL-10 can exert the antitumor effect by mechanisms such as the activation of natural killer cells, lymphocytes T, macrophages, and nitric oxide results controversial. Its high concentration induces the deregulation of the immune system, where a high level of IL-10 allows the tumor escape. In some cases, it could be propose as a biomarker for patient lifespan or chemotherapy respond.

Because of this, it is essential to study not only the mechanisms that allow this high expression of interleukin IL-10, but its effect on tumor cells and also. It is important to consider its relationship with other cytokines.

Conflict of interest

The authors declare that they have no competing interests.

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