Review

A balance of interleukin-12 and -23 in cancer

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Interleukin (IL)-12 and IL-23 share the IL-12p40 molecule. IL-12 promotes T helper (Th)1 immunity and IL-23 promotes Th17 immunity, and it has recently become apparent that the balance between IL-12 and IL-23 is important in carcinogenesis. A series of studies demonstrated that, where tumor initiation, growth, and metastasis are concerned, IL-12 may act independently of interferon (IFN)-γ, and IL-23 independently of IL-17A. This review explores the activity of IL-23 in carcinogenesis. In the context of the tumor-inhibitory effects of IL-12, and tumor-promoting effects of IL-23, we discuss the use of anti-IL-12p/23 monoclonal antibodies (mAbs) in autoimmune inflammatory disorders and the alternative specific neutralization of IL-23.

IL-12 and IL-23

The IL-12 cytokine family is consisting of IL-12, IL-23, IL-27, and IL-35. These are heterodimeric cytokines formed by two subunits [1]. IL-27 is formed by the pairing of the Ebi3 and p28 subunits, whereas IL-35 is formed by the pairing of Ebi3 and p35 subunits. The pairing of p19 subunit with p40 subunit forms IL-23, whereas the pairing of the p35 and p40 subunits forms IL-12 [1–3] (Figure 1). IL-12 receptor (IL-12R) is composed of IL-12Rβ1 and IL-12Rβ2, whereas IL-23 receptor (IL-23R) is composed of IL-12Rβ1 and IL-23R. IL-23R signaling is mediated by tyrosine kinase (Tyk)2 and Janus kinase (Jak)2, with a predominant activation of signal transducer and activator of transcription (STAT)3, and to a minor extent STAT4 (Figure 1). By contrast, the downstream signaling molecule of IL-12Rβ2 is predominantly STAT4. Human IL-23R is predominantly found on activated memory T cells, natural killer (NK) cells, and innate lymphoid cells (ILCs), and at lower levels on monocytes, macrophages, and dendritic cells (DCs). Mouse IL-23R is found on activated T cells, lymphoid tissue inducer (LTi) cells, ILCs, γδ T cells, DCs, and macrophages [3–6]. In this review we summarize the well-recognized role of host IL-12 in preventing cancer initiation, growth, and metastasis. We then discuss more recent evidence describing how IL-12 and IL-23 expression is regulated and the general role of IL-23 in immune reactions. We finish by contrasting the data that support both the tumor-promoting effect of host IL-23 and tumor-suppressing effect of exogenous IL-23. These findings have implications for the clinical translation of monoclonal antibodies (mAbs) targeting IL-12 and IL-23 in autoimmune inflammation and cancer.

IL-12 in tumor immunity

Although there are similarities between IL-12 and IL-23, there is increasing evidence that these cytokines modulate divergent immunological activities. Other than promoting the cytotoxic function of NK cells, IL-12 drives the development of Th1 cells via the activation of STAT4. These cytotoxic IFN-γ-producing Th1 cells are crucial for antimicrobial and antitumor responses [7]. The role of IL-12 and its downstream cytokine IFN-γ in antitumor immunity has been demonstrated [8,9] and extensively reviewed elsewhere [10,11]. In addition to activating antitumor effectors, IL-12 and IFN-γ also inhibit the expansion of intratumoral T regulatory cells (Tregs) and angiogenesis in the tumor microenvironment, thus enhancing tumor control [9]. More recently, engineered antigen-specific $CD8^+$ T cells expressing IL-12 have also been shown to suppress the growth of the poorly immunogenic B16 melanoma by reprogramming immunosuppressive myeloid-derived cells in the tumor microenvironment, in an IFN-γ-dependent manner. Strikingly, the antitumor response elicited by these IL-12-expressing $CD8^+$ T cells did not require the presence of host T cells and NK cells [12]. Another study using IL-12-producing B16 melanomas showed that $NKp46^+$ LTi cells induced tumor suppression independently of T and NK cells [13]. Clearly, the mechanism of IL-12-mediated tumor suppression is context dependent. Consistent with the role of IL-12 in activating multiple arms in antitumor immunity, IL-12/23p40-deficient mice and IFN-γ-deficient mice challenged with methylcholanthrene (MCA) have an increased rate and frequency of tumor growth compared to the wild type controls, suggesting a role of endogenous IL-12 and IFN-γ in protecting the host from the emergence of chemical carcinogen-induced, and perhaps spontaneous tumors [14,15].

Although the IL-12/IFN-γ axis is important in Th1 immunity, IL-12 can also have direct effects on immune

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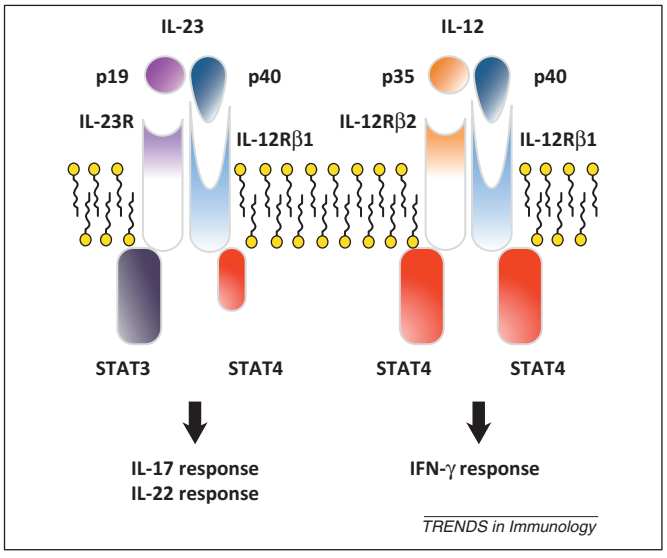

Figure 1. Interleukin (IL)-23 and IL-12. Composition of the IL-23 and IL-12 cytokines, presented together with their corresponding receptors and signal transducer and activator of transcription (STAT) signaling molecules. Abbreviation: IFN, interferon.

cells independent of IFN-γ induction [16–19]. Similarly, IL-12p35-deficient mice have also been shown to have an increased tumor growth in a mouse model of papilloma. Notably, IL-12/23p40-deficient mice were resistant to the carcinogen-induced papilloma formation, and the tumor-promoting role of IL-23 was illustrated [20]. Mice genetically deficient in IL-12/23p40 show no increased risk of developing tumors through their lifetime relative to normal mice [21], whereas a high incidence of lymphoid malignancy is described in mice genetically deficient only in the IL-12 pathway, due to ablation of the gene coding for the IL-12Rβ2 subunit of the IL-12 receptor [22].

IL-23 in immune responses

By contrast, IL-23 is crucial for the development of Th17 cells, a distinct lineage of $CD4^+$ T cells, characterized by their production of signature cytokines IL-17A, IL-17F, and occasionally IL-21 and IL-22 [23,24]. Endogenous Th17 cells mediate antimicrobial and antifungal responses, or in a pathogenic form, promote autoimmune diseases [23]. IL-23-driven IL-17-producing cells (Th17 cells and IL-17-producing innate cells) are generally essential for an antimicrobial response [3–5,25]. IL-23 is crucial for the function and cytokine production of Th17 cells *in vivo* [26,27]. In addition to Th17 cells, IL-23 also regulates the function of innate lymphocytes (NK cells, NKT cells, and γδ T cells) and ILCs [4]. Notably, these IL-23-regulated cells are also IL-17- and/or IL-22-producing cells. Although it remains unknown whether IL-23 affects the development of innate IL-17- and/or IL-22-producing cells *in vivo*, independent studies have demonstrated that IL-23 induces these cells to secrete IL-17 and/or IL-22 [4,28–31]. By using an IL-23R–GFP reporter mouse model, it has also been revealed that the IL-23R-expressing cells are predominantly enriched in the lamina propria (LP), in comparison to secondary lymphoid organs in naïve mice [6]. Collectively, the ready presence of IL-23R-expressing cells (mainly on innate cells) in the LP and mucosal interface, and the pathogen-associated signals that induce IL-23 secretion, demonstrate a role for IL-23 in host defense against pathogens [3,4,29].

Regulation of IL-12 and IL-23 production

DCs and macrophages are thought to be the main producers of IL-12 and IL-23 in response to Toll-like receptor (TLR) stimulation by pathogen and viral components and/or via CD40–CD40 ligand (CD40L) signaling [2,3,32–34]. What are the factors that induce DCs or macrophages to produce the appropriate cytokines to drive an inflammatory response? It is unlikely that there is a distinct population of naïve DCs or macrophages that are programmed to secrete either IL-12 or IL-23 upon infection or inflammation. It is more likely that IL-12 or IL-23 production and the levels and ratio that are secreted are regulated by microenvironmental signals. However, in most cases, DCs activated by TLR agonists or β-glucan, a widely expressed fungus-associated molecule, produce p40, p19, and p35 molecules, suggesting co-secretion of IL-12 and IL-23 [35–38]. A combination of nucleotide-binding oligodimerization domain (NOD) ligands or β-glucan, together with TLR2 agonists, preferentially induces IL-23 production by DCs *in vitro* [35]. Similarly, TLR8 and NOD signaling preferentially induce IL-1β and IL-23 secretion in DCs [37]. Furthermore, CD40 signaling can only trigger IL-23 secretion in colon-derived, but not the spleen-derived myeloid cells [33]. Thus, the secretion of IL-12 and IL-23 in an inflammatory environment may be also dictated by the presence of pre-primed antigen-presenting cells (APCs) *in vivo*. It was recently demonstrated that IFN-γ negatively regulated the secretion of IL-23 from lipopolysaccharide (LPS)-induced bone-marrow-derived macrophages [39]. Conversely, in the same year, it was also shown that IL-23 suppressed IL-12-dependent IFN-γ secretion in T cells [40]. Therefore, both IL-12 and IL-23 are also likely to regulate reciprocally and temporospatially each other in an inflammatory context.

IL-23 production in a tumor context

What about stimuli for IL-23 in a tumor context? Recently, in an inflammation- and mutated *Apc* (adenomatous polyposis coli)-driven colorectal cancer model, it was found that gut microbial products induced IL-23 secretion from a population of $CD11b^+$ myeloid cells, whereas IL-23 was also secreted by a population of $CD11b^-$ immune cells in the tumor microenvironment. Although the identity of these IL-23-producing $CD11b^-$ immune cells has not been fully defined, IL-23 signaling induced a protumor IL-17 response in the tumor microenvironment [41]. Thus, for a tumor site that is in close contact with microbes, the presence of microbial products might serve as an inducer of IL-23 production. Conversely, in tumor sites with a sterile inflammatory response, there may be some yet-to-be-defined endogenous TLR agonists, danger signals, or tumor-derived mediators in the tumor microenvironment that drive IL-23 production in tumor-associated macrophages or DCs.

IL-23 is a STAT3-regulated gene, as well as a STAT3 activator. Of note, persistent activation of STAT3 in a tumor cell can be transmitted to its surroundings, thus initiating a protumor activity cascade [42]. Tumor-derived

inflammatory mediators such as IL-6, ATP, prostaglandin (PG)E_2, and heat shock proteins (HSPs) are actively released into the tumor microenvironment in response to cellular stress or cell death [42,43], and may prime DCs for IL-23 production [36,44,45]. Interestingly, PGE_2 has also been shown to downregulate IL-12 production in LPS-stimulated monocytes [46]. ATP activates P2X purinoreceptor 7 (P2RX7) receptor on DCs, leading to the activation of NLRP3 (NLR family, pyrin domain-containing 3) inflammasome and the secretion of IL-1β [47]. It is thus likely that IL-23, IL-6, together with the NLRP3-depndent IL-1β secretion by DCs or macrophages may drive the formation of Th17 cells, instead of an antitumor Th1 response. In this light, an assessment of danger-signal-induced NLRP3 activation and IL-23 in tumor immunity is worthy of further investigation.

Tumor-initiating properties of IL-23

The role of IL-23 in promoting tumorigenesis (Table 1) was first demonstrated in experiments using IL-23p19-deficient mice that were found to be almost completely resistant to 7,12-dimethylbenz(a)anthracene (DMBA)/12-*O*-tetradecanoyl-phorbol acetate (TPA)-induced skin papillomas [20]. This study reported a significant increase in $CD8^+$ T cells infiltrating the DMBA/TPA-treated skin of IL-23p19-deficient mice compared to wild type control mice. This was also accompanied by a reduction in IL-17, matrix metallopeptidase (MMP)9, and CD31 expression, and a decrease in granulocytes ($Gr\text{-}1^+$) and macrophages ($CD11b^+$, $F4/80^+$). Furthermore, tumor growth in mice lacking IL-23 or IL-23R was also attenuated compared to the wild type controls [20]. These data suggest that IL-23 inhibits the immune surveillance activity mediated by cytotoxic T cells by potentially preventing their ability to infiltrate into the tumor. Subsequently, another study also confirmed that IL-23p19-deficient mice were resistant to DMBA/TPA-induced skin papillomas, and also to MCA-induced fibrosarcomas [48]. Importantly, this study also uncovered a role for IL-23 in suppressing the antitumor and antimetastatic functions of NK cells [48]. Notably, a number of experiments in this study illustrated no impact of loss of host IL-17A, clearly distinguishing the protumor effect of IL-23 from IL-17A. This does not rule out the potential role of Th17 cells in the protumor activity of IL-23, given that in some models, blockade of IL-17A or IL-23R produces a similar carcinogenesis phenotype [49]. Indeed, more recently the role of IL-23 in driving protumor inflammation was confirmed in a mouse model of *Apc*-driven colorectal cancer [41], in which a defective colonic epithelial barrier, microbes, and/or microbial products drove IL-23/IL-17-mediated protumorigenic inflammation. Strikingly, elimination of commensal microbes by antibiotic treatment reduced the tumor load in wild type, but not in the IL-23R-deficient colorectal cancer-prone mice. In addition to its role in driving inflammation, one study also reported that IL-23 signaling promoted the production of the immunosuppressive cytokine, IL-10, from intratumoral Tregs [50]. Collectively, this suggests that IL-23 promotes tumorigenesis by driving protumor inflammation to suppress antitumor effector cells.

In addition to IL-17A, IL-23 has been reported to regulate other Th17 cytokines, including other IL-17 isoforms and IL-22 [51,52]. Recently, IL-22 was reported to display both protumor and antitumor functions in the dextran sodium sulfate (DSS) colitis mouse colon cancer model [53]. In the early phase of colitis, it was suggested that IL-22 plays an antitumor role by aiding in colonic repair and resolution of inflammation. By contrast, increased levels of IL-22 during the recovery phase of colitis may prolong epithelial proliferation, thereby promoting the development of intestinal tumors. This observation that IL-22 was tumor suppressing in certain contexts was further supported in the APC^{min} model of spontaneous tumorigenesis, where a genetic mutation and not inflammation induces tumor development in the colon. In this model, APC^{min} mice lacking IL-22 displayed significantly reduced tumor numbers and size compared to wild type mice [53]. By contrast, it was reported in a human study that excessive IL-22 in the colon cancer and ulcerative colitis microenvironment led to tumor growth, inhibition of apoptosis, and promotion of metastasis, which was dependent upon STAT3 activation [54]. Hence the role of IL-22 in tumorigenesis is potentially complex and will require further investigation.

Table 1. Endogenous IL-23 promotes tumor growth.

IL-23 in promoting tumor	
Tumor model	**Study model**
De novo DMBA/TPA-induced skin papillomas	IL-23p19-deficient mice [20,48]
De novo MCA-induced fibrosarcomas	IL-23p19-deficient mice, anti-IL-23p19 mAb [48,57,95]
De novo Min colon carcinoma	Anti-IL-23R mAb [49]
De novo CPC-APC colorectal cancer	IL-23R-deficient mice [41]
PDV squamous cell carcinoma	IL-23R-deficient mice, anti-IL-23p19 mAb [20]
B16F10 melanoma	IL-23R-deficient mice, IL-23p19-deficient mice, anti-IL-23p19 mAb [20,48,95]
B16 melanoma	Anti-IL-23R mAb [50]
LL/2 lung carcinoma	IL-23R-deficient mice [20]
EP2 mammary carcinoma	Anti-IL-23p19 mAb [20]
EG7 lymphoma	IL-23p19-deficient mice, anti-IL-23p19 mAb [95]
EO771 mammary carcinoma	Anti-IL-23p19 mAb [95]
4T1.2 mammary carcinoma	Anti-IL-23p19 mAb [95]
H2N100 mammary carcinoma	Anti-IL-23p19 mAb [95]
3LL lung carcinoma	IL-23p19-deficient mice [48]
RM1 prostate carcinoma	IL-23p19-deficient mice [48]

The cancer immune interaction (cancer immunoediting) is also complex and involves three main phases [55]. The second and longest of these phases involves T cell-mediated tumor dormancy (equilibrium phase) best characterized in the MCA-induced fibrosarcoma model [56]. It was recently shown that depletion of IL-23 in mice bearing dormant tumors induced by MCA resulted in the elimination of the residual tumor cells, whereas neutralization of IL-12p40 allowed their outgrowth [57]. Surprisingly, in contrast to the aforementioned studies, chronically UVB-exposed IL-23p19-deficient mice were more likely to develop tumors, particularly nonepithelial sarcomas, compared to the wild type controls [58]. These data are in agreement with a previously demonstrated role for IL-23 in reducing UV-induced DNA damage and inhibiting UV-induced Tregs in an acute UV-induced immunosuppression model [59]. More studies comparing IL-12p35, IL-23p19, and IL-12p40 deficiency in cancer-prone mice are warranted to distinguish their roles in tumorigenesis.

The role of IL-23 in established tumors might be comparatively modest compared to that in tumor initiation, but nonetheless is relevant. In established lung metastases, the demonstration of enhanced IL-2 immunotherapy in IL-23p19-deficient mice suggests the potential use of anti-IL-23p19 mAb in combination with immunotherapies that can activate NK cells [48]. Indeed, administration of anti-IL-23p19 mAb in combination with NK cell-targeted immunotherapies, such as IL-2, or anti-erbB2 mAb, shows enhanced antitumor effects above either therapy alone [48].

In agreement with the role of endogenous IL-23 in promoting tumor growth gleaned from mouse models of cancer, independent clinical studies have reported that serum concentrations of IL-23 are increased in cancer patients in comparison with healthy individuals [60–63]. Notably, increased serum IL-23 is correlated with the disease stages of pancreatic cancer [63], and high serum IL-23 in breast cancer patients is associated with a poorer survival outcome [61]. In addition, it has been reported that patients with increased expression of IL-23 in their primary hepatocellular carcinoma (HCC) microenvironment have a higher potential to develop metastasis. IL-23 has been reported to enhance tumor cell motility and upregulate tumor cell MMP9 levels by activating the nuclear factor (NF)-κB/p65 pathway. Furthermore, the expression of IL-23 positively correlates with the expression of MMP9 and IL-17A in primary HCC [60]. Similarly, IL-23 promotes the proliferative capacity of IL-23R$^+$ primary human oral squamous cell carcinoma (SSC) cell lines, by activating the NF-κB/p65 pathway. Of note, tumor cell-derived IL-23 is secreted in an autocrine manner [64,65]. The pro-proliferative property of IL-23 has also recently been confirmed in human non-small cell lung cancer (NSCLC) cell lines [66]. Using genome-wide association studies, two potentially functional common variants of *IL-23R*, rs6682925 (T>C) located at 907 bp upstream from the transcriptional start position, and rs1884444 (T>G) located at codon 3 with amino acid His substituted by Gln in exon 2, have been shown to be associated with the risk of several solid cancers [67–69]. These same IL-23R polymorphisms have been found to predispose individuals to an increased risk of acute myeloid leukemia (AML) [70].

Tumor-suppressing properties of IL-23

In contrast to the role of endogenous IL-23 in promoting tumorigenesis, there have been some studies suggesting that IL-23 can potentially promote an antitumor effect (Table 2). For example, independent studies have demonstrated that mouse tumor cell lines engineered to overexpress IL-23 have impaired tumor growth *in vivo* [71–73]. Others have reported that the administration of high-dose IL-23, IL-23-expressing adenovirus, or IL-23-expressing DCs or bone-marrow-derived neural-like stem cells exhibit an antitumor effect on established tumors [74–77]. Collectively, these findings underscore the potential of IL-23-based therapy to inhibit tumor growth. By contrast, in some studies the administration of IL-23 could only significantly enhance the antitumor response in combination with peptide vaccination and/or adoptively transferred antigen-specific T cells [78,79]. As all of the presented studies did not assess the expression of IL-23R in the tumor cells, the role of IL-23 in directly modulating tumor biology remains unclear. Of note, in some of these studies, the antitumor effect of IL-23 was only exerted in the presence of host IL-12 and/or IFN-γ [73–75], rather than classical Th17 cytokines. It has been demonstrated that a high dose of IL-23 suppresses proliferation and also induces apoptosis in primary B-acute lymphoblastic leukemia (B-ALL) cell lines, through the upregulation of miR15a and the consequent downregulation of B cell lymphoma (Bcl)-2; an apoptosis regulator protein [80]. In addition, the administration of IL-23 has been shown to suppress the growth of xenotransplanted B cell lymphomas *in vivo* [80,81]. Thus far, only one study has reported that a higher level of intratumoral IL-23p19 transcript is

Table 2. Exogenous IL-23 suppresses tumor growth.

IL-23 in suppressing tumor	
Tumor model	**Study model**
Colon 26 colon carcinoma	Engineered IL-23-expressing cancer cell line [71,96,97]
MM45T.Li HCC	Engineered IL-23-expressing cancer cell line [72]
MA-891 mammary carcinoma	Engineered IL-23 expressing cancer cell line [98]
B16F10 melanoma	Engineered IL-23 expressing cancer cell line [73]
B16F1 melanoma	Engineered IL-23 expressing cancer cell line [99]
CT26 colon carcinoma	Engineered IL-23 expressing cancer cell line [99]
MCA205 fibrosarcoma	Systemic administration of high dose IL-23, administration of IL-23-expressing adenovirus [74,75]
GL26 glioma	Engineered IL-23-expressing DCs, engineered IL-23-expressing bone-marrow-derived neural stem-like cells [44,77]

associated with improved patient overall survival, in the context of ovarian cancer [82].

At first glance, this evidence may seem contradictory to the role of endogenous IL-23 in promoting tumorigenesis (Tables 1 and 2) [83]. However, the caveat is that these experiments utilized IL-23 in a nonphysiological manner and thus do not necessarily reflect the natural role of endogenous host IL-23 in modulating tumorigenesis. In addition to the differences between tumor models being tested, these contradictory findings may be partly explained by a recent study using human IL-23R^{+} lung cancer cell lines. This study reported that low doses of IL-23 promoted proliferation, whereas higher doses induced an antiproliferative effect [84]. In this regard, interpretation of studies that demonstrate that IL-23 inhibits tumorigenesis need to be carefully evaluated. Clearly, the amount of IL-23 expressed by a tumor cell may determine whether IL-23 has pro- or antitumor properties. A functional IL-23 receptor is consisting of IL-12Rβ1 and IL-23R. Although the downstream signaling molecule of IL-23R is STAT3, the downstream signaling molecule of IL-12Rβ1 is STAT4, a crucial transcription factor that drives Th1 response (Figure 1). In this light, ability of IL-12Rβ1 and STAT4 to mediate the antitumor activity of high doses of IL-23 (via engineered IL-23-expressing tumor cells, injection of IL-23-expressing adenovirus, transplantation of IL-23-expressing DCs, or systemic administration of IL-23) is worthy of further investigation.

Clinical observations concerning IL-12 and IL-23

Clinical observations have established that IL-12/23p40 is integral to the pathologies of psoriasis, psoriatic arthritis, and Crohn's disease (Figure 2). Ustekinumab (anti-IL-12/IL-23) is the first market-approved member of a new biological therapy family targeting IL-12 and IL-23 [85]. The molecular and cellular evaluations conducted for ustekinumab clinical programs provide insight into the pathology of these disorders, illustrating how a novel molecular entity can contribute to our understanding of disease. The emerging safety profile of ustekinumab remained favorable and did not suggest increased rates of infection or malignancy after 5 years of follow-up in 753 patients [86,87]. By contrast, psoriasis patients that received another anti-IL-12/IL-23 mAb, briakinumab, were reported to have increased frequency of serious adverse events such as serious infections, and cancer, although not statistically significant due to patient numbers [88,89]. However, given the potential latency of cancer and the importance of dosing, one cannot conclude yet about the impact of anti-IL-12/23 mAbs on cancer development. Notably, a recent study pooled the safety data of 2520 patients that received briakinumab from five phase II and III clinical trials and an open label extension trial [90]. It suggested an increased risk of any malignancies (2.6%), particularly in non-melanoma skin cancer (NMSC) (1.7%). Of significance was the observation that anti-IL-12/23 mAb therapy may increase risk of SCC. This difference in safety profile observed between ustekinumab and briakinumab may lie in its administered dose. Patients on briakinumab were generally dosed at 200 mg, whereas those on ustekinumab received 45–90 mg [87,90]. Furthermore, the clinical development of briakinumab has been discontinued [88,90–92]. Indeed, patients with psoriasis are recognized to carry a higher risk of cutaneous malignancy than the general population. This is felt to be largely secondary to the effects of immunosuppressive therapy and phototherapy used in the control of the disease. Cyclosporin, a conventional systemic treatment for psoriasis, has been shown to increase significantly the risk of cutaneous and other malignancies [93]. In addition, psoralen plus UV-A (PUVA) therapy has been clearly associated with photodamage and a persistent increased

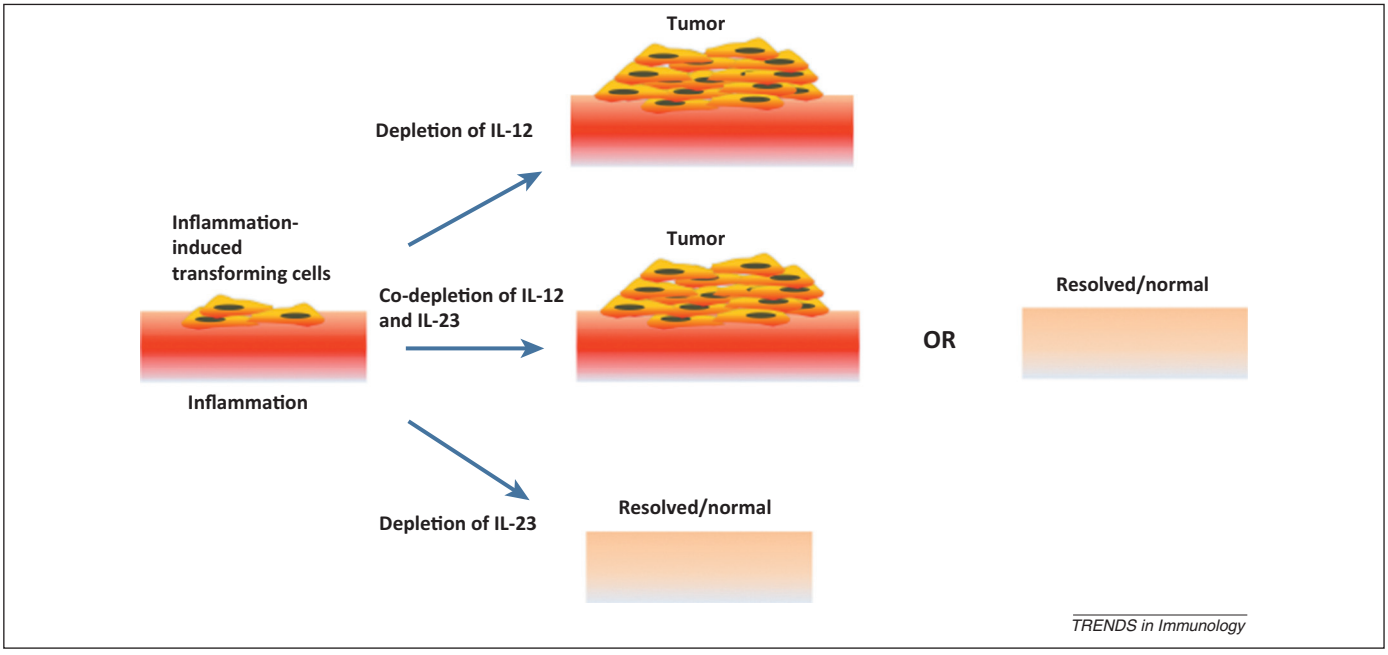

Figure 2. Inflammation and tumor immunity. A co-depletion of interleukin (IL)-23 and IL-12 may result in resolution of inflammation or expansion of inflammation-induced transformed cells. An absence of IL-12 compromises the antitumor T helper (Th)1 response, risking tumor formation in the host. By contrast, an intact antitumor Th1 response in an IL-23-depleted host suppresses potential tumor formation.

risk of cutaneous malignancy, particularly in patients subsequently exposed to cyclosporin [93]. An increased risk of NMSC also exists, at least theoretically, with narrow-band UV-B therapy (NBUVB) [93]. Interestingly, two patients who were previously treated with PUVA and NBUVB were reported to develop eruptive cutaneous SCC soon after commencement of ustekinumab [92]. In light of these studies, it will be important to monitor patients that receive anti-IL-12/23 mAb, for the development of malignancies such as NMSC, particularly on long-term treatment (Figure 2).

Concluding remarks

It should be appreciated that interpretation of mouse studies are complicated by the potential differences between mouse and human IL-12 and IL-23 biology. For example, pharmacological dosing of recombinant IL-12 has demonstrated efficacy in mouse tumor models, but has not translated to safe or efficacious therapy in humans. Also, recent findings suggest that Th cells are regulated differently in mice than in humans [94]. Given the species differences in IL-12 and IL-23 biology, it is difficult to interpret the relevance of mouse studies to humans. In addition, these models are not established as predictive for assessing human malignancy or infection risk. As outlined above, the mechanisms of IL-23 in modulating tumorigenesis and tumor immunity remain elusive, and the data supporting it are still confusing. However, from a clinical perspective, therapies targeting this inflammatory pathway may be beneficial to the host, in provoking antitumor immunity, and reducing autoimmunity. It is of great importance for us to assess extensively the potential side effects of such therapies.

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