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Role of IL-17 and IL-22 in autoimmunity and cancer

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KEYWORDS

IL-22;
Autoimmunity;
Cancer

PALABRAS CLAVE

IL-22;
Autoinmunidad;
Cáncer

Abstract The dysregulation of inflammatory cytokines can cause a variety of diseases, such as autoimmunity and cancer. Since their identification in 2005, Th17 cells and its signature cytokine IL-17, have been implicated in the pathogenesis of autoimmune diseases such as psoriasis and rheumatoid arthritis (RA), and inflammatory associated cancers such as colorectal carcinoma (CRC). Recently, IL-22 a Th17 related cytokine has been shown to be pathogenic in psoriasis and RA. In this review, we will summarize the biological functions of IL-17 and IL-22, their role in autoimmune diseases and briefly review results from clinical trials targeting IL-17 or its receptor for the treatment of autoimmune diseases. Next, we will discuss pre-clinical and clinical data supporting the rationale of targeting other cytokines implicated in the Th17/IL-17 pathway, such as IL-22 and IL-23. Finally, we discuss the role of IL-17, and in particular IL-22 in tumour immunity and possible therapeutic interventions.

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Papel de la IL-17 e IL-22 en autoinmunidad y cáncer

Resumen El desequilibrio de las citocinas inflamatorias puede causar una serie de enfermedades como son la autoinmunidad y el cáncer. Desde su tipificación en el año 2005, las células Th17 y su distintiva citocina IL-17 han estado implicadas en la patogénesis de enfermedades autoinmunes, como son la psoriasis y la artritis reumatoide (AR), e inflamatorias asociadas al cáncer, como es el carcinoma colorectal (CCR). Recientemente, se ha demostrado que la IL-22, citocina relacionada con Th17, es patogénica en la psoriasis y la AR. En esta revisión resumiremos las funciones biológicas de la IL-17 y la IL-22, su papel en las enfermedades autoinmunes y revisaremos brevemente los resultados de estudios clínicos enfocados en la IL-17 o su receptor para el tratamiento de enfermedades autoinmunes. Al mismo tiempo, analizaremos los datos preclínicos y clínicos que apoyan la razón de enfocar otras citocinas implicadas en la vía Th17/IL-17, como son la IL-22 y la IL-23. Finalmente, analizaremos el papel de la IL-17, y en particular de la IL-22, en la inmunidad tumoral y las posibles intervenciones terapéuticas.

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Introduction

The dysregulation of inflammatory cytokines can cause a variety of diseases, such as autoimmunity and cancer. In particular, Th17 cells and its signature cytokine IL-17 have been implicated in the pathogenesis of autoimmune diseases such as psoriasis and rheumatoid arthritis (RA), as well as a number of inflammatory associated cancers such as colorectal carcinoma (CRC). More recently, IL-22, another Th17 related cytokine has also been shown to be pathogenic in psoriasis and RA. In this review, we will a) summarize the biological function of IL-17 and IL-22 and their role in autoimmune diseases; b) briefly review the current data (including safety) of blocking IL-17 for the treatment of autoimmune diseases such as psoriasis; c) discuss pre-clinical and clinical data supporting the rationale of targeting other cytokines such IL-22 and IL-23 that are implicated in the Th17/IL-17 pathway, and d) discuss the role of IL-17, and in particularly IL-22 in tumour immunity and possible therapeutic interventions.

IL-17 and IL-22 - inflammatory cytokines with critical roles in mucosal immunity

IL-17 and IL-22 are two cytokines that have critical roles in the regulation of immune responses at mucosal surfaces.^{1,2} IL-17 (also known as IL-17A) has a number of different isoforms (IL-17A-IL-17F) and is the most commonly studied.³ IL-17 is secreted by a distinct subset of CD4⁺ T-cells defined as Th17 cells. The key cytokines required for Th17 differentiation from naive CD4 T-cells are IL-1, IL-6 and TGF- β , although the relative contributions of TGF- β and the proinflammatory cytokines, especially IL-1 β , to Th17 cell development appear to differ between mouse and human.^{4,5} While Th17 cells are a major source of IL-17, secretion is not limited to this subset with $\gamma\delta$ -T-cells,⁶ innate lymphoid cells⁷ and CD8⁺ Tc17 cells⁸ also able to produce IL-17 in response to stimulation. The receptor for IL-17 (IL-17R) is widely expressed on cells of both hematopoietic and non-hematopoietic lineages.⁹ IL-17 acts as an early mediator of the immune response at mucosal surfaces by inducing the infiltration, activation and survival of neutrophils as well as the induction of other innate responses including chemokine expression, G-CSF and IL-22 production.³

IL-22 is a member of the IL-10 cytokine family and is secreted by a wide variety of innate and adaptive immune cells including CD4⁺ T cells (Th1, Th17), CD8⁺ T cells, $\gamma\delta$ -T-cells, natural killer T (NKT) cells, and innate lymphoid cells (ILCs).^{10,11} Additionally, a new subset of CD4⁺ T-cell termed Th22 that produces IL-22 but minimal IL-17 has also been described as a major source of IL-22 in humans.¹² In mice, these IL-22 only producing cells have not been defined as a separate subset, although they can be found *in vivo* and were demonstrated to be important in host protection against enteropathogenic bacteria.^{11,13} The IL-22 receptor is heterodimeric, composed of IL-22R1 and IL-10R2.¹ While the IL-10R2 subunit is ubiquitously expressed, IL-22R1 expression is specifically restricted to non-hematopoietic cells. These include intestinal and respiratory epithelia cells, keratinocytes, hepatocytes as well as tissue cells

in the pancreas and kidneys and thymic epithelial cells and specific tissue resident stem cells.¹⁴ IL-22 can act directly on these cells as outlined in Figure 1, altering the expression of genes involved in; innate immune defences to bacteria including β -defensins 1 and 2, S100A7, S100A9, S100A10, S100A13, enhancing inflammation by promoting CXCL1, CXCL5, CXCL9 chemokine expression, and release of cytokines TNF, IL-6 and G-CSF; upregulating expression of genes involved in tissue remodelling such as MMP1 and 3, and MUC1, MUC3, MUC10, promoting cell proliferation through signalling through the *Stat3* pathway and increasing cell survival through the upregulation of anti-apoptotic genes such as BCL- χ L and BCL-2 (reviewed in references 10 and 14). IL-22 can also stimulate the production of IL-20 in keratinocytes, a cytokine with similar functions to IL-22 that also binds to the IL-22 receptor and can enhance and prolong the local effects of IL-22.¹⁵ In pancreatic cells and hepatocytes, IL-22-IL-22R signalling contributes to tissue regeneration and promotes wound healing by enhancing cell proliferation and survival to reduce the impact of cellular damage.^{16,17}

Both IL-17 and IL-22 have critical roles in coordinating both innate and adaptive microbial and fungal immune responses, with the absence of either cytokine rendering mice highly susceptible to fungal¹⁸ and bacterial infection.^{19,20} Humans lacking functional IL-17R²¹ or with altered development of Th17 cells due to a mutation in *STAT3*²² are highly likely to develop chronic *Candida albicans* and *Staphylococcus aureus* infections. IL-23, a cytokine of the IL-12 family, is produced by activated dendritic cells and macrophages and is important in the activation of Th17, $\gamma\delta$ -T-cells and ILCs, leading to induction of immune responses and IL-17 and IL-22 secretion. IL-23 secretion is induced through recognition of bacterial products by toll like receptors.²³⁻²⁵ Given their inflammatory nature, the balance of IL-22 and IL-17 requires tight control, with dysregulation of this balance now linked to the development of a number of auto-immune diseases and cancer.

Role of IL-22 and IL-17 in auto-immunity and tissue protection

IL-22 is often co-secreted with IL-17 and thus is widely viewed as a Th17 cytokine. However, it is evident that an array of cell types can produce IL-22 and sometimes independent of IL-17. Although both cytokines are often implicated in similar conditions, this section of the review will focus on IL-22 given the number of excellent reviews that have been written on the role of IL-17 in autoimmunity.^{5,26} IL-22 has been demonstrated to play a key role in the pathogenesis of psoriasis, a disease marked by an increase in keratinocyte proliferation and development of scaly lesions on the dermis.²⁷ In patients, IL-22 expression and cytokine levels were significantly increased in psoriatic skin biopsies compared to healthy controls.²⁸ In addition, the level of IL-22 in the blood of psoriasis patients correlated with the severity of disease. This observation was also confirmed in several different mouse models of psoriasis^{29,31} which mirrored the clinical observations. Strikingly, IL-22 KO mice or mice treated with

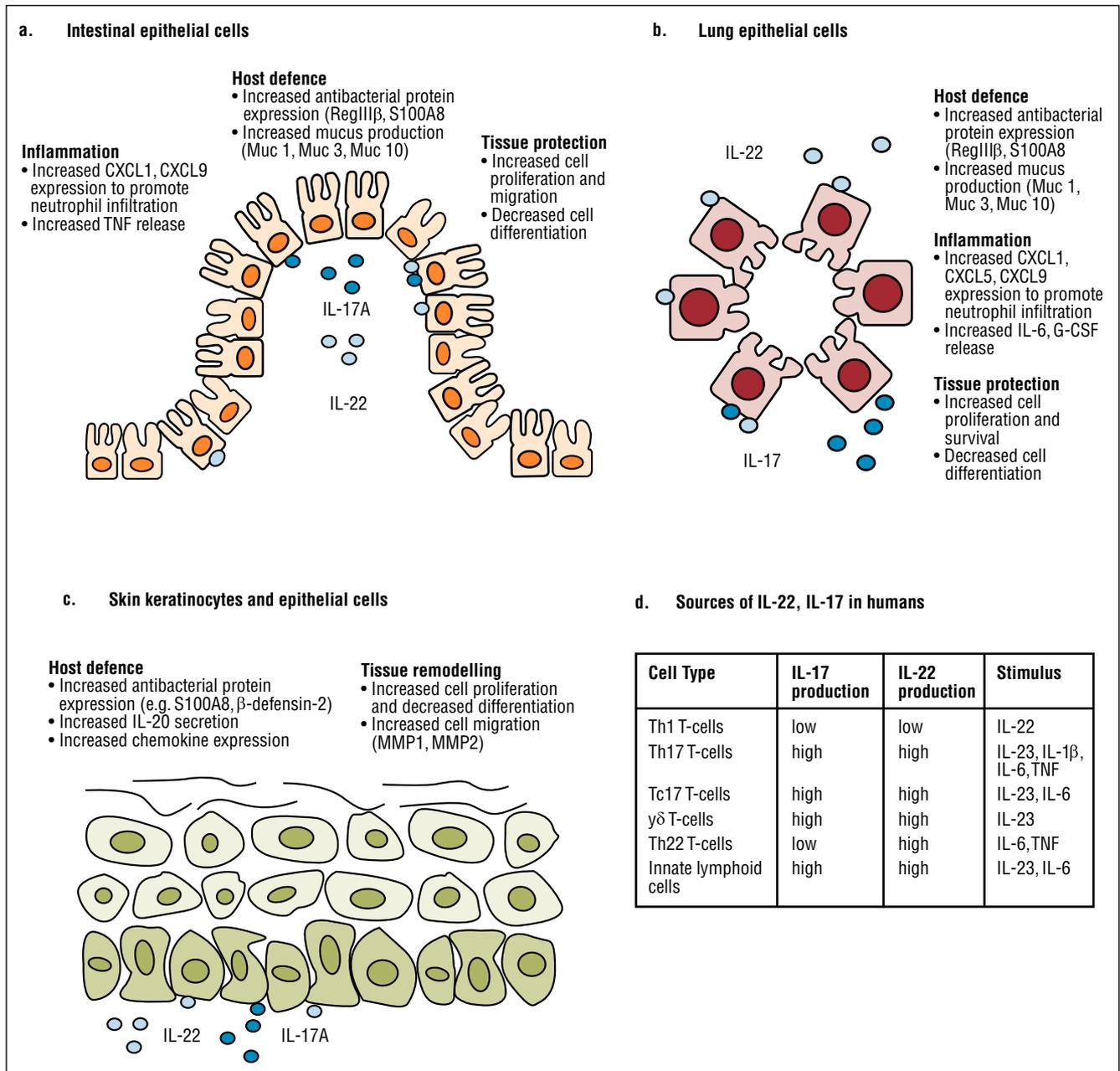


Figure 1 Cellular sources of IL-17 and IL-22 and their effects at mucosal surfaces. IL-22 and IL-17 act at local mucosal surfaces including: (a) intestines, (b) lungs, and (c) skin to alter the behaviour of local epithelial cells, endothelial cells, keratinocytes and stem cells. IL-22 mediates its functions through: 1) increasing local defences to bacteria through upregulating expression of antibacterial proteins, 2) promoting inflammation through chemokine expression and cytokine release, and 3) protecting and remodelling damaged tissues by increasing cell proliferation, survival and migration. Lymphocytes are the major source of IL-22 and IL-17 with the different lymphocyte subsets and stimuli inducing cytokine expression outlined in (d). Figure adapted from Sonnenberg et al.¹⁰

an IL-22 neutralizing antibody had a much milder disease phenotype compared to wild type or untreated animals. Anti-IL-22 neutralization was also effective at treating developed psoriatic disease, suggesting IL-22 neutralization as a novel therapeutic option for psoriasis.³⁰

While IL-22 has a defined pathogenic role in psoriasis, it has been reported to have both pathogenic and protective roles in other inflammatory conditions. IL-22 has been implicated

in rheumatoid arthritis, where an increase in IL-22 and IL-17 producing lymphocytes were found in patient’s synovial fluid.³²⁻³⁴ This finding was confirmed in mouse models where both IL-22 and IL-17 KO mice had attenuated disease.^{35,36} An increase in frequencies of circulating Th17 and Th22 cells was observed in the blood of patients with rheumatoid arthritis and ankylosing spondylitis.³⁷ Interestingly, genome wide association studies have identified common mutations

in the IL-23R as a factor in the disease development of Ankylosing spondylitis.³⁸ In intestinal inflammation, the role for IL-22 in disease development is not clear. IL-17 and IL-23 dysregulation have been strongly linked to Crohn's disease and severity³⁹⁻⁴¹ with increased levels of IL-22 also being detected in these patients.⁴²⁻⁴³ It has also been implicated in increasing intestinal tissue damage in a mouse model of ileitis.⁴⁴ In contrast, IL-22 has been strongly linked to reducing intestinal damage and promoting tissue repair in animal models of inflammatory bowel disease⁴⁵ and colitis.⁴⁶ In models of airway inflammation, IL-22 has also been implicated in both increasing, and reducing inflammation and providing protection from tissue damage.^{47,48} This alternating role was dependent on the model of lung inflammation used, as well as the presence of IL-17.

In non mucosal surfaces, IL-22 has been shown to have a vital role in tissue protection of some organs. In a model of acute liver injury, concanavilin A (ConA) induced immune destruction of hepatocytes in IL-22 KO mice, or mice treated with IL-22 neutralizing antibodies were more sensitive to disease and death from liver hepatitis compared to wildtype mice.^{17,49} It has also shown a protective role in a mouse model of pancreatitis¹⁶ and a critical role in protecting intestinal and liver stem cells against inflammation induced destruction.^{50,51} This protective role of IL-22 is linked to its ability to regulate the expression of genes involved in apoptosis, proliferation and wound healing.⁵² Hence, therapies that can enhance IL-22 production have been proposed for the treatment of certain diseases such as pancreatitis and hepatitis.¹⁴ An overview of the pre-clinical and clinical evidence of the pathogenic or protective roles of IL-22 and IL-17 in autoimmune and inflammatory conditions is listed in Tables 1 and 2, respectively.

Targeting IL-17/IL-17R, IL-23, IL-22 in psoriasis and other auto-immune diseases

With both clinical and pre-clinical studies identifying IL-23, IL-22 and IL-17 as potential therapeutic targets in a number

of autoimmune diseases, development of biological inhibitors have quickly followed. Phase II and Phase III clinical trials have been completed to determine the effectiveness of IL-17, IL-22 and IL-23 neutralization, in psoriasis, arthritis and Crohn's disease (overview of clinical trials in).⁵³ The anti-IL-23/IL-12 p40 subunit monoclonal antibody, ustekinumab (Stelara, CNT01275) is the most developed new therapy for psoriasis, having completed phase III clinical trials and is now FDA approved for the treatment of moderate to severe plaque psoriasis.⁵⁴⁻⁵⁶ Administration of two doses of 45 mg or 90 mg of ustekinumab over a 12 week period reduced psoriasis area-and-severity score (PASI) by 75% (target of clinical trial) in 67.5% and 73.8% of patients respectively. This was significantly improved compared to the TNF α inhibitor etanercept, which achieved 75% reduction of PASI scores in 56.8% patients. While the long term safety profile of ustekinumab remains favourable,⁵⁷ strikingly, psoriasis patients that received another anti-IL-12/IL-23p40 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.⁵⁸ Potentially, this may be due to the increased dosage utilized. While ustekinumab targets the p40 subunit of IL-23 that is commonly shared with IL-12, antibodies directed against the p19 subunit of IL-23 are currently in clinical trials with the aim of alleviating psoriasis symptoms while still maintaining a patient's ability to generate a Th1 response.⁵³

Neutralizing antibodies directed against IL-17 (ixekizumab and secukinumab) or its receptor (brodalumab) are alternative therapy options for psoriasis, having recently completed phase II and phase III clinical trials with universally excellent results. In phase II clinical trials, a 75% improvement in PASI scores in 75-85% of patients at the higher doses tested was achieved for all three antibodies.⁵⁹⁻⁶¹ Side effects reported with anti-IL-17 therapy included respiratory infections and a few cases of neutropenia however the overall safety profile of IL-17 neutralizing antibodies appears favorable. Secukinumab has also completed a phase III clinical trial

Table 1 Protective or pathogenic role of IL-22 in mouse models of autoimmunity and inflammation

Disease where IL-22 is pathogenic	Model	IL-17 implicated	References
Psoriasis	IL-23 induced dermal inflammation	nd	31
Psoriasis	Transfer of pathogenic CD4 ⁺ CD45RB high into SCID mice	Yes	30
Psoriasis	Imiquimod induced psoriasiform	nd	29
Rheumatoid arthritis	Collagen induced arthritis	Yes	36
Airway inflammation	Bleomycin induced airway inflammation	Yes	48
Ileitis	<i>Toxoplasma gondii</i> -induced immunopathology	No	44
Disease where IL-22 is protective	Model	IL-17 implicated	References
Inflammatory bowel disease	CD4 ⁺ CD45RB high transfer, DSS induced colitis	nd	45
Ulcerative colitis	CD4 ⁺ CD45RB high transfer, DSS induced colitis	nd	46
Airway inflammation	Bleomycin induced airway inflammation	Yes	48
Airway inflammation	<i>B. subtilis</i> inhalation	Yes	47
Acute liver injury	ConA induced liver inflammation	No	17, 49
Pancreatitis	Cerulein-induced pancreatitis	nd	16

ConA: concanavilin A; DSS: dextran sodium sulphate; nd: not determined.

Table 2 Association of IL-17, IL-22 and IL-23 in autoimmune and inflammatory diseases

Disease	Clinical evidence	References
Psoriasis	Increase in IL-17, IL-22 producing cells in both skin and serum of patients	28, 87, 88
Arthritis, RA and AS	Increase in Th-17 cells in RA synovial fluid Increase in circulating Th-17 and Th-22 cells in patients Correlation between IL-23R gene mutation and disease development	32-34, 37, 38
Atherosclerosis	Coronary muscle infiltrating T-cells produce IL-17 and IFN- γ	89, 90
Crohn's disease	Correlation between IL-23R gene mutation and disease development Increased expression of IL-17, IL-22 and IL-23 in patient biopsies and serum	39-43
MS	Correlation between IL-23R gene mutation and disease development Expression of IL-23 in active MS lesions	91-93

AS: ankylosing spondylitis; MS: multiple sclerosis; RA: rheumatoid arthritis.

as a treatment for moderate to severe psoriasis, where it has reportedly demonstrated improvements compared to the TNF α inhibitor etanercept, and is expected to receive approval as a treatment for psoriasis.⁶² An anti-IL-22 antibody, fezakinumab (ILV-094) is currently in development, having completed phase I trials for psoriasis (ClinicalTrials.gov identifier: NCT00563524) and phase II trial for rheumatoid arthritis (ClinicalTrials.gov: NCT00563524) and atopic dermatitis (ClinicalTrials.gov identifier: NCT01941537) with the results of these studies yet to be published.

The success of IL-17 or IL-23 neutralizing antibodies in psoriasis has led to the testing of these biological agents against other autoimmune disorders. The treatment of active psoriatic arthritis with ustekinumab in a phase III trial significantly improved clinical scores at 24 weeks in 42.4% and 49.5% patients given 3 doses of 45 mg or 90 mg ustekinumab respectively, compared to 22.8% of patients given a placebo.⁶³ Responses were also maintained after a year in patient's maintenance dosed every 12 weeks. IL-17 inhibition with secukinumab was also very successful in a phase II trial for the treatment of active ankylosing spondylitis, improving disease in 59% treated patients compared to 24% in placebo groups at week 6 after two doses of 2 \times 10 mg/kg secukinumab given at week 0 and week 3.⁶⁴ Patients with rheumatoid arthritis also responded to anti-IL17 (secukinumab) or IL-17R (brodalumab) blockade; however in both trials, the primary clinical measure was not significant compared to placebo.^{65,66} In Crohn's disease, ustekinumab therapy induced a clinical response in approximately 30-45% of patients compared to 17% in placebo after 8 weeks, with greater responses at the highest dose tested (single dose of 6 mg/kg).⁶⁷ Despite significant evidence of a role of IL-17 in Crohn's disease, blocking IL-17 (secukinumab) in patients was unsuccessful.⁶⁸ Brodalumab also appeared unsuccessful in treating patients with moderate to severe asthma⁶⁹ and ustekinumab was ineffective for the treatment of multiple sclerosis.⁷⁰ Thus, while the efficacy of IL-17 or IL-23 blocking antibodies was clear and dramatic in psoriasis, the results so far for other auto-immune condition have been less effective and it is unlikely that all therapies will be equally as impressive. Nevertheless inhibition of these cytokine pathways is a promising new line of therapy for inflammatory disease and the completion of a number

of current phase II and phase III trials will clarify which diseases best benefit from inhibition of which cytokine or receptor.

Role of IL-17 and IL-22 in tumor immunity

Given the inflammatory nature of Th17 cells and IL-17, a key question is what role they have in tumor-promotion or suppression? These questions have been the focus of intense investigations by many laboratories since Th17 cells and/or the cytokine IL-17 have been found in many different types of human tumours, including lymphoma, melanoma, breast cancer, colon cancer, gastric cancer, hepatocellular cancer, pancreatic cancer, ovarian cancer and prostate cancer.⁷¹ As many comprehensive reviews have been written on this topic,^{26,71-73} we will briefly summarize the main findings before moving on to discussing the role of IL-22 in tumour immunity.

Overall, the presence of Th17 cells and/or IL-17 has been reported to be a poor prognostic indicator in some cancer types and a favorable indicator in others.^{71,74} Similar observations have also been made in different mouse models of cancer using gene-targeted mice or over-expression in tumours.⁷³ From these studies, a number of key points have emerged, including the importance in not equating Th17 cells with the cytokine IL-17. Given that other cells of the innate and adaptive immune system such as $\gamma\delta$ T cells, and NK-T cells can also produce IL-17 and its related family of cytokines,⁷⁵ it may be important to determine if the cellular source of IL-17 dictates its tumour promoting or suppressive function. Indeed the role of IL-17 in tumour immunity can be modulated by the presence of other cytokines such as IL-22 and TNF α in the microenvironment.¹¹ Additionally, it is now appreciated that Th17 cells display a great degree of context-dependent plasticity; in mice, Th17 cells have been demonstrated to acquire functional characterization of Th1 cells which are important in anti-tumour immunity. Induced regulatory T cells (iTregs) have also been reported to convert to Th17 cells and vice versa depending on the cytokine milieu.^{71,74} Another issue is the potential heterogeneity of Th17 cell subsets in the tumor microenvironment. Different types of Th17 cells such as IL-17⁺IFN- γ ⁻ and IL-17⁺IL-10⁺ have been

phenotyped in autoimmune and inflammatory diseases.⁷¹ This suggests that Th17 cells and/or IL-17 depending on the cancer cause, type and location, and its interaction with other factors in the tumor microenvironment will dictate what role they play in tumour immunity.⁷² Thus, a clear understanding of the functional relevance of Th17 cells and/or IL-17 during different stages of tumor growth and development is required to enable rational therapeutic intervention.

IL-23 is another pro-inflammatory cytokine generally associated with Th17 cells and is crucial for its function and cytokine production *in vivo*.^{58,74} However, IL-23 has tumour promoting effects independent of IL-17 as demonstrated by a number of mouse models of cancer.⁵⁸ Moreover, clinical studies have correlated increased serum concentrations of IL-23 with the disease stages of different cancers such as breast and pancreas (Refer to Ngiow et al., for a full review on the role of IL-23 in tumour immunity).⁵⁸ In addition to Th17 cells, IL-23 also regulates the function of innate lymphocytes (NK cells, NKT cells, $\gamma\delta$ -T-cells and ILCs) through its induction of IL-22. Similar to IL-17, tumor promoting or suppressing roles have been attributed to IL-22 (Table 3).⁷⁶ However, the few studies reporting the tumor suppressive effects of IL-22 generally were performed in a non physiological setting involving exogenous injection of IL-22 over a period of time,⁷⁷⁻⁷⁹ and may not necessarily reflect the natural role of endogenous host IL-22 in modulating tumorigenesis. In contrast, using IL-22 deficient mice, different groups have demonstrated that endogenous IL-22 promoted tumorigenesis in several mouse models of inflammation/carcinogen induced cancer.⁸⁰⁻⁸² A caveat with the results obtained using the IL-22^{-/-} mice particularly in the colitis associated cancer models is the alteration in their colonic microbiota.⁸³ Given that commensal microbial elements have recently been associated with inflammation mediated tumour development,⁸⁴ this can affect interpretation of whether IL-22 plays a direct or indirect role in tumour promotion particularly in tissue sites where the interactions between the epithelia and microbiota is intense. Consideration also has to be given to the presence of IL-22BP, a soluble decoy receptor which binds to IL-22 with much higher affinity than membrane IL-22R and serves to regulate its availability.⁸² In humans, increased expression of IL-22 or its receptor was reported to correlate with disease progression and decreased overall survival in a number of cancer types including, pancreas, gastric and colorectal (Table 3). Notably, these cancers are inflammatory in origin and occur in mucosal sites which are the target tissues of IL-22.⁸⁵ It may be interesting to determine if IL-22 also plays a role in cancers arising from non mucosal sites such as breast or prostate as well as its impact on metastases.

IL-22R is specifically expressed on non-hematopoietic cells, but it has also been reported to be expressed on many cancer of epithelial origin,¹⁴ although it may not always be functional.⁸⁶ Although IL-22 can have anti-inflammatory properties through its induction of tissue protective factors, it's role in inducing proliferation, anti-apoptotic proteins, inflammatory cytokines and chemokines and its downstream signalling through STAT-3, a well established

oncogene probably explain its role in tumorigenesis.¹⁴ IL-22 signalling also induces cell specific factors¹⁴ which may also have tumor promoting function. Whether IL-22 exerts its protective versus inflammatory function will depend on a variety of factors such as its concentration and duration, the target tissues and the cytokine milieu.¹¹ For example, the presence of IL-17 can determine the protective versus pathogenic function of IL-22 depending on the disease model¹¹ and thus it will be useful to assess the presence of IL-17 and/or other cytokines in cancers where IL-22 is overexpressed.

The overexpression of IL-22 in several cancer types and its association with worse prognosis/survival (Table 3), suggests that the IL-22-IL-22R pathway is a potential target for therapeutic intervention. Antibodies that neutralize IL-22 or block its receptor are both valid approaches for immunotherapies depending on the specific situation. For example, if the key pro-tumorigenic effect of IL-22 was on tumour growth and proliferation, neutralizing anti-IL-22 antibodies may be an option. In contrast, if inflammatory cytokines and/or factors induced by IL-22R signalling from non tumour epithelial cells were the key effects of IL-22, blocking IL-22R may be more advantageous given that it can also neutralize the function of IL-20 and IL-24 which exert IL-22-like effects and signals through IL-22R.¹⁴ Given that IL-22 does not impact on the immune system, targeting IL-22 may be safer than its upstream inducers such as IL-23 and TNF α which have more pleiotropic effects and are important in protection against infection. Nevertheless, adverse effects with targeting this pathway may occur given the tissue protective and anti-microbial effects of IL-22. For example in a mouse model of colitis-associated cancer, IL-22^{-/-} mice unexpectedly developed higher tumour load compared to wild-type mice suggesting that IL-22 deficiency might have led to delayed colonic repair and increased inflammation, resulting in tumour promotion. Furthermore, in another inflammatory mouse model of CRC, Huber et al., demonstrated that early IL-22 neutralization resulted in increased tumours whereas tumour numbers were decreased following late neutralization of IL-22.⁸² Thus, to obtain its optimal therapeutic index, the timing, dose and duration of anti-IL-22/IL-22R therapy needs to be assessed.

In summary, current research has clearly demonstrated how IL-17 and IL-22 are key mediators in the development of psoriasis, which has led to their development as new therapeutic targets. Results from ongoing clinical trials will inform us as to the targeting of which cytokine can best impact on this disease. Further research to clearly demonstrate IL-22 and IL-17 are key mediators in the pathogenesis of other inflammatory diseases such as colorectal cancer will allow the therapeutic potential of these cytokines to be broadened.

Funding

M.W.L.T is supported by a CDF1 Fellowship and Project grants from the National Health and Medical Research Council of Australia (NH&MRC) and Prostate Cancer Foundation of Australia.

Table 3 Tumour suppressive or protective role of IL-22 in tumour immunity

Tumour type	Experimental model	Key results	Reference
Colon carcinoma overexpressing IL-22 (Colon26/IL-22)	BALB/c WT mice	No difference in tumour growth in mice injected subcutaneously or intraperitoneally with parental or Colon 26/IL-22, although an increase in survival in the latter group was reported	79
EMT6 murine breast cancer	Athymic nude mice (Swiss nude)	7 day release of IL-22 through implanted osmotic pump reduced tumour proliferation in vivo tumor growth as measured by uptake of [¹⁸ F]3'-deoxy-3'-fluorothymidine (FLT) using positron emission tomography (PET) scan	77
Renal cell carcinoma	BALB/c nude mice	IL-22 dose-dependently suppresses RCC cell line A498 cells in vitro and induces growth inhibition of A498 cell-bearing mouse xenografts	78
Bacteria driven CAC	129SvEv.RAG ^{-/-} mice infected with <i>Helicobacter hepaticus</i> and treated with carcinogen 2-azoxymethane (AOM)	Depletion of IL-17 ⁺ IL-22 ⁺ colonic innate lymphoid cells with anti-Thy1 prevented transition of colitis to CRC. IL-22 blockade ameliorated established colitis and reduced tumour burden	80
APC ^{min/+} genetic driven adenomas	APC ^{min/+} x IL-22 ^{-/-} mice	These mice developed fewer tumours in colon compared to APC ^{min/+} mice	82
DSS-induced CAC	IL-22bp ^{-/-} mice	These mice have increased availability of IL-22 due to lack of IL-22 decoy receptor resulting in increased tumor numbers and score	82
DEN-induced HCC	IL-22 ^{-/-} mice	Reduced tumorigenesis	81
Pancreatic ductal adenocarcinoma	Human	High expression of IL-22 or IL-22R correlated with decreased overall survival following surgery	94
Gastric cancer	Human	Higher percentage of intratumoral CD4 ⁺ IL-22 ⁺ T-cell and Th22-cell were found in patients with TMN at Stage IV compared to Stage 1-III and correlated with reduced overall survival	95
Gastric cancer	Human	Increased frequencies of Th22 and Th17 cells were significantly higher in stage III-IV GC patients versus stage I-II and correlated with patients' overall survival	96
HCC	Human	Significant up-regulation of IL-22 in human HCC tumor infiltrated leukocytes (TILs) compared to peripheral lymphocytes. IL-22 expression was significantly higher in Edmondson Grade III-IV HCC patients versus Grade I-II, confirmed by both real-time polymerase chain reaction and immunohistochemistry	81
CTCL	Human	IL-22 and CCL20, but not IL-17, expression is elevated in both sera and lesional skin in CTCL patients and correlated with disease severity	97
CRC	Human	Elevated serum IL-22 correlated with chemoresistant condition of CRC	98
CRC	Human	Significant upregulation of IL-22 in human CC tumor infiltrated leukocytes (TILs) compared to peripheral lymphocytes	99
Small and large cell lung cancer	Human	IL-22 is frequently expressed in lung cancer tissue	86

CAC: colitis-associated cancer; CTCL: cutaneous T cell lymphoma; CRC: colorectal cancer; DEN: diethylnitrosamine; DSS: dextran sodium sulphate; HCC: hepatocellular carcinoma.

Conflicts of interest

The authors do not have any financial conflict of interest that might be construed to influence the results or interpretation of this manuscript.

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