REVIEW

Interrelationship and Sequencing of Interleukins 4, 13, 31, and 33 – An Integrated Systematic Review: Dermatological and Multidisciplinary Perspectives

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Abstract: The interrelations and sequencing of interleukins are complex (inter)actions where each interleukin can stimulate the secretion of its preceding interleukin. In this paper, we attempt to summarize the currently known roles of IL-4, IL-13, IL-31, and IL-33 from a multi-disciplinary perspective. In order to conduct a comprehensive review of the current literature, a search was conducted using PubMed, Google Scholar, Medscape, UpToDate, and Key Elsevier for keywords. The results were compiled from case reports, case series, letters, and literature review papers, and analyzed by a panel of multi-disciplinary specialist physicians for relevance. Based on 173 results, we compiled the following review of interleukin signaling and its clinical significance across a multitude of medical specialties. Interleukins are at the bed rock of a multitude of pathologies across different organ systems and understanding their role will likely lead to novel treatments and better outcomes for our patients. New interleukins are being described, and the role of this inflammatory cascade is still coming to light. We hope this multi-discipline review on the role interleukins play in current pathology assists in this scope.

Keywords: interleukin cascade, IL-4, IL-13, IL-31, IL-33

Introduction

Interleukins are a diverse group of molecules exerting a plethora of autocrine and paracrine immune functions. They exhibit a pattern of interrelationing, where each interleukin can stimulate the secretion of its preceding interleukin. At present, 41 different members of this group of cytokines have been described, numbered from 1 to 41.[1] With the most recent member of this group being discovered in 2019, it is evident we are still in the infancy of our understanding of how these molecules come to be and how they modulate intercellular signaling.[2] In this paper, we attempt to summarize their current known clinical roles from a multi-disciplinary perspective. Classically, the interleukin cascade begins with a triggering stimulus, and the subsequent release of either damage-associated molecular patterns (DAMPs), or pathogen-associated molecular patterns

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(PAMPs), depending on the stimulus. In response to this trigger, dendritic, epithelial, fibroblast, and other resident immune cells that are present nearby, will secrete IL-1 as the initial step in immune activation leading to fever, upregulation of intracellular adhesion molecules, leukocyte stimulation and chemotaxis, and to a release of acute phase reactants. Release of subsequent interleukins will: act as polarizing cytokines for naïve T-cell differentiation (mainly IL-2, 4, 12, 22, and 23); lead to the activation of B-cells, and their differentiation into plasma cells (IL-4, 5, 6, 13, and 14); stimulate hematopoiesis in bone marrow stromal cells (IL-3 and 11); and further stimulate and promote chemotaxis of leukocytes into the damaged area, either directly, or by modifying local expression of adhesion molecules, chemokines, and vasoactive peptides (most other interleukins). The aforementioned cells, along with local stromal and epithelial cells, go on to secrete every other known interleukins.[1,3] Thus, a positive feedback loop is created, with downstream interleukins acting to stimulate cells that release more of the same signaling molecules, and, in turn, perpetuate this inflammatory cascade (Figure 1, Table 1).

Materials and Methods

In order to conduct a comprehensive descriptive review of the current literature, a search was conducted using PubMed, Medscape, UpToDate, and Key Elsevier for the terms "IL-4", "IL-13", "IL-31", "IL-33" (OR) "Interleukin 4", "Interleukin 13", "Interleukin 31", "Interleukin 33" in combination with the terms (AND) "Dermatology", "Rheumatology", "Cardiology", "Neurology", "Melanoma", "Systemic Sclerosis", "Atopic Dermatitis", "Psoriasis", "Rheumatoid arthritis", "Ankylosing spondylitis", "Systemic Lupus erythematosus", "Memory impairment", "Behcet", "Neurodegenerative diseases", "Alzheimer", "Parkinson", "Amyotrophic lateral sclerosis", "Autoimmune encephalitis", "Multiple Sclerosis", "Toxoplasmosis", "Neurocysticercosis", "Zika", "Intracerebral Hemorrhage", "Epilepsy", "Seizure", "Psychiatric disorder", "Pruritus", "Schizophrenia", "Depression", "Autism", "Cardiomyopathy", "Myocarditis", "Heart failure", "Fibrosis", "Kawasaki", "Atherosclerosis", "Ischemic heart disease", "Infarction". The results were compiled from original articles, case reports, case series, letters, and literature review papers, and analyzed by a panel of multi-disciplinary specialist physicians for relevance and pertinent information.

Results

Based on 173 relevant results, we compiled the following review of interleukin signaling and its clinical significance across a multitude of medical specialties (Figure 2).

Discussion
Cardiology

Interleukin 4 (IL-4) is an anti-inflammatory and pro-fibrotic cytokine that regulates multiple biological functions and therefore has many implications in different pathologies.[12,13] This cytokine stimulates the inflammatory response by activating the synthesis of collagen (types I and II) by fibroblasts, and also enhances the proliferation of fibroblasts, therefore contributing to the development and progression of fibrosis.[14,15] IL-4 also augments platelet-derived growth factor (PDGF) and contributes to the increase of macrophages within developing regions of fibrosis. In this spirit, there are many cardiac diseases in which IL-4 is playing a major role. The patients with hypertensive cardiomyopathy had higher concentrations of IL-4, but it is still unknown whether chronically elevated IL-4 is sufficient to initiate a fibrotic response, leading to cardiac fibrosis and dysfunction.[16] Inflammatory fibrosis (induced through overproduction and deposition of collagen by the fibroblasts) is also a typical feature of myocarditis and heart failure. Some studies in mice have already demonstrated a clear correlation between high levels of IL-4 and left ventricular enlargement (in response to sustained pressure overload), and depressed cardiac
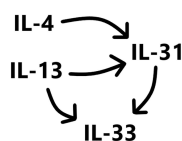
Figure 1 A snippet of the interleukin cascade. IL-4 and IL-13 are released under certain inflammatory stimuli. In turn they induce the release of IL-31, and IL-33; the latter is also induced by IL-31.

Table I IL-4, IL-13, IL-31 and IL-33-Secreting Cells, with the Respective IL Receptors and Signaling Pathways Which They Activate
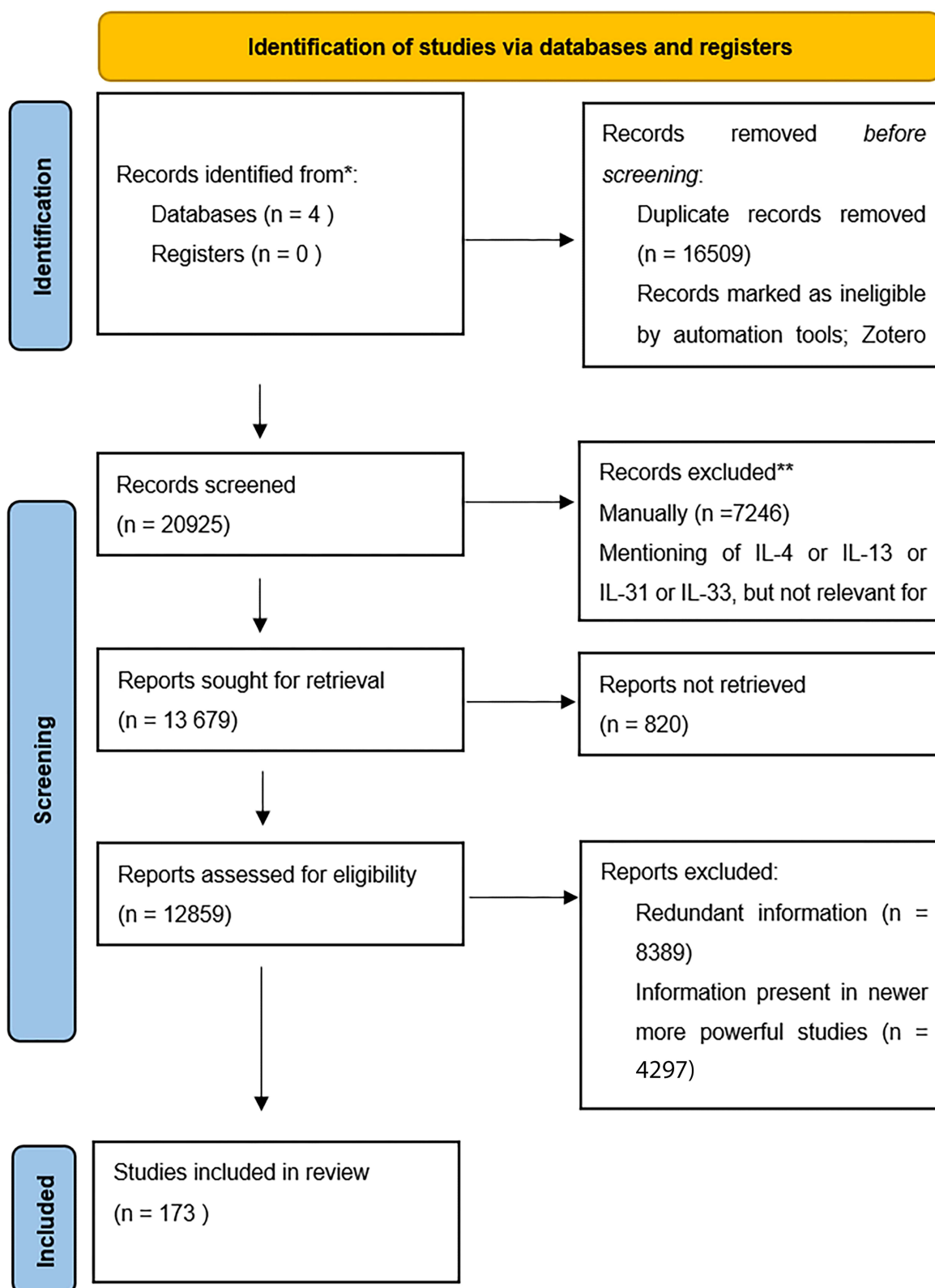
Cytokine	Secreting Cells	Receptors	Activated Signaling Pathway
IL-4	Th2 cells, mast cells, eosinophils, basophils	IL-4 receptor alpha chain (IL-4Rα)	JAK/STAT and IRS-1/IRS-2 pathways
IL-13	Th2 cells, mast cells, eosinophils, basophils, NK cells, CD4+ T cells, nuocytes,	IL-4 receptor alpha chain (IL-4Rα), IL-13 receptor alpha I (IL-13Rα1),	JAK/STAT and IRS-1/IRS-2 pathways type II IL-4 receptor/ IL-13 receptor, which is comprised of IL-4Rα and IL-13Rα1.
IL-31	Th2 Ly, CD4+ T cells	IL-31RA, OSMR	PI3K/AKT, MAPK, STAT pathway, JAK1 and JAK2
IL-33	Macrophages, dendritic cells, damaged epithelial cells,	Interleukin I receptor-like I (ST2), ST2 is the only receptor for IL-33	IARK-1, IARK-4, and MAPK kinases, JNK, ERK1/ 2

Note: [4–11].
Abbreviations: IL-, interleukin; Th, T helper lymphocytes; CD, cluster of differentiation; OSMR, oncostatin M receptor; JAK/STAT, Janus kinase-signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; JNK, Jun kinase; ERK, extracellular signal-regulated kinase.

function (fibrotic cardiomyopathy).[17,18] This important role of IL-4 in cardiac remodeling was also shown in human patients.[19,20] Besides of the important role of IL-4 in upregulating fibrogenesis, it was shown that its neutralization leads to the attenuation of cardiac fibrosis, and administration of anti-IL-4 antibodies suppresses hypertension in rats.[21,22] These findings are of great clinical interest and may serve as a potential target for future therapeutic interventions. IL-4 also has proinflammatory effects and, on one hand, determines the accelerated apoptosis of vascular endothelial cells, and, on the other hand, determines the increased endothelial oxidative stress, leading to atherogenesis.[23] Through this effect, this cytokine induces early lung vascular inflammation, leading to the development of pulmonary hypertension and subsequent right ventricular hypertrophy and fibrosis.[24,25] Another study on mice has shown that administration of IL-4 may augment cardiac M2-like macrophages and improve cardiac function after a myocardial infarction.[26] Some pathological events were incriminated, such as: microvascular development in the viable myocardium and local formation of thicker connective tissue in the infarcted ventricular wall, helping in improving ventricular function. Thus, systemic administration (or maybe intracoronary injection while doing a percutaneous coronary intervention) of IL-4, may be a very promising therapeutic option for acute myocardial infarction. Another recent study demonstrated a close correlation between increased basophil count after myocardial infarction and IL-4 and, respectively, IL-13 levels, suggesting a contribution to tissue repair and infarct healing.[27]

Discovered by Minty and McKenzie in 1993, IL-13 is one of the powerful cytokines with broad functions, playing important roles in inflammation and immune responses.[28,29] Widely expressed in most tissues, such as the heart, lung, liver and skin, IL-13 is not only involved in cardiac inflammatory diseases, such as myocarditis, but it is also relevant in the development of acute or chronic cardiovascular diseases with other pathogenic mechanisms, such as myocardial infarction and heart failure.[30] Many sources suggest that IL-13 is associated with cardiac fibrosis, cardiomyocyte proliferation and myocardial hypertrophy. One study in aging mice models has shown that IL-13 is related to excessive collagen production, cardiac fibrosis and remodeling, leading to progressive cardiac dysfunction.[31] Also, a higher serum level of IL-13 has been detected in vivo in patients with chronic heart failure and dilated cardiomyopathy, the authors concluding that in the near future, IL-13 might be a potential predictor or therapy target in these patients.[32,33] Regarding atherosclerosis and ischemic heart disease, since 2013, Stanya et al have demonstrated that increased weight gain, hyperglycemia, and hepatic insulin resistance are commonly encountered in mice with IL-13 deficiency, indicating that IL-13 might inhibit atherogenesis.[34] Many studies demonstrated that IL-13 is markedly expressed in myocardial infarction, and that it is also involved in cardiac wound healing and remodeling after an acute injury. Hofmann et al have shown the evolution of IL-13 concentration in acute myocardial infarction (registering an immediately increasing level, a peak at 3 days after infarction and a decline towards day 7), thus suggesting a close relation between this cytokine and cardiac function after infarction. In mice with IL-13 deficiency, significantly poor echocardiography parameters (within 7 days after myocardial infarction) suggest that IL-13 is involved in cardiac remodeling and might be a good prognostic marker in the very early phase of infarction.[35] Another study evidenced that a reduction of IL-13 levels, registered at 3 months after primary angioplasty for acute myocardial infarction, is associated with a worse prognosis, so IL-13 level could be a novel prognostic marker in STEMI patients.[36] On the other hand, IL-13 is an important regulatory

Identification of studies via databases and registers

Identification

Records identified from*:
Databases (n = 4)
Registers (n = 0)

Records removed *before screening*:
Duplicate records removed (n = 16509)
Records marked as ineligible by automation tools; Zotero

Screening

Records screened (n = 20925)

Records excluded**
Manually (n =7246)
Mentioning of IL-4 or IL-13 or IL-31 or IL-33, but not relevant for

Reports sought for retrieval (n = 13 679)

Reports not retrieved (n = 820)

Reports assessed for eligibility (n = 12859)

Reports excluded:
Redundant information (n = 8389)
Information present in newer more powerful studies (n = 4297)

Included

Studies included in review (n = 173)

Figure 2 Compiling of results.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[191] For more information, visit: http://www.prisma-statement.org/.

factor involved in the pathogenesis of pulmonary vascular remodeling and in the development of pulmonary artery hypertension.[37] Concerning the role of IL-13 in inflammatory heart diseases, it was demonstrated that IL-13 deficient mice develop severe myocarditis, having poor prognosis, and that experimental administration of IL-13 could significantly improve heart inflammation and cardiac injury induced by myocarditis.[38,39] IL-13 is also associated with progression of valvular heart diseases. Rotter et Vianello have demonstrated a close correlation between higher IL-13 levels and severity of aortic valve diseases, suggesting that IL-13 might induce fibrosis, increased collagen depositing and valvular calcification.[40,41] Taken together, it seems that further research revealing the role of IL-13 in cardiovascular diseases may lead to a promising immunotherapy in these patients.

Interleukin-31 (IL-31) is a proinflammatory cytokine from the gp130/IL-6 cytokine family, synthesized mainly by activated CD4+ T cells, being involved in different cardiac diseases.[42,43] Some studies report a close relationship between a certain genotype of IL-31 (rs4758680 allele) and the susceptibility of developing dilated cardiomyopathy in Han Chinese people; patients with this IL-31 genotype (rs4758680) had a higher chance of developing a poorer outcome.[44] The researchers also discovered that IL-31 acted through the receptor complex of IL-31RA, therefore inducing left ventricular hypertrophy and a loss of sarcomeres and cardiac fibroblasts, finally affecting myocardial contraction.[45–47] Another cardiac pathology in which IL-31 is involved is Kawasaki disease. Pro-inflammatory cytokine IL-31 triggered release from eosinophils might be the key mechanism that explains this association.[48] Some authors suggest that IL-31 may also be a predictor of coronary lesion development in patients with Kawasaki disease.[49]

IL-33 (a recently identified member of IL-1 family) is a complex immunomodulatory cytokine, acting like a pro- and anti-inflammatory factor, depending on the disease.[50–53] This cytokine was identified on endothelial and epithelial cells, smooth muscle cells, keratinocytes, fibroblasts, activated macrophages. It acts through the ST2 receptor just like an alarm factor. Its release is promoted by stressful conditions, inducing protective measures in neighboring cells.[54–58] In the human heart, IL-33 is mainly present in endothelial cells, cardiomyocytes and fibroblasts, functioning as a cardioprotective cytokine. It is also an indicator of cardiac stress in pressure overload situations (hypertension, heart failure, aortic stenosis and cardiomyopathies), and it favorably regulates the cardiac remodeling process.[59–61] In chronic heart failure, the levels of sST2 are elevated and they are strongly associated with heart failure severity and with adverse outcomes.[62] As such, IL-33/sST2 might become a powerful prognostic biomarker in chronic heart failure (with a reduced ejection fraction) and also a very good stratification marker (by being unaffected by body mass index, renal function, or age, as opposed to natriuretic peptides). Like a biomarker of cardiac mechanical strain, IL-33/sST2 may also have prognostic value in hypertension.[63] It was demonstrated that higher sST2 levels are associated with alterations of left ventricular geometry and with an increased systolic blood pressure.[64–66] In the same spirit, there is evidence about a close correlation between pulmonary arterial hypertension and sST2 release, secondary to an increased right ventricular afterload and a high myocardial stretch.[67,68] Some authors pointed out that elevated sST2 was associated with systolic dysfunction and right ventricular dilatation and it independently predicts 1-year mortality in PAH patients.[69] IL-33 is playing an important role in atherosclerosis and in ischemic heart disease. It may be used as an alarm signal and a diagnostic marker, as suggested by a research study wherein patients with acute coronary syndrome showed a significantly higher serum concentration of IL-33 (attributed to the myocardial damage) in comparison with the healthy control group.[70] There is much evidence regarding the protective role of IL-33 in atherosclerosis. It was demonstrated that the administration of recombinant IL-33 in mice may reduce the number of cardiomyocyte deaths, it might decrease plaque burden and secondary infarct size, and it might reduce cardiac remodeling.[71–73] Also, in men, the IL-33/sST2 pathway may inhibit the development of atherosclerosis, and sST2 administration may improve systolic function.[74,75] Thus, the clinical use of IL-33/sST2 may be soon a very useful diagnostic and prognostic biomarker in many cardiovascular diseases. Starting from the suggested benefit of IL-33 in some cardiovascular pathologies further work is needed to confirm these results in order to be able to use this cytokine as a valuable instrument for the prevention and treatment of cardiac diseases.[76]

The cardiovascular system is markedly influenced by IL-4, IL-13 and IL-31, these cytokines playing various roles (sometimes at the opposite poles – anti-inflammatory and pro-inflammatory) with (pro)fibrotic activities which in turn influence the cardiac remodeling processes; IL-4 increases the number of fibroblasts and macrophages in a damaged site and is involved in hypertension (systemic and pulmonary), cardiac dysfunction and ventricular enlargement; IL-13 inhibits

atherogenesis, is involved in cardiac wound healing, remodeling and hypertension (pulmonary), while IL-31 plays a role in (left) ventricular hypertrophy and Kawasaki disease, regulating in a positive way the remodeling of the heart.

Dermatology

The role of interleukins in dermatology is vast, having relevance in a large number of pathologies, extending from the neoplastic ones to immunological ones. We can witness the dysregulation of inflammation manifesting as dermatoses that come in all shapes and sizes; sometimes, this can be highlighted by different dermatoses appearing in the same patient, on a similar inflammatory substrate.[77] Local inflammation may also lower the threshold for the development of a lesion, a good example being what it is seen in the Koebner phenomenon.[78] Treatments aimed at interrupting this inflammation are often employed successfully in such diseases.[79] Likewise, inflammation is a substrate for the appearance of various types of skin cancer.[80,81] Melanoma is one of the most severe neoplastic diseases encountered in dermatologic practice, and it often poses a diagnostic challenge due to possible similarities with benign lesions, usually forcing excision for proper diagnosis.[82] Still, the therapeutic approach in this disease is often an even greater challenge. Below we explore the key roles interleukins play in these diseases, and what possible therapeutic options they might create. IL-4 may have a positive immunomodulatory role in melanoma, with overall protective effects. Direct activation of IL-4 receptors in cultured melanoma cells demonstrated significant reduction in the size of the cell-cultured tumor, along with changes in tumor antigen expression.[83] Melanoma has some of the highest concentrations of IL-4-α receptor when compared to other solid tumors. The in vitro stimulation of this receptor with recombinant human IL-4 (rhIL-4) inhibits cell growth in a dose-dependent manner. Furthermore, IL-4 overexpressing transgenic mice were injected with B16F10 melanoma cells and were compared to non-transgenic mice with the same tumor cell line. The overexpressing mice were observed to have decreased tumor volumes and weights as compared to the non-transgenic mice, showing that IL-4 stimulation has a protective effect in vivo as well. The proposed mechanism for IL-4′s role in melanoma is highlighted through: the upregulation of p53 and p21; the activation of the JAK/STAT6 pathway; upregulation of proapoptotic proteins, including bax, caspases −3, −8, and −9; and through the downregulation of cell survival protein bcl-2.[84] While this beneficial effect of IL-4Rα activation appears to show promise in opening the way for new and innovative treatments for melanoma, a Phase 2 clinical trial using rhIL-4 to directly treat human subjects was unable to demonstrate a significant benefit in terms of survival and tumor growth. Thirty-four eligible patients were treated with 5 μg/kg/day rhIL-4 for two 28-day cycles with a 7 day rest period in between cycles. Complete reduction was witnessed in one patient, 27 had progressive disease, 2 remained stable, 1 had a premature death related to melanoma, and 3 were lost during the assessment. While the response rate was limited, the study mentions that the administering route may have been inadequate for delivering IL-4 at the local level of the tumor. Direct treatment with rhIL-4 was poorly tolerated by the subjects, leading to 4 patients completely dropping out of the study, while 11 had to receive dose reductions. The one patient who did benefit, seemed to have a long-lasting remission at 16 months, when contact was lost.[85] Further experimental studies using different administering routes need to be undertaken, before IL-4 therapy can be completely dismissed as a possible treatment in melanoma.

IL-13 seems to play a role in the increased proliferation of certain tumors, including gliomas, melanoma, thyroid, breast, pancreatic, and ovarian cancers.[86] Certain subtypes of these tumors express an alternate form of interleukin-13 receptor (IL-13Rα2) which is associated with increased tumor proliferation, immune escape, and poorer prognosis. In the case of melanoma, the frequency of this mutation appears to be around 7.5%, as estimated by Okahamoto et al, in a study using the immunohistochemical staining of 187 primary melanomas. It was well preserved in the metastases of these tumors, with 90% of metastases being positive in the one studied patient identified with IL-13Rα2+ variant melanoma. This mutation appears to increase tumor size by promoting neovascularization of tumor tissue, possibly through the upregulation of amphiregulin.[87] The receptor is relatively specific to malignant tumors, as it is not expressed in healthy tissues outside of spermatocytes, and thus it is an excellent target for future oncologic therapy. Some authors have observed that inflammation can induce IL13Rα2 expression, but this appears to be a pathologic manifestation related to certain diseases.[88] IL-13 plays an important role in immune regulation, and its direct inhibition would likely be undesirable. Targeted therapy against the mutant receptor, however, remains an option. Many of the following treatments are still in their experimental phases and their application in the treatment of melanoma has not yet been tested, but the

rationale for their use in melanoma parallels that of other solid tumors that express IL13Rα2, such as glioblastoma multiforme, where its association with a poor prognosis is better established. These therapies include: anti-IL13Rα2 antibodies, which could bind to the mutant receptor and activate the complement system, deliver pseudomonas exotoxin into the tumor, or bind titanium oxide microdiscs which shear the tumor through mechanical forces when exposed to an alternating magnetic field; autologous dendritic cell vaccines that have been exposed to IL-13Rα2; and chimeric antigen receptor-modified cytotoxic T cells.[89]

Interleukin-31 is secreted mainly by activated CD4+ Th2 cells and mast cells. Only one receptor is known (IL-31R) which is present on a diverse group of both immune and non-immune cells. Activation of this receptor causes actions exerted downstream via the JAK/STAT, ERK/MAPK and PI3K/AKT pathways. IL-31 induces the release of chemokines CXCL 1 and 3, and CCL2, 7, 13, and 15; upregulates matrix metalloproteinases 1, 3, 7, and 25; upregulates IL-6, 16, and 32; and causes the release of VEGF and EGF. It has been studied for its involvement in maintaining pruritus, dermatitis, and psoriasis. Mouse models have demonstrated that upregulation of IL-31 produces an atopic dermatitis-like phenotype.[89] IL-31 and IL-4 levels are significantly increased in patients with psoriasis and atopic dermatitis who present pruritus when compared to healthy control groups. This appears to be a unique cytokine pattern related to pruritus. Different patterns were observed in the patient groups depending on their respective pathology, with IL13/33 being decreased in psoriasis patients, while the inverse was true for atopic patients.[90] The interleukin 4/13 pattern appears to be central to the pathogenesis of atopic dermatitis. Indeed, IL-4 and IL-13 share a common receptor chain and overlap in their signaling pathways where they can both activate type 2 IL-4R. Their individual effects are primarily due to the ratio of expression of type 1:type 2 IL-4aR complexes on their target cells. Non-hematopoietic cells primarily possess type 2 receptors, while type 1 is preferentially expressed in leukocytes. Myeloid cells contain both type 1 and type 2 receptors and are therefore responsive to both interleukins.[91] In atopic dermatitis, IL-13 appears to stimulate epidermal hyperplasia, while IL-4 induces chemotaxis of eosinophils. Both IL-13 and IL-4 must work together synergistically to increase lymphocyte and macrophage proliferation. Knock-out mice studies have shown that while IL-13 is the main contributor to the pathogenesis of atopic dermatitis, IL-4 is necessary for upstream polarization of Th2 cells. In its absence, IL-13-dependent effects are dampened. However, it seems that activation of alternative IL-13 induction pathways via IL-33, IL-25, and TSLP will produce a similar clinical phenotype.[92,93] This opens up the possibility of IL-13 targeting, such as with tralokinumab, as treatment for atopic dermatitis. This is a recent medication, but it has shown promising results in clinical trials for the treatment of atopic dermatitis.[94] Dupilumab, an IgG monoclonal antibody that targets the alpha subunit of the IL-4 receptor, and thus inhibiting both IL-4 and IL-13 pathways, has been approved for use in the treatment of severe atopic dermatitis. There is strong evidence that it decreases the impact of atopic dermatitis, with significant improvements seen in objective clinical severity scores, quality of life, reductions in pruritus, and histological studies.[95] IL-4 and IL-13 binding to IL-4α leads to phosphorylation of Janus Kinases 1 and 3, which, through a cascade of downstream tyrosine protein phosphorylation events, activate signal transducer and activator 6. This upregulates cellular transcription in those immune cells, responsible for the pathologic events seen in atopic dermatitis. This pathway is probably centrally responsible for the manifestations seen in atopic dermatitis. Inhibitors of the JAK/STAT6 pathway, such as leflunomide and ruxolitinib, may be employed with some success in treatment.[96] Ruxolitinib even has the advantage of being formulated for topical administration, and may even be more effective than some topical corticosteroids in the treatment of atopic dermatitis, further highlighting what an integral part the IL-4/IL-13 pathway plays in this disease.[97] IL-32 agonism may also have a role in the treatment of atopic dermatitis. IL-32 appears to control inflammation in atopic dermatitis by reducing inflammatory cell chemotaxis, inhibiting miR-205 expression, suppressing NF-κB activation, and decreasing TNFα, IL1, and IL-6 signaling. Mice induced to express an atopic dermatitis phenotype with the help of phthalic anhydride, were treated with recombinant human IL-32γ. The mice demonstrated histologic improvement at 4 weeks with decreased epidermal thickening and reduced leukocytic infiltration.[98] It is therefore important to recognize the nuance that inflammatory cytokines play in dermatological diseases, with a potential to act as both aggravating and relieving factors. Future therapies that interrupt or accentuate these pathways will probably see development in the coming years. There is an increasing demand for newer therapeutic agents which help fight various diseases through these cytokines: drugs which employ IL-4 (and possibly make use of its receptors) may fight against melanoma, inhibiting its growth; tumor growth inhibition could also be obtained by using

anti-IL-13 agents, in tumors such as gliomas, melanoma and cancers of the breast, thyroid, pancreas and ovaries; not only anti-IL-13 medication could be beneficial for patients suffering from atopic dermatitis, but the entire IL-4/IL-13 axis; IL-31, being responsible for pruritus, psoriasis and other skin diseases is a future target for medication.

In 2020, IL-31′s receptor targeting, which was considered a key element in (moderate-to-severe) prurigo nodularis treatment, encountered clinical success in a randomized clinical trial: patients received subcutaneous nemolizumab (a human monoclonal antibody) and after 4 weeks their pruritus score improved (as compared to placebo) and after 12 weeks, some lesions subsided.[99] Pruritus in prurigo nodularis and IL-31 have long been considered for therapy targeting; also, IL-31 is involved in the development of pruritus not only in the latter disease, but also in other dermatological diseases which present with pruritus, such as: atopic dermatitis or psoriasis. Patients suffering from pruritic diseases have been found to have elevated serum levels of IL-31 and its respective receptor.[100]

Rheumatology

The accumulation of proinflammatory cytokines plays a central role in the pathogenic chain of systemic sclerosis (SSc).[101] SSc is an autoimmune disease with an inflammatory substrate that evolves into extensive multiorgan fibrosis.[102] The pathogenesis of SSc involves an immunological alteration followed by vasculopathy and cutaneous and visceral fibrosis.[106] Endothelial lesions appear to be the origin of "cascading" events, which end with the accumulation of cytokines and chemokines with a proinflammatory potential, along with a number of growth factors that promote fibrogenesis. The mechanisms of the fibrotic process are not clear, but the development of fibrotic lesions seems to be conditioned by the chronic inflammation present in SSc.[101] Inflammation is maintained by the marked expression of cytokines: IL-17A, IL-4, IL-25, transforming growth factor (TGF) β1.[102] Activated inflammatory cells accumulate in the damaged vascular endothelium and turn into myofibroblasts that expose α-actin smooth muscle (α-SMA).[101] At the origin of this disease one finds an endothelial cell lesion, activated in the context of overexpression of surface selectin E and adhesion molecules: ELAM-1 (endothelial leukocyte adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1). Leukocytes are chemotactically activated by activated endothelial cells. Through diapedesis, CD4 + Th lymphocytes pass into the perivascular space and constitute inflammatory infiltrates.[103,104] Leukocytes attach to the endothelial wall, activated by a ligand, P-selectin. Monocytes and macrophages adhere to endothelial cells via L-selectin and integrin α-2 molecules present on their surface. Transforming growth factor β (TGFβ), produced in excess by mast cells, activates dermal fibroblasts.[105] The substrate of endothelial alteration is based on the production of anti-endothelial antibodies and on the existence of anti-ICAM-1 antibodies.[106] Hyperactivated endothelial cells provide connective tissue growth factors and interleukins such as: IL-1, IL-4, IL-6, IL-8, TGFβ, TNFα. All of these cytokines, and especially TGFβ, induce hyperactivation of the fibroblast responsible for excessive fibrosis. PEDF (pigment epithelium-derived factor), normally present in the epidermis in the germ layer, has been identified both perivascular and in resident fibroblasts at the base of the reticular dermis.[107,108] IL-4 is responsible for promoting proliferation, extracellular matrix deposition, and chemotaxis in fibroblasts. It is elevated in the blood of patients with systemic sclerosis. In particular, an alternative variant, IL-4δ2, seems to be related to this disease state. This RNA variant is normally present in other tissues including the thymus, lung, gut, and placenta. An increased ratio of IL-4 to IL-4δ2 mRNA is, however, associated with a variety of rheumatic pathologies, including SSc, rheumatoid arthritis, and possibly asthma. The transcribed IL-4δ2 protein may act as an antagonist of IL-4 via competitive inhibition on its receptors in a variety of immune cells, including multiple subtypes of lymphocytes and of macrocytes. In contrast, it seems to have an analogous role to IL-4 in fibroblasts.[109] This, therefore, may be a key mediator to the aberrant deposition of collagen seen in SSc, having both immunomodulatory and fibrogenic activities. Anti-IL-4 therapy has been proposed in SSc. Neutralizing IL-4 antibodies when given to tight-skin mice inhibit the deposition of dermal collagen.[110] Further human studies would be required to clarify whether IL-4 could be used in the treatment of SSc. Studies have also noted the involvement of IL-13 in the pathogenic chain of SSc. In this regard, a group of researchers have identified the molecular mechanism by which CD8 + T lymphocytes produce IL-13. They analyzed the confocal images of blood samples, and those of hardened skin. The thickened skin samples were pre-frozen, then stained by immunofluorescence techniques. Subsequently, CD8 + T lymphocytes were isolated from the fibrous skin and blood samples. In the early stages of SSc, fibrous skin contains elevated levels of CD8+ T lymphocytes that produce IL-13. CD4+ T lymphocytes

also synthesize IL-13, but to a lesser extent. For these reasons, it was observed that IL-13 generating CD8+ T lymphocytes play a key role in excessive tissue fibrosis.[111] Moreover, it has been observed that elevated levels of IL-13 producing CD8+ T lymphocytes in fibrotic tissue are associated with a high level of GATA-3 transcription factor. In other words, these lymphocytes, which overexpress the transcription factor, produce an excess of IL-13 that precedes extensive fibrosis. Experimental deletion of small interfering RNA (siRNA) was followed by IL-13 synthesis inhibition. The authors analyzed the molecular process in depth and noted that the T-bet transcription factor modulates the manifestation of GATA-3 factor. In turn, GATA-3 regulates the differentiation of T helper cells and modulates the expression of several cytokines: IL-4, IL-5, IL-13.[111] Although the authors believed that the T-bet factor does not regulate GATA-3, later in 2018, they observed that the T-bet transcription factor canceled GATA-3, and through IFNγ transcription, is able to block the synthesis of IL-13. They concluded that in fibrous skin and in the blood of patients with the diffuse subset of SSc, CD8 + T lymphocytes overexpress GATA-3 transcription factor and induce a high level of T-bet transcription factor.[111] Early endothelial injury induces microvasculopathy by reducing the number of capillaries. Neoangiogenesis and a faulty vascular repair mechanism affect both blood capillaries and lymphatic vessels, leading to edema.[112] Newer studies have shown that angiogenesis is promoted by high levels of endothelin-1 (ET-1). Also, it was observed that microangiopathy is associated with a high level of vascular endothelial growth factor A (VEGF-A). Excessive fibrosis is subsequent to vasculopathy and is induced by fibroblast activation. Therefore, the fibroblast initiates an aberrant production of type I collagen that deposits in the skin and viscera.[109] Excessive collagen deposition is responsible for the hardening of the skin.[113] IL-31 plays a role in SSc by direct stimulation of a variety of skin cells, including macrophages, fibroblasts, vascular endothelial cells, and mesenchymal fat cells. Increased levels of this interleukin have been observed in both skin biopsies and blood samples of SSc patients. When stimulated by IL-31, fibroblasts undergo a phenotypic change that increases their proliferation independent of the TGFβ pathway. Collagen protein deposition is also increased via the STAT3 pathway. IL-31 also appears to mediate vascular inflammation and contribute to the aforementioned vasculopathy.[114] IL-31Ra seems to be upregulated in surrounding tissue cells during the SSc disease state, showing that this axis is likely stimulated in an aberrant manner.[115] IL-33 has been studied as a disease marker in SSc. It follows the disease state of SSc tightly, with increases in affected individuals, and whose drops correlate well with treatment efficacy.[116] Certain gene polymorphisms, such as the rs7044343 that encode for IL-33 may lead to more severe diseases.[117]

Ankylosing spondylitis (AS) is an immune-mediated chronic inflammatory rheumatic disease that strongly associates with the HLA-B27 allele. The role of HLA-B27 in the pathogenesis of AS is not very clear. One of the theories issued, the theory of arthritogenic peptides, supports that HLA-B27 has a key role in directing joint-specific peptide fragments to cytotoxic CD8+ T lymphocytes. HLA-B27 binds specific peptides and presents them to activating CD8+ T lymphocytes. This theory cannot be fully supported because arthritogenic peptides have not been identified in the joints, as is the case in reactive arthritis caused by Chlamydia. Most likely, HLA-B27 modifies the person's microbiome.[118] IL-4 attenuates the manifestation of ankylosing spondylitis. Arthritis has been observed to be relieved by IL-4 agonism, whereas anti-IL -4 antibodies appear to worsen symptoms.[119] The reasons why, are less clear. When IL-4 is injected intra-articularly in proteoglycan-induced arthritis mice models, there is a decrease in both clinical and histologic changes associated with arthritis. It's possible that monocyte/macrophage polarization plays a role in this, as IL-4 appears to promote the phenotypic shift from M1 to M2 macrophages both in vitro and in mouse models.[120] While the clinical utility of IL-4 agonism is still under investigation, IL-4 may not play a key pathogenic role in the development of AS, as levels of IL-4 levels appear to not be significantly increased in these patients, as compared to those of healthy controls.[121] IL-33 may also play relevant roles in AS. Both the concentrations of IL-33 and of its decoy ligand, sST2, were markedly higher in serum samples of patients with AS, as compared to controls when measured by ELISA (P < 0.0001).[122] The significance of IL-33 elevations in AS is less well established. It may act to promote angiogenesis and sustain inflammation locally. One possible clinical utility would be in the differential diagnosis with psoriatic arthritis, which is often difficult as both diseases affect the axial skeleton and are associated with the HLA-B27 genotype. Here, elevated serum IL-33 could be used to plead for the occurrence of ankylosing spondylitis.[123]

Similar to SSc, the pathogenesis of SLE is heterogeneous. Stimulation of the immune system under the action of antigens (environmental factors or infectious agents) activates B lymphocytes and T lymphocytes. Antigen presenting

cells recruit these antigens and expose them to T lymphocytes. Therefore, T lymphocytes induce the synthesis of cytokines (IL-6, IL-10, IL-12, IL-23) which leads to an increase in the number of monocytes and lymphocytes. On the other hand, high levels of IL-17 and IL-21 induce an overproduction of T lymphocytes. At the same time, the increase of IFNγ in SLE induces defective T lymphocytes. High concentrations of interleukins activate B lymphocytes to plasma cells that produce elevated autoantibody titers characteristic of SLE. The presence of autoantibodies causes the deposition of circulating immune complexes and complement fractions in various organs, causing damage. B lymphocytes also function as antigen presenting cells to the T lymphocytes they activate. In other words, the activation of T and B cells is reciprocal, self-sustaining and amplifies the autoimmune process. And in the case of SLE, interleukins maintain the inflammatory process and activate autoimmune mechanisms.[124] Overall, serum levels of IL-4 are generally reduced in lupus patients. However, increases of IL-4 expressing Th lymphocytes are seen in the dermal and epidermal biopsies of SLE patients.[119] This incongruence has led to some speculation as to what IL-4′s mechanism is in SLE. It may act to promote tissue fibrosis, synovial proliferation, osteoclastic bone resorption, the production of autoantibodies from B-cells, and a decrease the immunomodulatory role of T-cells. One interesting observation has been that neutralizing IL-4 with antibodies leads to delays in end-stage renal disease in patients with glomerulosclerosis, as a consequence of lupus nephritis.[125,126] It is therefore reasonable to conclude that localized IL-4 elevations may still contribute to the end-organ damage seen in SLE, but this is not reflected in the serum levels of patients. At the same time, a study from 2002, by Sugimoto et al, found that a cytokine profile which favored a higher number of IL-4 producing cells was registered in patients who also suffered from SLE renal involvement.[127] A more recent research developed on Wild-type/IL-4 knockout BALB/c mice found that IL-4 has a central role in developing lupus-like disease and IL-4 inhibition in human lupus might improve the clinical aspects of this disease.[128] IL-13 is a clearer contributor to the inflammation seen in SLE, with marked elevations seen in affected patients, especially in those with lupus nephropathy.[129] An activating genotype of IL-13, rs20541, also carries with it an increased risk of developing SLE.[130,131] Similarly activating IL-31 mutations rs4758680 G/T and rs7977932 C/G also carry an increased risk of developing SLE. This is possibly due to IL-31′s ability to increase inflammatory IL-6 release from inflammatory cells.[130,131] Increasing evidence, such as the 2011 study by Yang et al, supported by Moreau et al in 2021, has revealed that IL-33 plays an important role in the development of SLE (in the acute phase), being significantly increased in these patients' serum.[132,133] However, IL-33 acts as a double-edged sword, having also protective properties in what concerns the development of SLE, as demonstrated in a young mice population study from 2020; further research needs to be done in order to explore this protective role.[134]

The pathogenesis of rheumatoid arthritis (RA) takes place in stages and is triggered by a series of environmental factors that can act on a predisposing genetic field. Following the citrullination process, proteins behave like an antigen and the immune system loses its tolerance. "Self" becomes "non-self", and as a result, B lymphocytes are activated and synthesize an increased titer of cyclic citrullinate peptide (CCP) antibodies. The inflammatory infiltrate comprises many macrophages, mast cells, natural killer (NK) cells, T lymphocytes, B lymphocytes, plasma cells and dendritic cells. Macrophages, T lymphocytes, and B lymphocytes release chemokines, matrix metalloproteinases (MMPs) and cytokines (TNFα, IL-6, IL-1, IL-15, IL-17) that promote chronic inflammation of the synovial membrane in the joints.[135] IL-4 acts as an anti-inflammatory cytokine in rheumatoid arthritis. Mouse models show that knockout of IL-4 leads to increased arthritic changes due to loss of regulatory control over proinflammatory mediators IL-1, IL-12, TNFα, IFNγ, and VEGF.[119,136] This joint inflammation is reduced when recombinant IL-4 is administered, possibly due to a switch of Th1-type response towards a predominantly Th2-type that acts as a positive feedback loop sustaining increased IL-4 signaling.[137] IL-4 also has an inhibitory effect on B cell development, and thus can decrease the citrullination process described above.[119] In a phase two clinical trial, patients treated with methotrexate were compared to a treatment group receiving a low dose combination of IL-4, IL-10, and anti-IL-1 antibodies. Disease activity was measured using standardized clinical scales, alongside with the assessment of inflammatory markers (ESR, CRP), and subjective pain in both groups, over the course of year. No statistical significance was found between either group, in any of the categories, showing that these anti-inflammatory signaling molecules may be effective in the treatment of RA.[138] Contrary to what has been discussed so far, increased serum and bronchial fluid levels of IL-4 have been associated with lung fibrosis in RA. However, these IL-4 levels were significantly increased in those with pulmonary fibrosis, as

compared to both patients with RA, but without lung fibrosis and controls, and there was no difference in IL-4 levels between those with RA without fibrosis and the controls. IL-4 may therefore be a marker of this disease, but likely results as a response to the uncontrolled inflammatory response rather than from its pathogenesis.[139] IL-13 has an analogous anti-inflammatory effect to IL-4 in RA, but whose increased level is associated closely to the disease state. Decreases in IL-13 levels are also concurrent with an improved clinical response to TNFα inhibitor medication in these patients.[140] This cytokine therefore has the potential to become a marker for disease activity. One study even suggests a cutoff value of 10.73 pg/mL as an accurate diagnostic indicator of early RA, and finds it more accurate at predicting disease activity than either CRP, ESR, or anti-CCP antibodies alone.[141] Increased cytokine signaling via the IL-33 axis has been implicated in RA as well. IL-33′s ligand, ST2 is primarily located on mast cells, Treg cells, and eosinophils, where it tends to stimulate these cells to increase protein synthesis, multiply, or release other cytokines. This proinflammatory activity may contribute to the pathogenesis of RA. High levels of IL-33 are associated with increased RA severity, whereas administration of ST2 inhibitors reduces articular inflammatory infiltrates, bone erosions, and synovial hyperplasia.[141] Indeed, some authors have even suggested that this cytokine, through its alarming role, may be the triggering mechanism for the development of RA.[143] An interesting observation has been demonstrated with Rituximab and Tocilizumab, where higher pretreatment serum levels of IL-33 may predict a positive response. This result has not been observed with TNFα inhibitors.[117]

IL-4 is involved in SSc (in the excessive fibrotic skin response), in AS (by inhibiting the clinical manifestations of the disease), in SLE, where it promotes fibrosis, synovial proliferation and osteoclastic bone resorption; in RA it seems to have anti-inflammatory properties. IL-13 is also involved in SSc, in the pro-fibrotic response, in SLE where patients have increased serum values corresponding to the disease activity (with high titers in the acute phase of the disease), and in RA, with effects analogous to those of IL-4.

IL-31 acts as a stimulating agent in SSc, with effects on macrophages, fibroblasts, endothelial and adipose cells, effectively promoting excessive fibrosis. IL-33 is involved in SSc, acting as a disease marker with values evolving parallel to the disease, in AS, where it sustains local inflammation and promotes angiogenesis, and in RA, where it act as a pro-inflammatory factor, with high levels reflecting the disease severity.

Neurology

A large number of cytokines are known to play an important role in neuroinflammation and in an array of neurological diseases. While IL-4 and IL-13 have been intensively studied for their role in the immune regulation of the CNS, more recently discovered IL-31 and IL-33 emerge as potential biomarkers and therapeutic targets in CNS afflictions. We further summarize the current available evidence on the implications of these cytokines in specific neurological conditions.

IL-4 is one of the most important cytokines in neuroinflammation and it can exert either pro- or anti-inflammatory effects in specific neuronal populations. Overall, low levels or absence of IL-4 seem to increase vulnerability to neuroinflammation.[5] A very intriguing study by King et al found that patients with mild cognitive impairment (MCI) preceding Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) have high levels of peripheral IL-4, while patients with established dementia showed no difference to controls.[144] Furthermore, the study evidenced that lower IL-4 levels correlated with a more severe disease course. These findings indicate that neuroinflammation, with IL-4 as one of the major mediators, plays an important role in early cognitive neurological diseases' pathogenesis. Multiple studies have identified that mice with absent or suppressed adaptive immunity exhibit cognitive impairment and decreased learning abilities, as well as reduced neurogenesis. After performing specific cognitive tasks, these mice exhibited increased IL-4 production in meningeal T-cells. Interestingly, the cognitive defects have been shown to be reduced by restoration of the T-cell population.[144,145] Moreover, aging mice with cognitive impairment or AD models demonstrate improvement in neuronal connection strength, memory and learning tasks, after IL-4 administration, either direct or as genes via a viral vector.[144] A study from 2020, by Dawling et al, supports the positive role that IL-4 injections have on cognitive improvement in AD mice models by activating microglial changes in such neurodegenerative diseases.[146]

IL-13 and IL-4 share a common alpha chain complex receptor, formed through heterodimerization of IL-4R alpha chain (IL-4Rα), with IL-13 receptor alpha 1 chain (IL-13Rα1), thus the role of IL-13 in memory and cognitive

impairment having also been studied. The study of Brombacher et al demonstrated that IL-13-deficient mice have significant working memory impairment and reduced reference memory.[147,148] The authors also suggest that both IL-4 and IL-13 can stimulate astrocytes from the meninges and hippocampus during complex cognitive tasks, thus exhibiting important targets for dementia disorders treatment. A more recent study from the same group showed that IL-4 and IL-13 deficient mice have significantly impaired learning and reference memory, while IL-4 alpha receptor deficiency only impairs reference memory, with sparing of spatial learning abilities.[149] IL-33 is a more recently discovered cytokine pertaining to the IL-1 family with multiple roles in neurological diseases' pathology. A study by Xiong et al identified through immunohistochemical studies that IL-33 and its receptor, ST2, are overly expressed in the vicinity of amyloid plaques and neurofibrillary tangles in the glial cells of patients with AD, as compared to controls.[150] Later, serum and CSF IL-33 levels have been found to be lower in patients with mild cognitive impairment and Alzheimer's disease. Moreover, the ST2 receptor levels are higher in the same patients.[151–154] Genetic studies in the Chinese Hunan Han population have identified that a specific single nucleotide polymorphisms (SNPs) in the IL-33 gene was associated with late-onset AD, while a larger study in a Caucasian population further identified two SNPs associated with increased AD risk.[154,155] In animal models, similar observations were confirmed and studies established that IL-33 expression in astrocytes increases with age and aging. IL-33 deficient mice display a disease course similar to AD, with increased neurodegeneration and abnormal tau deposition. Interestingly, the administration of IL-33 in animal models improved memory and learning impairments, increased amyloid plaque clearance and reversed synaptic plasticity deficiencies.[151,153–156] A more recent study by Reverchon et al observed that IL-33 injections into the hippocampus of mice induced increased inflammatory responses and spatial memory impairment.[5] This induced overexpression of IL-1β in glial cells was registered within the first two days after injection, but IL-1αβ deficient mice were resistant to cognitive decline.[156] All the aforementioned findings highlight the versatile modulating role of IL-33 in the brain, with positive or negative influence on cognitive impairment and neurodegeneration.

A recent study by Yan et al identified significantly higher levels of Th2 cells producing IL-4 and a significant decrease in naive B cells levels in patients with Parkinson's disease (PD) as compared with controls.[157] Previous studies have suggested the cytotoxic effects of IL-4 and IL-13 on dopaminergic neurons in the brain, with increased survival upon administration of IL-4 antibodies.[148,158,159] This can be partially explained by the increased expression of IL-13Rα1 receptor, a component of the common alpha chain complex receptor mediating both IL-4 and IL-13 functions, in the substantia nigra and ventral tegmental area neurons, which are preferentially affected in PD. Moreover, mice with IL-13Rα1 deficiency demonstrated resistance to dopaminergic neuron loss during chronic inflammation, further supporting previous evidence.[148,158,160] In humans, genetic studies have placed the genes encoding this receptor on the X chromosome, within the PARK12 region, known to be a risk factor to PD development.[148,160,161] More recently, Aguirre et al identified in humans two rare SNPs in IL-13 and IL13RA1 genes that were related to early onset PD and increased the cytotoxicity of IL-13 on human neurons in vitro.[161] This data highlights the potential role of both IL-4 and IL-13 as therapeutic targets in Parkinson's disease. Additionally, IL-33 was identified as a possible contributor to neuroinflammation in PD development, in a few in vitro studies. Moreover, increased expression of IL-33 in the midbrain and striatum was found in patients with PD as compared to controls.[153]

In a mouse model of amyotrophic lateral sclerosis (ALS), IL-4 administration induced microglia proliferation with a skew towards embryogenic traits, resulting in improved locomotion and slower disease progression. However, no improved motor neuron or overall survival was observed, suggesting a more complex interplay of cytokines in ALS.[162] Multiple studies have identified that serum IL-33 levels are significantly reduced, and that the ST2 receptor levels are increased in patients with ALS, in contrast to healthy controls.[151,153,154] Interestingly, long-term IL-33 administration to transgenic mice with G93A-superoxide dismutase-1 mutation, specific for ALS development, induced delayed disease onset only in females.[163]

Current available data suggest that IL-4 plays a neuroprotective and anti-inflammatory role in models of experimental autoimmune encephalomyelitis (EAE).[5,164,165] Some studies showed that IL-4 deficit in the CNS of mice led to increased neuroinflammation and a more severe clinical course of the disease.[164,165]

IL-13 was successfully identified in the active lesions in the spinal cord of multiple sclerosis (MS) patients and a positive correlation between IL-13 levels and EDSS scores in relapsing-remitting MS was established.[166] Other studies

observed increased IL-13 production in patients with glatiramer acetate treatment. In animal models, it was demonstrated to have anti-inflammatory effects in EAE mice alone, or in combination with IL-4. A few studies on mice also suggest that IL-13 expression and function might be influenced by gender, with possible implications in the higher female prevalence of MS.[148] Studies have identified high levels of IL-33 and ST2 receptor in the plasma and in the brain and spinal cord lesions (both acute and chronic) of MS patients, as compared to controls. The suggested function of IL-33 was to modulate both the immune response as well as CNS myelination.[149,151,154,167] In MS patients with IFN-β-1a treatment plasma IL-33 levels were reduced.[155] In some animal models, higher endogenous IL-33 production delayed EAE onset and reduced disease severity.[151,154] In other studies on mice, IL-33 antibody administration produced a similar effect, while treatment with IL-33 increased neuroinflammation and worsened the disease course of EAE.[153,154] The exact effect of IL-33 on the remyelination of MS lesions is also controversial, some studies indicating inhibition of CNS myelination, while others indicate favoring of myelin repair.[153–155,168]

A few studies have identified higher expression of IL-33 in the serum and CSF of patients with neuro-Behcet disease (NBD) (in comparison with patients suffering from non-inflammatory neurological diseases), as well as an association with higher levels of specific chemokines.[153,154] However, the exact role of IL-33 in NBD needs further clarifications.

A recent study by Ygberg et al demonstrated that the immunological response to a viral infection matures during childhood and adolescence.[156] In this study, CSF expression of IL-4 and IL-13 was found to increase with age in response to viral infections, suggesting their importance in the risk of developing of long-term sequelae.[168] In their study, Silva et al found that IL-4 knockout mice with experimentally induced neurocysticercosis had lower cerebral edema, lower inflammatory infiltrates and prolonged survival of the parasites in the brain.[169] This indicates that IL-4 is preferentially expressed in response to infections in an attempt to reduce brain damage, possibly explaining the previous observations that asymptomatic patients from endemic areas exhibit increased production of IL-4 and IL-13.

IL-33 has been more extensively studied in different types of infections.[151,153,154,170–173] In cerebral malaria models, IL-33 levels are increased and IL-33 treatment reduced the parasitic load in the early phase of the infection.[151,154] Moreover, ST2 receptor deficient mice did not develop the disease, had a longer survival and displayed no neurological signs or no cognitive impairment in comparison with wild type mice.[171,173] Multiple studies on ST2 receptor deficient mice infected with Toxoplasma gondii observed an increased susceptibility to infection, increased parasite load and encephalitis symptoms.[138,140,142] These findings suggest that IL-33 induces a more severe neuroinflammatory response to parasitic infections and leads to the emergence of brain lesions and neurological signs. One of the proposed mechanisms for IL-33 attenuation by parasitic or viral-induced encephalitis is through the downregulation of the inducible nitric oxide synthase (iNOS) expression in the brain.[172] In the presence of bacterial endotoxins, IL-33 production is increased, while deficits fail to stimulate microglia to produce a proper neuroinflammatory response. In other studies, IL-33 was positively correlated with IL-1b expression, with implications in the pro-inflammatory response to viral infections such as Zika or HIV.[153]

Early studies of IL-4 and IL-13 have discovered increased production in the microglia of the mouse models in response to experimental ischemic lesions, in an attempt to restrict the neuroinflammatory response and neuronal damage.[148,174] An interesting study by Kolosowska et al studied the effects of exogenous IL-13 administration in mice with middle cerebral artery occlusion during the acute phase. The authors conclude that early IL-13 treatment determined a reduced inflammatory infiltration in the ischemic area and reduced lesion volumes, as well as a neuroprotective effect in the peri-ischemic area, with overall improvement of clinical symptoms at 14 days post-occlusion.[174] However, another study demonstrated that IL-13 and IL-4 play no major role in the ischemic stroke outcome in mice with combined genetic deletion of IL-4, IL-5, IL-9, and IL-13.[175] Studies on acute ischemic stroke patients have identified an increase in serum IL-33 and ST2 receptor and further established a negative correlation with lesion volume and patient outcome. In animal models, ST2 receptor deficiency resulted in larger ischemic lesions and more severe behavioral and neurological deficits on the long term. Consequently, many studies on exogenous IL-33 administration in mice found a strong anti-inflammatory effect after experimental ischemia, with reduced neuronal damage and reduced neurological deficits. Other studies even highlight a neuroprotective effect of IL-33 in atherosclerosis pathogenesis in mice. However, IL-33 does not directly exert its action on neurons or glial cells, but through the stimulation of IL-4 production in T-cells in the

brain.[151,153,154] These findings indicate that IL-33 can become a reliable diagnostic and prognostic marker in stroke patients, as well as an early treatment option to reduce long-term effects.

IL-4 and IL-13 are not considered major players in traumatic brain injury recovery.[162] However, more recent studies on mice with TBI who received intranasal IL-4 or IL-13 found reduced neuronal tissue loss, improved white matter integrity and improved long-term functional outcomes, suggesting a more complex interplay than previously regarded and opening new treatment possibilities.[176,177,178] In trauma animal models, IL-33 was found to be immediately released by damaged oligodendrocytes, with consequent influence on local astrocytes and microglia chemokine production. Moreover, IL-33 deficient mice demonstrated larger lesions and impaired recovery after TBI, whereas IL-33 treatment, after experimental TBI in mice, reduced myeloid cell infiltrates, tissue damage and demyelination, with an additional overall improved recovery by inducing Th2 responses and activating meningeal ILC2s. Thus, IL-33 is considered one of the alarms released after injury to activate both CNS and immune cells to promote recovery. In animal models with intracerebral hemorrhage (ICH), IL-33 was found to be predominantly produced in astrocytes and microglia around an intracerebral hematoma. Similarly to cerebral ischemia, IL-33 exerts a neuroprotective effect in mice with ICH, reducing neuronal death, brain edema and pro-inflammatory responses when exogenously administered.[151,153,154] In a recent study on patients with spontaneous ICH, Miao et al found that higher levels of IL-33 were negatively correlated with initial NIHSS severity scores and hematoma volume, characterized better outcomes for patients and even established a cut-off level for poor prognosis.[179] In contrast, in subarachnoid hemorrhage (SAH) models, studies identified high levels of both IL-33 and ST2 receptor in the CSF, along with increased levels of other pro-inflammatory cytokines, suggesting a potential neurotoxic effect of IL-33.[154]

A few studies have identified a relationship between IL-33/ST2 pathway and epilepsy.[153,180–182] Plasma ST2 levels were found higher in patients with increased epileptiform abnormalities after SAH, as well as patients with focal temporal lobe epilepsy.[153,180] Moreover, oxidative stress index, which is significantly higher in patients not responding to antiepileptic drug treatment, was positively correlated with IL-33 levels.[182] Memory performance was also correlated with IL-33 levels in temporal lobe epilepsy.[180] In an animal model of recurrent neonatal seizures, IL-33 administration improved learning, memory, and behavior deficits, as well as body weight gain secondary to seizures by inhibition of apoptosis, endoplasmic reticulum stress, and neuroinflammation.[181] Thus, IL-33 seems to be a new, promising treatment option for reducing the negative impact of recurrent seizures.

IL-31 is a novel cytokine with the special function of connecting the immune system with the skin and the peripheral nervous system, by inducing pruritus behavior, but not directly skin inflammation. Interestingly, the infliction of pain mediated by the Y neuropeptide interneurons determines a reduction in itch perception induced by IL-31 in patients with atopic dermatitis.[183,184] Studies on neurons from the dorsal root ganglions suggest that IL-31 might be involved in neuronal proliferation, survival, and metabolism.[173] However, its importance in neurological conditions needs further research. IL-33/ST2 signaling has been observed to exert a stimulatory effect on sensory neurons, with an increase in the levels of both cytokine and receptor in inflammatory spinal cord lesions in mice. Studies have identified an important role of IL-33 in hyperalgesia induction and neuropathic pain through the modulation of TNF-α, IL-1β in animal models. Moreover, IL-33 is considered one of the inductors of inflammation responsible for cancer-related pain, making it a potential target for palliative treatments development.[151,153,154]

An interesting inverse relationship between allergies and glioblastoma multiforme (GBM) led to the investigation of IL-4 and IL-13. Cell cultures from patients with GBM seem to have a high expression of receptors for IL-4 (IL4Rα) and IL-13 (IL-13Rα2), the latter being found only in glioblastoma cells and presenting as a promising GBM biomarker. Other studies have identified the crucial role of IL-4 in tumor control through the mediation of angiogenesis and eosinophil recruitment, specific polymorphisms being correlated with better survival.[5,148] Studies on IL-33 have deemed it a diagnostic and prognostic marker in specific types of cancer, including gliomas. Multiple studies have identified that the IL-33 and ST2 receptor levels are elevated in tumor tissues in comparison with normal brain tissue, and correlate with tumor progression and decreased survival.[151,153,154] Other studies have identified that IL-33 recruit and activate a large array of immune cells, creating a favorable environment for tumor proliferation.[154,185] A recent study identified that IL-33 significantly reduces the efficacy of temozolomide, an important chemotherapy agent for CNS tumors.[186]

Thus, the development of treatments targeting the blockage of IL-33/ST2 signaling pathway might improve glioma survival.

A very intriguing study by Thurmann et al determined that elevated IL-13 levels during pregnancy increased the risk of children to later develop behavioral problems, especially hyperactive/inattentive disorder. However, the elevated levels of IL-13 were found to occur secondary to an insufficient supply of polyunsaturated fatty acids.[187] More studies are required to elucidate the importance of IL-13 levels during pregnancy. In addition to the previously described roles, IL-33 seems to promote the normal development of the nervous system. Some studies have identified that IL-33 is required for normal synapse numbers and circuit function in the thalamus and spinal cord, while others have highlighted its importance in oligodendrocyte maturation and myelination during the early postnatal period. The IL-33/ST2 pathway also seems to play an important part in sustaining the blood–brain barrier integrity and function. Interestingly, the IL-33 gene is one of the five genes that promote astrocyte differentiation in the human forebrain. In addition, a study on the behavior of IL-33 knockout mice revealed reduced anxiety behaviors and impaired social recognition, despite intact sociability, suggesting the involvement of IL-33 in the normal maturation of the forebrain.[153,188,189]

A recent review of the current literature by Pandolfo et al concluded that elevated IL-33 levels, in humans and animal models, correlate with a change of the phase of specific psychiatric diseases. The authors suggest that when a stressor arises in an individual with genetic susceptibility, an abnormal increase in IL-33 occurs and determines acute symptoms in schizophrenia and affective disorders, as well as the appearance of a new recurrence in major depression disorder.[190] In patients with schizophrenia, IL-33 and ST2 levels have been positively correlated with cognitive performance, but there was difference in the levels of each molecule between patients and healthy controls. Genetic studies have revealed that specific IL-33 polymorphisms can determine a decreased risk of susceptibility to developing schizophrenia, as well as an increased risk of developing major depressive disorder.[151,153,154] Previous studies on IL-33 deficient mice high-lighted the appearance of anxiety and abnormal social behaviors, but the exact implications of IL-33/ST2 signaling pathway in schizophrenia or autism spectrum disorder remain unknown.[151,188] We are still at the beginning of our understanding of the complex relationship between cytokines, neuroinflammation and neurological disorders, but the aforementioned studies have shed light on some pieces of the puzzle. IL-4, IL-13 and IL-33 seem to be a few of the important therapeutic targets of CNS diseases that need to be considered in further research.

IL-4 is a cytokine with pro- and anti-inflammatory effects in the CNS; high serum levels of IL-4 can be found in patients suffering from MCI, AD, DLB, PD. In ALS and EAE, IL-4 has positive effects (such as improving symptoms or a protective role). IL-4 and IL-13 both help in the immune regulation of CNS and are seen as targets for dementia treatment. IL-13 alone is linked to cognitive impairment and reduced reference memory when in low levels. In MS, IL-13 is involved in active lesions, while elevated levels during pregnancy are linked to behavioral problems in children; it also has neuroprotective effects in the peri-ischemic area of the brain in mouse models. IL-31 creates a favorable micro-environment for tumor proliferation. At last, IL-33 has low levels in the serum and CSF of AD patients, is increased in NBD, PD and MS patients. IL-33 is also involved in the maturation of brain tissue, and it activates immune cells for recovery in traumatic lesions.[189,190]

Conclusions

As we can see, interleukins are at the bedrock of a multitude of pathologies across different organ systems and understanding their role will likely lead to novel treatments and better outcomes for our patients. IL-4 promotes fibrosis, atherosclerosis, remodeling of tissues, as well as cognition. IL-13 promotes fibrosis, tissue remodeling, cognition, modulates neuroinflammation, and inhibits atherosclerosis. IL-31 promotes angiogenesis, pruritus, and tissue remodeling. IL-33 acts as an alarm in response to acute stress. The tables below (Tables 2 and 3) summarize the activities these interleukins play and their role in the aforementioned pathologies. As the interleukins rely on their preceding signaling molecules to accentuate their own signal, so too can we draw upon the works and knowledge of preceding researchers in order to further our own practice. New interleukins are being described, and the role of this inflammatory cascade is still coming to light. We hope this multi-discipline review on the role interleukins play in current pathology assists in this scope.

Table 2 Overview of the Activities of IL-4, IL-13, IL-31 and IL-33

Interleukins	Activities					
	Anti-Inflammatory	**Pro-Inflammatory**	**Growth Factor Release**	**Pro-Fibrotic**	**Up-Regulating**	**Down-Regulating**
IL-4	√	√	PDGF	√	p53, p21, JAK/STAT6, bax, caspase-3, −8, 9	
IL-13	√			√	Amphiregulin	
IL-31	√	√	EGF, VEGF	√	Matrix metalloproteinases 1, 3, 7, 25, IL-6, IL-16, IL-32	
IL-33	√	√				bcl-2, iNOS

Note: [12,13,23,31,38–43,48,50–53,83,84,87,89,170].
Abbreviations: IL-, interleukin; JAK/STAT, Janus kinase-signal transducer and activator of transcription; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; iNOS, the inducible nitric oxide synthase.

Table 3 Summary of Key Findings for IL-4, IL-13, IL-31, and IL-33

IL-4	IL-13	IL-31	IL-33
Promotes fibrosis	Promotes fibrosis	Promotes dilated cardiomyopathy (rs4758680 allele)	Alarm factor as a response to stress
Plays a role in fibrotic cardiac myopathy	Promotes cardiac remodeling		Cardioprotective role
Plays a role in hypertensive cardiomyopathy	Inhibits atherosclerosis	Role in cardiac hypertrophy	Beneficial role in pressure-overload cardiac remodeling
Promotes atherosclerosis	May be a possible prognostic marker in myocardial infarction	Key role in Kawasaki disease	Inhibits atherosclerosis
Promotes pulmonary hypertension	Promotes pulmonary hypertension	Upregulates matrix metalloproteinases	Beneficial role in cardiac remodeling post-infarct
Beneficial role in cardiac remodeling post-infarct	Regulates inflammation in myocarditis	Stimulates fibroblasts in SSc	Inhibitory role in atopic dermatitis
Attenuates manifestations in AS	Contributes to inflammation in SLE	Promotes angiogenesis	Possible marker in SSc
Possible role in aggravating lupus nephritis	Possible diagnostic indicator in RA	Promotes pruritus	Aggravates inflammation in RA; may predict response to certain treatments
Attenuates inflammation in RA	Diverse pro-tumor effects	Promotes atopic dermatitis	Promotes cognition
Anti-tumor effects in melanoma	Promotes atopic dermatitis		Promotes motor neuron integrity in ALS
Promotes pruritus- Promotes atopic dermatitis	Key cytokine in systemic sclerosis		Promotes neuroinflammation
Key cytokine in systemic sclerosis	Promotes cognition		Modulates CNS myelination
Protective role in neuroinflammation	May play a role in Parkinson's disease		Reduces CNS Ischaemic damage
Promotes cognition	Protective role in neuroinfections		Role in seizure recovery
May play a role in Parkinson's disease	Increases production of microglia		Promotes neuropathic pain
Neuroprotective role in infections			Role in normal neural development
Increases production of microglia			

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