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Review Article

An overview of inflammation: pathways & gene therapy

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ABSTRACT
When the immune system encounters harmful stimuli such as pathogens, harmed cells, toxins, or radiation, inflammation results, and it serves the twin purposes of removing the stimuli and kicking off the healing process. Inflammatory signal transduction, most commonly the NF-kB, MAPK, and JAK-STAT pathways are triggered by inflammatory stimuli, including infectious and non-infectious ones as well as cell damage. The activation of inflammatory pathways, the production of inflammatory markers, and the attraction of inflammatory cells to the region occur when cell surface pattern receptors detect harmful stimuli. The severity of the inflammatory response is crucial because autoimmunity, excessive tissue damage, and chronic inflammation such as atherosclerosis, diabetes, asthma, etc result from acute inflammation that is unable to control pro-inflammatory stimuli. Any flaw in the inflammatory reaction could shorten life expectancy and induce morbidity. An alternative strategy would involve using transgenes to deliver various therapeutic genes, inflammatory cytokine inhibitors, and other therapeutic medicines locally to the inflammation site. Several viral and non-viral vectors are being used in experimental pharmacology. With an emphasis on gene therapy for diverse inflammatory illnesses, we have explored inflammatory pathways in this article.

Keywords: Inflammation, Signalling pathway, NF-Kb, Gene therapy.

INTRODUCTION
The immune system encounters harmful stimuli such as pathogens, harmed cells, toxins, or radiation, and inflammation results, it serves the twin purposes of removing the stimuli and kicking off the healing process. [1] Cellular and molecular interactions often effectively reduce the risk of harm or infection during acute inflammatory reactions. This mitigation strategy decreases acute inflammation and restores tissue homeostasis. [2] Localized immune, vascular, and inflammatory cells' responses to infection or damage cause redness, swelling, heat, discomfort, and loss of tissue function, which are symptoms of inflammation at the sites of tissue. [3] Leukocyte recruitment and accumulation, inflammatory mediator release, and changes in vascular permeability are all significant microcirculatory events that take place throughout the inflammatory process. When a tissue is injured, the body starts a chemical signaling cascade that encourages actions meant to heal the damaged tissues. These signals cause leukocyte chemotaxis or the movement of leukocytes from the bloodstream to injured sites. These switched-on leukocytes create cytokines that trigger inflammatory reactions. [4]
Effective and well-managed inflammation is a beneficial process that aids in the removal of harmful stimuli and the restoration of normal physiology, which is precisely controlled by an intricate molecular cascade. Each flaw in the inflammatory response has the potential to increase morbidity and reduce lifespan. The intensity of the inflammatory process is crucially significant because if acute inflammation fails to control pro-inflammatory stimuli, this results in chronic inflammation, autoimmunity, and excessive tissue damage. [5] The study of gene therapy is currently at the forefront of medicine thanks to developments in biotechnology. Successfully transferring and expressing a range of human genes into the target cells the prerequisite to effective gene therapy has previously been achieved in several systems. This can be done safely utilizing a variety of viral and non-viral vectors. [6] Even though gene transfer clinical trials have shown these techniques can be utilized to treat a range of inflammatory diseases in a safe and efficient manner.

Molecular Basis Of Inflammation
When an appropriate stimulant, such as microbial infection, external invaders, or any irritant, is present in a host with a functioning innate immune system, inflammation normally begins within minutes. Immune cells such as mast cells, lymphocytes, dendritic cells, macrophages, as well as neutrophils play crucial roles throughout the

inflammatory response since inflammation is predominantly brought through the innate immune system. Inflammatory processes are also aided by non-immune cells such as epithelial, endothelial, and fibroblasts. When a bacterial infection occurs, immune cells use specialized receptors to quickly identify pathogens. Inflammatory cytokines like interleukin-1 & 6 (IL-1, IL-6), chemokines, and tumour necrosis factor (TNF) are produced when pathogen-specific receptors are activated. By altering capillary endothelial permeability and attracting neutrophils and extra plasma (which contains antibodies and complement factors) to the infection site, these mediators significantly speed up the progression of inflammation. [7] Although the details of the first stimulus and its site inside the body have a role in inflammatory response processes, all of them share a similar mechanism that is best described as follows: Inflammatory pathways are engaged, inflammatory markers are secreted, and inflammatory cells are attracted to the location when cell surface pattern receptors recognize harmful stimuli.

Activation of pattern recognition receptors

Pattern-recognition receptors (PRRs), which are made by immune system cells from both the innate and adaptive types are created. These are specialized trans-membrane receptors that serve as the first line of defence against inflammatory stimuli for host cells. The germline-encoded receptors defined as PRRs are capable of detecting both cellular damage and infectious microbes. [8] PAMPs, which stand for pathogen-associated molecular patterns and are universally conserved in microorganisms, are used in the diagnosis of infections. Recent research has shown that PRRs are also responsible for identifying endogenous substances produced by wounded cells, sometimes known as damage-associated molecular patterns (DAMPs). [9] As of right present, PRR families are split up into four main categories. These families include cytoplasmic receptors such as NOD-like receptors (NLRs) and retinoic acid-inducible gene (RIG)-I-like receptors as well as trans-membrane proteins such as C-type lectin receptors (CLRs) and toll-like receptors (TLRs). [3] TLRs undergo conformational changes after ligand binding, which are necessary for the recruitment of adaptor molecules with TIR (Toll/interleukin-1 receptor/resistance protein) domains to the TIR domain of the TLR. [10] Four adaptor molecules exist: MyD88-adaptor-like (MAL), TIR-domain-containing adaptor protein producing IFN-b (TRIF)/TIR-domain-containing molecule 1 (TICAM1), TIR-associated protein (TIRAP), and TRIF-related adaptor molecule (TRAM). [11]

The creation of a complex containing TNFR-associated factor 6 (TRAF6), IL-1R-associated kinase (IRAKs), and interferon regulatory factor 5 (IRF-5) is triggered when TIR-domain-containing adaptors like TIRAP and MyD88 are drawn to the receptor by its ligands. [10] TRAF6 performs as an E3 ubiquitin ligase in the presence of the E2 ubiquitin ligase complex composed of UEV1A and UBC13 and catalyzes the formation of the K63-linked polyubiquitin chain on both TRAF6 and IKK-g/NF-kB essential modulator (NEMO). The TAK1 complex (TGF-b-activated kinase 1) is stimulated by this ubiquitination, and when it is activated, it phosphorylates NEMO by the IKK complex. [12] Inhibitor of nuclear factor-κB (IkB) that has been phosphorylated is degraded by the proteasome and K48-linked ubiquitination. Pro-inflammatory cytokine genes begin to express themselves as a result of freed NF-kB translocating into the nucleus. TAK1 simultaneously activates AP-1 and the MAP kinase cascades, two steps required for the activation of cytokine genes. Type I IFNs and proinflammatory cytokine genes are activated by TRIF, which also activates NF-kB and IRF-3. [13,14]

Activation of inflammatory pathways

Inflammatory stimuli that activate intracellular signaling pathways result in the production of IL-1, IL-6, and TNF, which are inflammatory mediators. These cytokines interact with TLRs, IL-1 receptors, IL-6 receptors, and TNF receptors to cause inflammation. [15] Nuclear factor kappa-B (NF-kB) and mitogen-activated protein kinase (MAPK) pathways, as well as Janus kinase-signal transducer and activator of transcription (JAK-STAT), are all activated by receptor activation. [16,17]

NF-κB pathway

The NF-kB family contains three proteins with transactivation domains: c-Rel, Rel B, and p65. Other relatives of this family like p50 and p52 have DNA dimerization and binding domains, but their transactivation domains are not as strong. [18] The majority of NF-kB proteins are present in the cytoplasm of cells and they are connected to the IkB group of inhibitor proteins (IkBα, IkBβ, and IkBε). The NF-kB proteins are kept in their cytoplasmic localization by the IkB proteins, which obstruct the NF-kB nuclear localization signal. [19] IkB kinases (IKK), whose activity is substantially stimulated by substances like TNF-α and IL-1b that promote the NF-kB pathway, regulate the phosphorylation of the IkB proteins. [20,21] The related modulatory protein, IKKγ or NEMO, and the two kinase subunits, IKKα and IKKβ, make up the IKK complex. These kinases share 52% amino acid identity and kinase, leucine zipper, and helix-

loop-helix domain structural similarities. IKKα and IKKβ can interact with each other through their leucine zipper domains to create both heterodimers and homodimers. [22]

Specific serine residues in each IKK subunit activation loop are phosphorylated when cells are treated with substances that activate the NF-kB pathway. [23] The IkB proteins are subsequently phosphorylated by IKK on two nearby serine residues in the amino terminus, causing their ubiquitination which was followed by the 26S proteasome's elimination of them. In the nucleus, these proteins attach to particular components in the promoter regions of the target genes to activate gene expression. This process results in NF-kB translocation. [20-24] Phosphorylation of serine 276 by protein kinase A in p65 promotes the protein associated with the co-activator protein CBP, increasing p65 transcriptional activity and the transactivation domain of p65 residues can be directly phosphorylated by the IKKs. [25] In addition to phosphorylating the NF-kB precursor p105, stimulation of IKK kinase activity can also result in p50 being processed and translocated to the nucleus more quickly. As a result of these findings, it is clear that p65 and p105 phosphorylation play an important role in the NF-kB pathway activation. [26]

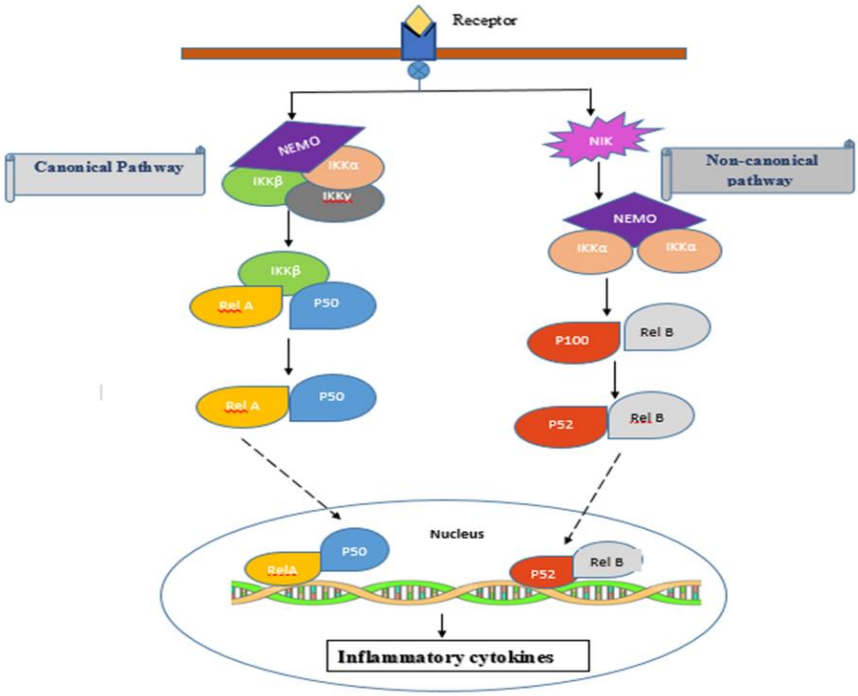

Figure 1: Overview of nuclear factor-κ B activation pathways.

MAPK pathway

Dual specificity kinases phosphorylate threonine and tyrosine in a Thr Xaa-Tyr motif in a loop close to the active site to activate MAPKs, which are proline-directed threonine and serine protein kinases. [27] At least a few of the mammalian-specific MAPK subfamilies include p38 isoforms (p38s), extracellular signal-regulated kinase 5 (ERK5), and c-Jun N-terminal kinases (JNKs). [28] Signal-regulated kinases that are outside of cells in almost all organs, ERK1/2 isoforms are expressed. ERK1 and ERK2, which share 83% of their protein sequences, are controlled by comparable chemical signals and have similar roles in many different contexts. [29] It is commonly acknowledged that many extracellular activators, including hormones and growth factors, primarily activate ERK1/2 through the Ras-Raf-MEK module. Ras can be recruited and phosphorylated by plasma membrane-based receptor tyrosine kinases, which are activated by extracellular signals. Raf is then recruited by Ras and phosphorylated. Raf then phosphorylates the MEK1/2 enzyme downstream, which in turn phosphorylates the Thr-Glu-Tyr (TEY) sequence on ERK1/2, activating it. [29,30]

JNK1, JNK2, and JNK3 are three genes that have their mRNAs alternatively spliced to create at least 10 different JNK isoforms. [31] On tyrosine and threonine, upstream kinases MKK4 and MKK7 phosphorylate JNK. [32] Many upstream kinases are known as MAP3Ks, including MEKK1, MEKK2, MLK1, MLK2, and MLK4, phosphorylate, and activate MKK4 and MKK7, which in turn are activated. [33] The caspase inhibitor c-FLIP is degraded by the E3 ubiquitin ligase Itch in response to TNF-α stimulation, and this has been

demonstrated to be facilitated by JNK activation. [34]

Four p38 MAPKs exist: two that are 75% homologous, α and β, and two that are more distantly related, γ and δ. The same upstream kinases, MKK3 or MKK6, activate all of them in response to both inflammatory and stressful stimuli. [35] The p38γ and δ variants are more efficient than downstream kinases at phosphorylating transcription factors such as Elk-1, stress-activated protein kinase-1 (SAP-1), and activating-transcription-factor (ATF)2. Regulating the expression of genes involved in the inflammatory response post-transcriptionally is one of p38α and likely β main roles. [36] Phosphatases, particularly the MAPK phosphatases, also known as dual specificity phosphatases, inactivate MAPKs. Corticosteroids and inflammatory stimuli both activate the dual-specificity phosphatase-1 enzyme. [37,38]

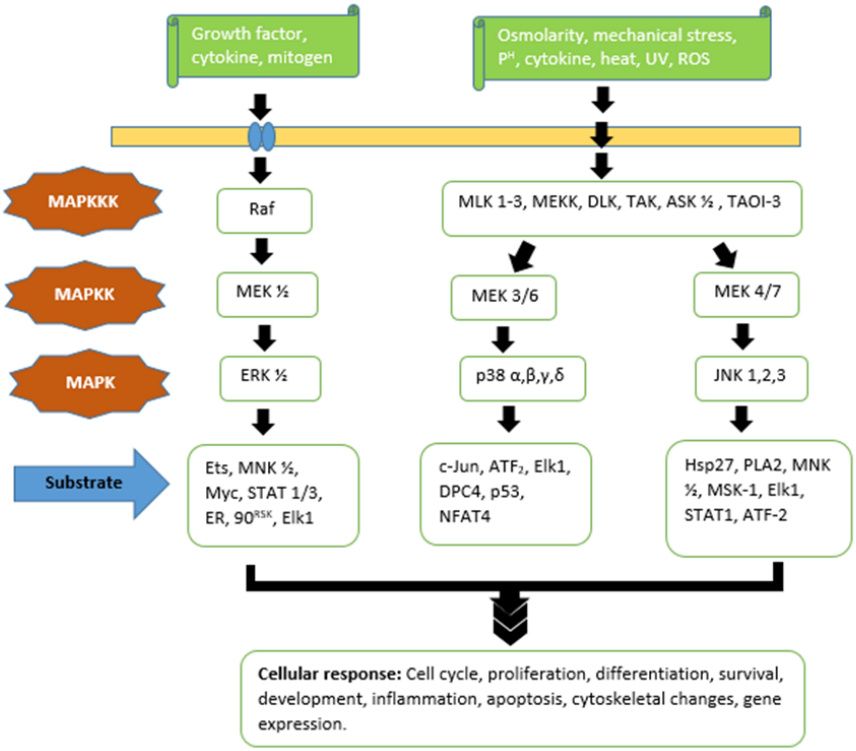

Figure 2: MAP kinase cascades.

JAK/STAT signaling pathway

This signaling pathway is composed of three main components: JAK, tyrosine kinase-associated receptor, and STAT. [39] JAK1, JAK2, JAK3, and Tyk2 are the four primary members of the JAK family, each of which has about 1000 amino acids. [40] The cytokine-stimulated signal transduction pathway is JAK/STAT signaling, also known as the IL-6 signaling route. [41] Each JAK protein has four domains: a four-point-one, ezrin, radixin, and moesin domain at the N-terminus, an SH2 domain, a pseudokinase domain, and a traditional protein tyrosine kinase domain. [40] One of the most important cytokine-activated transcription factors in the immune response is JAKs, and it has a downstream target in the cytoplasm called the STAT family. Seven individuals make up the group: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. [42] The following domains make up the majority of the structurally functional regions of STAT proteins: an N-terminal conserved domain, an SH3-like domain a DNA-binding domain, an SH2 domain, and a C-terminal transcription domain. [43]

The JAK/STAT pathway is activated by numerous ligands, such as cytokines, growth hormones, growth factors, and their receptors. Two JAKs are sufficiently close to one another for trans-phosphorylation, the binding of cytokines to their receptor sites takes place during ligand-mediated receptor multimerization and activates JAKs. [44] The phosphorylated JAK activates the receptor and phosphorylates its primary substrate STAT. Then it has been phosphorylated and forms dimers with other STAT family members, that have conserved SH2 domains. The dimer is subsequently moved into the nucleus where it attaches to particular DNA sequence adjustment zones to either inhibit or activate the target genes' transcription. [45]

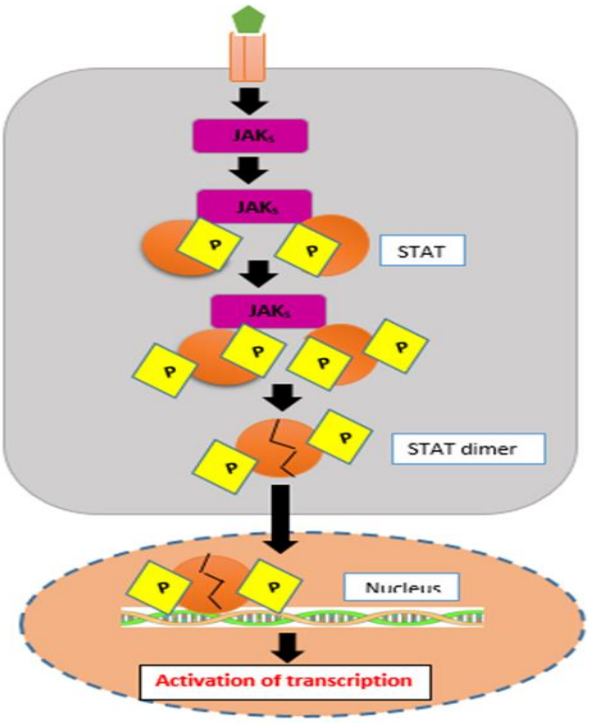

Figure 3: JAK/STAT signaling pathway

Release and recruitment of inflammatory mediators and cells

Cells respond to the inflammatory process by releasing specialized chemicals such as vasoactive amines, pro-inflammatory cytokines, an acute-phase protein, peptides, and eicosanoids. These chemicals mediate the inflammatory process by halting additional tissue damage. [45] Numerous cell activities are significantly influenced by cytokines. But because of their function in immune system regulation, they are particularly significant. Acute-phase response is also released as a result of cytokine production. The most notable secretions produced by these interactions are IL-1, IL-8, TNF-α, IL-6, and IL-12. [46]

Strategies For Gene Delivery

Both viral and non-viral vectors can be used to deliver appropriate genes. In place of the viral wild-type genes, the target genes are carried via virally generated transfection vectors. Thus, vectors merely transfer the desired genes into the host cell and do not replicate within it. Adeno and adeno-associated, retro, lentiviruses are commonly used in gene therapy. [46] The genome of the host cell becomes permanently expressed with the help of the retroviruses' integration of their DNA. The only cells in which they may integrate their DNA are mitotic cells. [47] Lenti viruses, a subgroup of retroviruses, can infect both dividing and non-dividing cells. Adenoviruses can encase up to 30 kilobases (kb) of exogenous material, but retro- and lentiviruses may only inject 8 kb of exogenous material. [48] Adenoviral vectors have the drawback of inducing both an acquired and innate immune response, which contributes to the transgene's limited expression. The adeno-associated virus gets around these constraints. [49] Lipoplexes, polyplexes, and liposomes are non-viral vectors. Mammalian cells' anionic plasma membranes absorb lipoplexes and polyplexes through electrostatic interactions. Thus, lipoplexes and polyplexes typically produce a higher level of transfection in a variety of cell lines compared to anionic liposomes, which encapsulate nucleic acids. [50] In contrast to viral vectors, the time that the responsive gene expression lasts is rather brief. Non-viral vectors, however, have the benefit of not triggering an inflammatory reaction in the host and having the capacity to carry foreign material of basically infinite size. [51] Another method of transferring genes is to give naked plasmid DNA. This method nearly never triggers an immune reaction, but the transfection effectiveness is relatively low, and methods to increase the efficiency, like electroporation, can cause significant tissue damage. [52]

Target For Gene Delivery

Atherosclerosis

A comprehensive investigation revealed that *in vivo* adenoviral nitric oxide synthase(NOS) gene therapy increased the migration of monocytes and lymphocytes in rabbits fed a diet high in cholesterol

in addition to increasing the expression of adhesion molecules like intracellular adhesion molecule 1 (ICAM) and vascular cell adhesion molecule 1 (VCAM-1). [53] Furthermore, it was shown that *ex vivo* liposome-mediated eNOS gene transfection in a rabbit heart decreased leukocyte infiltration, which was connected to a reduction in NF-kB activation as well as an increase in endothelial ICAM and VCAM expressions. [54]

The ability to transfer the genes for antioxidant enzymes like catalase(CAT), glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), and superoxide dismutase (SOD) has shown promise for the treatment and prevention of atherosclerosis. This is partly a result of the reduced inflammatory processes. [46] By delivering the SOD gene to endothelial cells, positive benefits were seen *in vitro*, including decreased low-density lipoprotein oxidation and decreased VCAM expression. [55,56] However, manganese SOD gene transfer only effectively treated endothelial dysfunction when atherosclerotic plaques weren't present. [57] Studies done *in vitro* showed that oxLDL-induced smooth muscle cell growth and cytotoxicity were reduced by catalase gene delivery. [58,59] By preventing the redox-sensitive transcription factor AP-1, catalase may prevent atherosclerosis by decreasing both the death of endothelial cells and oxidative stress. [60] NF-kB activation, hydroperoxide-induced apoptosis, [61] and basal and IL-1-induced VCAM-1 expression were all reduced by *in vitro* GPx gene transfer to rabbit aortic smooth muscle cells. [62] Over-expression of GPx in endothelial cells decreased apoptosis and repaired the defective homocyst(e)ine induced endothelium-dependent relaxation. [63] Anti-ischemic and anti-ischemia-reperfusion damage protection was provided by HO-1 gene delivery. [64] Delivering the HO-1 gene may have impacted by lowering oxidative stress [65,66] and increasing eNOS expression, which will decrease endothelium apoptosis, activation, and dysfunction. [67,68]

The redox-sensitive transcription factor NF-kB regulates the expression of genes linked to inflammation during atherogenesis, including adhesion molecules, chemokines, and cytokines. [69] NF-kB is inactivated using a recombinant double-stranded DNA with a strong affinity for the transcription factor that is introduced as a decoy-cis element. This DNA binds to the transcription factor as well as prevents its expression. [70] Nevertheless, *in vitro* up-regulation of IkB-alpha through adenoviral gene transfer of secretory leukocyte protease inhibitor (SLPI) and elafin inhibited the activation of NF-kB, which led to decreased levels of IL-8 and TNFα in macrophages and endothelial cells, respectively. [71] More recently, NF-kB decoy oligonucleotides were enclosed in echogenic liposomes, where the application of ultrasound at a particular region might trigger the release of the drug and increase absorption. This approach has the potential to be effective in mediating the regulation of NF-kB directly in an area that is prone to atherosclerosis. [70] PPARγ partially blocks the actions of the transcription factors AP-1, STAT, and NF-kB to prevent the production of pro-inflammatory genes in macrophages. [72] Adeno-associated virus [73] or Hemagglutinating virus of Japan-liposome intramuscular injection decreased the atherosclerotic plaque area and the infiltration of macrophages in apoE-deficient mice. This anti-atherogenic impact was associated with a decreased expression of the genes for IL-12, IFNγ, and MCP-1. [74] A chemokine called MCP-1 regulates the influx of monocytes into the artery wall during atherogenesis. As a result, gene delivery techniques have been used to try to abolish the MCP-1 pathway, which is a very intriguing therapeutic approach. [75] A human MCP-1 gene mutant with an N-terminal deletion (7ND-MCP-1) that prevents MCP-1-mediated monocyte chemotaxis has been created. [76] Reduced MCP-1 and VCAM-1 expression was seen in human aortic endothelial cells following the activation of genes responsible for atheroprotection by nuclear Factor-Erythroid 2-Related Factor 2 (Nrf2) adenoviral gene transfer. [77] Similar to this, *in vivo* Nrf2 activation suppressed VCAM-1 signaling in atheroprotected areas of the mouse aorta that are characterized by laminar flow. [78]

Rheumatoid Arthritis

The overexpression of inflammatory cytokines by immune cells that are activated and fibroblast-like synoviocytes (FLSs) is thought to be a key factor in the onset and development of rheumatoid arthritis (RA). [79] One of the widely used approaches to treating RA is the suppression of pro-inflammatory cytokines and the amplification of anti-inflammatory cytokines. [80] In collagen-induced arthritis (CIA) animal studies in mice and rats, the reduction of IL-18 [81], IL-33, and IL-19 [82] has shown a significant therapeutic impact, but no clinical trials have been carried out so far. [83] Despite high inflammatory levels, IL-4 and IL-10 gene therapy in CIA animal models showed joint protection and prevented cartilage degeneration. [84] MiRNAs may control the synthesis of matrix metalloproteinases (MMPs), cytokines, and chemokines. RA-FLSs had higher levels of miR-203 than FLSs from healthy donors at the basal level, and this overexpression in RA-FLSs resulted in significantly higher levels of IL-6 and MMP-1. [85]

In RA-FLSs, TNF-α enhanced the activity of the miR-17∼92 cluster, which was regulated by the activated B cell transcription factor NF-kB. MMP-1 and the pro-inflammatory cytokines IL-8 and IL-6 both are upregulated in RA-FLSs after being transfected with the precursor of miRNA-18a, a member of the miR-17∼92 cluster. [86] As a blocker of TNF-α signaling, MiR-17 attacked the ubiquitin-proteasome system. The synthesis of MMP-1, MMP-13, and IL-6, IL-8 that is stimulated by TNF- α in RA-FLSs is reduced by transfection with miR-17 precursor. This demonstrates the potential protective effect of miR-17 in the degeneration of cartilage. [87] FLSs overexpress the antisense RNA zinc finger NFX1-type containing 1, which positively controls FLS invasion and migration. In the peripheral blood mononuclear cells of people with clinical RA, nuclear enriched abundant transcript 1 (NEAT1) is overexpressed. Inflammation was reduced in CIA mice by NEAT1 lncRNA silencing because it limited immune cell differentiation. [88]

Adenoviral vector-based intra-articular (i.a) gene therapy has recently been investigated, in adjuvant arthritis rats to see if local constitutive production of IFN-β might have any positive effects. [89] It was proven that transferring IFN- β, cDNA through an adenoviral vector into the synovium decreased arthritic activity. IFN- β gene treatment also protected against the degeneration of joints. [90] The severity of murine CIA was reduced when decoy oligonucleotides for NF-B were administered i.a. In accordance with these findings, a potent NF-kB inhibitor called SP100030 significantly reduced joint edema in mice with CIA. [91] By lowering levels of TNF-α and IL-1β, removing joint edema, and minimizing joint damage, the NEMO peptide dramatically lessened the harshness of CIA in mice. [92] The NEMO binding domain peptide was administered intravenously to rats with adjuvant arthritis, and it greatly decreased the severity of arthritic activity and radiological damage. [93] In Rhesus monkeys with CIA, the specific promotion of synovial apoptosis has been investigated by local delivery of adenoviral vectors encoding TNF-α related apoptosis-inducing ligand, the tumour suppressor protein p53, Fas-associated death domain protein, phosphatase, and tensin homologue, a repressor of PI 3-kinase/Akt signaling pathway responsible for cell growth, proliferation, and survival, or all of these methods demonstrated a reduction in inflammatory cell infiltration, an increase in synovial apoptosis, and stimulation of cartilage to produce new matrix, which all contributed to the improvement of arthritic symptoms. [94] For arthritis gene therapy, natural angiogenesis inhibitors are promising candidates. High concentrations of hypoxia-inducible factors which are generated in response to tissue hypoxia, increase the activity of vascular endothelial growth factor. As a result, preventing angiogenesis is probably a good way to lessen inflammation and the severity of the disease. [95]

Asthma

The main cause of allergic airway reactions was shown to be an imbalance of T-helper types 1 and 2 (Th1 & Th2), which generate IFN and IL-4, IL-5, and IL-13. Since regulatory T cells (Tregs), TGF-β (transforming growth factor), and IL-17 secreting Th17 cells implicated in neutrophilic inflammation in asthma, which release inhibitory IL-10, the situation has become more complex. But this also presents new avenues for intervention. [96] Recent research has shown that treating a subset of severe asthmatic patients with anti-IL-5 antibodies lowers the aggravation rate in those who have recurring exacerbations and is proof of eosinophilic airway inflammation. [97] Airway hyper-responsiveness (AHR), cellular invasion of lung tissue, eotaxin concentration in broncho-alveolar lavage (BAL), & pulmonary IL-5 mRNA can all be decreased in a mouse model of allergic inflammation by intravenously administering lentiviruses that express siRNA against the IL-5 receptor. [98] In a rat model, it has been shown that antisense IL-5 or IL-4 treatment administered systemically by a recombinant, adeno-associated virus decreases allergic inflammation, IL-5/IL-4 production, along with airway remodeling. [99] Another significant phase 2a study found that inhaling TPI ASM8 (Topigen Pharmaceuticals/Pharmaxis, Frenchs Forest, Australia), which contains two altered phosphorothioate antisense oligonucleotides that inhibit CCR3 (receptor for eotaxin) and the common chain of the IL-3, IL-5, and GM-CSF receptors, can lessen allergen-induced airway eosinophilia. [100]

The transcription factor STAT series of signal transducers and transcriptional activators participates in a wide variety of signaling processes. By activating the characteristic T-cell transcription factors (T-box expressed in T cells [Tbet], retinoid-related orphan receptor **γτ** [ROR] and Guanosine, adenosine, thymidine, adenosine (GATA-3), forkhead box P3 which play a significant role in T-cell development, they may be used as therapeutic targets. [101] IL-4-/IL-13-preactivated human lung epithelial cells' ability to express eotaxin mRNA might be suppressed *in vitro*, according to research, by using STAT6 siRNA to silence the STAT6 gene. This suggests that mucosal cells may respond to this method in persistent chronic asthma-associated lung inflammation. [102] Additionally, it was demonstrated that GATA-

3-specific DNAzyme and short hairpin RNA reduced asthmatic inflammation in a mouse model. [103] Recent research using a decoy oligonucleotide inhibiting STAT1 and STAT3 transcription factors decreased allergy inflammation and lung CD40 expression in an animal model of OVA-induced allergic inflammation. [104] Dendritic cells offer an appealing target for treating allergic airway disorders given their crucial role in triggering and maintaining Th2 responses. [105] Dendritic cell-T-cell interaction must last long enough and be strong enough to cause T-cell differentiation and division. These extra signals can come from co-stimulatory molecules like CD80, CD86, and CD40. In a mouse asthma model, targeting CD86 with inhaled antisense oligonucleotides lowered AHR, pulmonary inflammation, mucus production, and BAL eotaxin levels while suppressing CD86 activation of eosinophils, macrophages, and dendritic cells. [106] Following activation of a variety of membrane receptors (such as the FcRI receptors and the tumour necrosis factor receptor), sphingosine kinase (SphK) regulates intracellular sphingolipid levels. When lymphocytes, eosinophils, and mast cells migrate, SphK plays a crucial role. In a mouse model of allergic asthma, SphK blocking by siRNA decreased Th2 cytokines, allergen-specific IgE, and pulmonary inflammation. [107]

Diabetes

Preventive, adjuvant, and curative gene therapy techniques can be used to treat diabetes. Curative approaches involve resuming insulin production and secretion by affecting insulin transgene expression or by inducing islet neo-genesis ectopically, whereas preventive and adjunctive approaches primarily solve the autoimmune pathogenesis of type I diabetes and the immune function to islet grafts post-transplantation, respectively. [108] IL-1 antagonism and salsalate-mediated NF-kB regulation are now two methods that have demonstrated how a focused regulation of inflammation may ameliorate the condition. [109] The ability of these treatments to improve insulin secretion in those with diabetes and pre-diabetes, as well as insulin sensitivity, together with a reduction in HbA1c, has been demonstrated in numerous trials utilizing the IL-1 receptor antagonist (IL-1Ra) as well as salsalate. [110] Inflammatory cytokines and hyperglycemia both boost twelve-Lipoxygenase (12-LO) expression. [111] Insulin resistance and adipose tissue inflammation have both been linked to 12-LO activation. Gene deletion and pharmacological 12-LO suppression reduced the onset of diabetes in NOD mice (a T1DM model), Zucker diabetic fatty rats, and diet-induced obese mice (a T2DM model). [112] Histone deacetylases (HDAC) I, IIA, IIB, III, and IV play a role in inflammation in a number of illnesses, including diabetes. Although there are no human studies yet, animal studies have shown that HDAC inhibition helps to preserve cells. Additionally, linkage research has shown that HDAC2 is close to a locus in 6q21 that is linked to both T1DM and T2DM. HDAC IIA inhibitors have been shown to increase beta cell mass. [113] Sirt1 activation may serve an anti-inflammatory role in the islets. After exposure to cytokines, sirt1 expression has been found to decrease in pancreatic islets, preventing NF-kB mediated cytokine-induced β-cell damage. [114] Caenorhabditis elegans-expressing FAT-1 transgenic mouse with the FAT-1 gene, which codes for an enzyme that transforms n-6 to n-3 fatty acids, exhibited increased synthesis of n-3 PUFA. After numerous low-dosage STZ injections, this has been discovered to safeguard against the onset of diabetes and shows decreased levels of IL-1, TNF-α, NF-kB, and 12-HETE. [115]

These adipose-mesenchymal stem cells underwent morphological changes when pancreatic duodenal homeobox1 (PDX-1) has been injected; cluster formations were seen and cells started to congregate, indicating some crucial processes necessary for the growth and differentiation of the pancreas. This kind of stem cell can be further grown into cells that produce insulin since it is widely accessible and capable of expressing the PDX-1 gene. [116]Numerous insulin-secreting duct structures formed in the liver and diabetes entered remission when the PPAR agonist was supplied along with Pdx1, Ngn3, and MafA3 genes. This is due to the fact that these genes drive pancreatic development, which in turn promotes the maturation of beta cells and the production of endocrine precursor cells. [117] Hematopoietic stem cells (HSCs) and the proinsulin II gene were used in the transplantation in another investigation. To examine sialitis, an inflammation of the salivary gland and insulitis, an inflammation defined by the entry of immune cells into and surrounding the islets, these HSCs were engineered to express the proinsulin II gene. They were subsequently implanted into non-obese diabetic mice. [118] To treat diabetic RIP-GP mice, which produce the glycoprotein of the lymphocytic choriomeningitis virus and the insulin promoter from rats, a recent study combined the GAD65 DNA vaccination with an anti-IL-1 antibody. The results show that diabetes is protected against by the anti-IL-1/GAD65 DNA vaccination combination, but not by anti-IL-1 monotherapy. [119]

CONCLUSION

It is generally known that the inflammatory reaction is typically triggered in response to two different types of stimuli, such as damage and infection. Inflammation is primarily mediated by three pathways: NF-kB, MAPK, and JAK-STAT. Diseases related to inflammation can result from the deregulation of any or all of these processes. A better knowledge of both the molecular mechanisms as well as pathways underlying the inflammatory response would enable the prevention and treatment of inflammatory diseases. Inflammation commonly plays a crucial role in the pathological development of illness and has emerged as a crucial therapeutic target for the development of cutting-edge pharmaceutical therapies.

Gene therapy has made significant contributions to basic research, and its use as a key experimental tool will facilitate the creation of direct therapeutic applications. Although clinical trials using both intra and *ex-vivo* gene transfer have demonstrated that these technologies can be used safely and effectively to treat a variety of inflammatory illnesses, some important drawbacks prohibit their implementation in clinical settings. With multiple potential benefits beyond systemic approaches of targeted therapy, local delivery of therapy chemicals via gene transfer is a valuable direction to treat a variety of diseases. The treatment of life-threatening neurological illnesses caused by a single mutated gene shows significant promise when using gene therapy.

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