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INFLAMMATION: A POTENTIAL SCENARIO ON NOVEL TARGETS AND TARGETED DRUG THERAPY

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ABSTRACT: Inflammation is the vascular event shown by the body against the external material by activating different cells and releasing various chemical mediators to prevent noxious effects. Many drugs like steroidal and non-steroidal drugs are available till the date to treat inflammation but have a number of side effects and centralized on to counteract the COX and LOX pathways. This perspective will use to search for new drugs that can work to target other pro-inflammatory mediators involve in inflammation and act as target for the inhibition of inflammatory processes and minimize the side effects. The therapeutic targets are any proteins, receptors, pro-inflammatory mediators or enzymes that can be involved in the inflammatory reaction. The targeted therapy acts on it and inhibits targets to combat the inflammation. The recent study assembles the data on novel targets and future anti-inflammatory drugs and the best treatment for incurable inflammatory diseases.

INTRODUCTION: Inflammation is the patho-physiological response of vascular tissues to any injury, infectious agents, or chemicals and involves the five characteristic signs as redness, swelling, fever, pain, and loss of function. The inflammation is the defense mechanism of the body and also involve in the healing mechanism of the body; it prevents any noxious effects due to external material [1]. However, if untreated it may produce diseases like rheumatoid arthritis, inflammatory bowel diseases, *etc*. The mechanism of inflammation involves number of cells of body and their secretions to produce inflammatory signs.

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The most important cell involved in the inflammatory reaction is the mast cells and release histamine in response to stimuli [2]. The steps involved in the mechanism of inflammation as shown in **Fig. 1**.

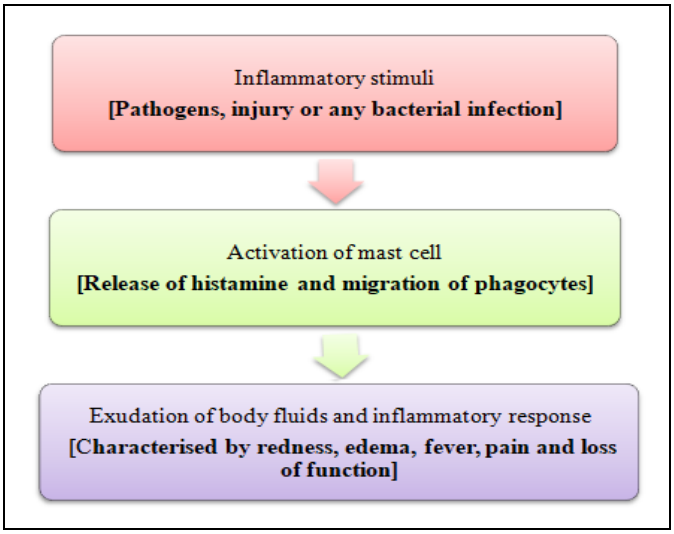

FIG. 1: MECHANISM OF INFLAMMATION

The steroidal and non-steroidal anti-inflammatory drugs are helpful to minimize the symptoms of inflammation. The salicylates were the active compound in the 19th century and discovered from the Willow species and synthesized into the aspirin [3]. The inhibition of the mediator prostaglandin was the mechanisms of NSAIDs were developed in 1970. The drugs to control selectively the COX-2 and COX-1 that is central to physiological processes and whose inhibition was considered a major factor in the development of adverse reactions were discovered and developed in 1990s [4]. The drugs from analgesics such as aspirin and other NSAIDs nowadays have been restricted due to their potential side effects. The gastrointestinal ulceration and bleeding, hypertension, hyperglycemia, renal damage is most common side effects of the non-steroidal anti-inflammatory drugs [5, 6]. Besides these side effects, the greatest disadvantage in presently available potent drugs lies in their toxicity and reappearance of symptoms after discontinuation.

The biochemicals play vital role in the progression of inflammation like interleukins [7, 8], tumor necrotic factors [9], MAP kinases [10-12], matrix metalloproteinases, *etc*. Pathophysiological studies indicate the presence of other chemical mediators and inhibition of such mediators can relief inflammatory diseases, thus offering new targets for anti-inflammatory drugs. Therefore, the present review gathers information on the novel targets of anti-inflammatory drugs and the future anti-inflammatory agents to treat chronic and incurable inflammatory diseases.

Novel Targets of Anti-Inflammatory Agents:

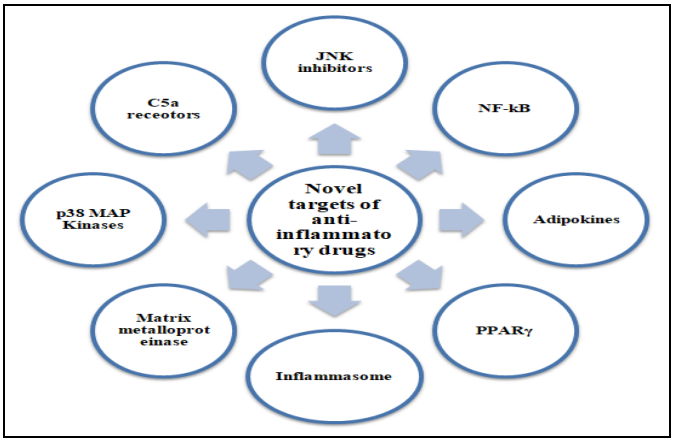

FIG. 2: NOVEL TARGETS OF ANTI-INFLAMMATORY AGENTS

C5a Receptors: C5a is a 74 amino acid protein that is superfluous during the inflammation reaction, and both C5a and C3a show their potential by binding with receptors located on the surface of cells. C5a plays a crucial role in variety of inflammatory reactions and serves up as a target to battle processes [13, 14]. The recruitment of neutrophils and stimulation of mast cell for degranulation to release histamine which causes vasodilation and muscle contraction due to activation of complement anaphylatoxins produces chemotactic agents [thesis Finckh 2009]. The C5a receptor antagonists attract the attention of new targets to design anti-inflammatory agents. The C5a interaction its receptor is well understood, a two-site binding model has been proposed and C-terminal region of C5a may fit into a binding pocket formed around the fifth transmembrane domain effector site [15]. C5a receptor antagonists are of two types such small peptides and non-peptides. Few reports indicate that anti-C5a antibodies block C5a actions which inhibited the complement, induced inflammation in rats and primates [16] and also resulted in decreased polymorphonuclear cell activity *in-vitro* including chemotaxis, chemi-luminescence and lysosomal enzyme release [17].

Based on the C5a and C5a receptor interactions, designed peptide antagonists consisting of 64-75 amino acids of carboxy-terminal of C5a [18]. Modification at the tail would make antagonistic property retaining other peptide portions intact. C5aRAM a monomer and C5a RAD a dimmer these new C-terminal tail truncated cysteine-containing antagonists have been reported to have antagonistic activity on neutrophils *in-vivo* without agonistic activity with Ki 79 [19].

A cyclic small, six amino acids peptide, AcPhe [L-ornithine-Pro-D cyclohexylalanine-Trp-Arg] and AcF-[OPdChaWR] effective against C5a and LPS-induced neutropenia. This was acetylated analog of F-[OPd-ChaWR] with better metabolic stability and intravenous administration of this compound also reduced the serum TNF-α level [20].

Many non-peptide small molecules have been synthesized and screened for C5a receptor antagonistic activity. The synthesis of N-(4-dimethyl amino) phenylmethyl N-(4-isopropyl)-phenyl-7-methoxy-1, 2, 3, 4-tetrahydronaphthalen-

1-carboxamide that inhibited binding of ^{125}I-labeled C5a to human neutrophils with Ki 2.2 nM. The C5a induced Ca^{+2} mobilization, chemotaxis, and superoxide species generation in human neutrophils also inhibited [21]. Substituted 4, 6-diamino-quinolines were stated to possess weak C5a antagonistic property targeting the site 1 binding region of the C5a receptor [22].

p38 MAP Kinases: A member of MAP kinase involved in multiple signaling processes, which is activated in inflammation by LPS, stress or cytokines [23]. The production of pro-inflammatory cytokines takes place due to the activation of p38 MAP kinase along with capsase-1 which is involved in apoptosis of cells and activation of transcription factors [24, 25]. p38 MAP kinases were involved in LPS-induced mesencephalic neurons death in rats [26] and phosphorylation of transcription factors responsible for 5-LO synthesis [27]. Increase expression of COX-2 has been reported due to oxidative stress in antigen-stimulated mast cells is mediated by p38 MAP kinases resulting in increased levels of eicosanoids [28]. Hence, inhibition of p38 MAP kinase forms a new strategy for treatment of inflammatory disease [29, 30].

Pyridinyl imidazole as aryl or hetero aryl-substituted imidazoles has been identified as potential leads for p38 MAP kinase inhibition [31]. Isotopically labeled studies revealed that imidazole bind to p38 is molecular target, but previously triaryl imidazoles were known as cytokine production inhibitors. Generally pyridine at the Ar1 or Ar2 demonstrated better p38 MAP kinase inhibition activity which is attributed to strong hydrogen bond formation between the nitrogen of pyridyl with NH of Met109 and penetration of aryl group into hydrophobic area of the enzyme that is not accessed by ATP's [32].

The pyridinyl imidazole competes at the ATP binding site of the enzyme were illustrated in crystallographic studies and biochemical information [33, 34]. Though pyridinyl imidazoles have potent p38 kinase inhibitors they are also establishing hepatotoxicity due to interference with hepatic cytochrome P450. Thus, widespread investigation has been completed to take apart the p38 inhibition and hepatotoxicity of pyridinyl imidazoles [35].

The synthesis of dihydroquinazolinones have been done and tested for p38 MAP kinase inhibitory activity [36, 37]. The dihydroquinazolinones have similar binding interactions with the enzyme as those of pyrimidynyl or pyridinyl imidazoles. The hydrogen bond formation with the enzyme backbone by the carbonyl group at the 2nd position showed a similar pattern to that of hydrogen bond formed by the nitrogen of pyridine or pyrimidine ring in imidazoles.

The novel p38 kinase inhibitors like urease substituted with pyrazoles [38, 39], theophanies [40], and alkyl-substituted isoxazoles [41] and purines [42] were discovered. The urea group acts as hydrogen bond donor and acceptor site shown by molecular modeling and crystallography information. Disubstituted urease containing t-butyl-pyrazoles binds with the allosteric domain of p38 α other than ATP binding site. BIRB 796 a pyrazole urea derivative is in the clinical phase II trials, demonstrated inhibition potency in picomolar concentration. The crystallographic examinations reveal that large conformational changes occur when the urea inhibitor binds with the kinase.

VX-745 had to be terminated after clinical trials phase II due to adverse effects on CNS revealed by the annual report of Vertex Pharmaceuticals Cambridge, USA, while few p38 inhibitors VX-702 and VX-850 have shown encouraging results in phase II clinical trials to study the safety, tolerability and clinical activity.

Matrix Metalloproteinase: MMPs are a subfamily of metzincins functionally related to zinc-dependent endopeptidases, which hydrolyze extracellular matrix in human body [43]. Identification of more than 24 MMPs have been reported and are divided into five subgroups based on the substrate specificity as stromelysins (MMP-3, -7, 10 and -11), collagenase, (MMP-1, -8, -13 and -18), gelatinases (MMP-2 and -9), membrane-type MMPs (MT-MMPs) (MMP-14, -15, -16, -17, -24 and -25) and nonclassified other MMPs (MMP-19, -20, -23, -26, -27 and -28) [44, 45]. The vital role played by activated MMPs in degradation of extracellular matrix during tissue repair and angiogenesis. The degradation of collagen types I, II and III carried out by MMP-2, -14 along with collagenases [46, 47].

Several pathological conditions like metastatic tumors and several inflammatory diseases such as inflammatory bowel disease, RA and osteoarthritis in which MMPs play a critical role [48, 49].

Many research strategies have been progressed to decrease the biochemical actions of MMPs like hindered one or more MMP activations. The design of synthetic molecule that inhibits MMPs aimed to mimic the natural inhibition by TIMP, but more accomplishment is associated with synthetic small molecules that bind the active site of MMPs. Zinc is the core center for MMPs activity and thus synthetic molecules have investigated that bind the zinc moiety of MMPs. Several zinc-binding groups have demonstrated wide range MMP inhibition. The zinc-binding groups are hydroxymate, carboxylate [50], phosphoric acid, sulfonamide, sulfyhydril, and phosphonamide and among them hydroxymate have shown heartening activity.

Several nonselective MMP inhibitors experienced set back during the clinical trial studies due to the unexpected adverse effects. These adverse effects of inhibitors were established due to inhibition of other MMPs that are involved in normal physiological functions, and inhibition of these MMPs cause excessive deposition of matrix leading to fibrosis [51, 52]. Thus, selective MMP inhibitors have the advantage over the classical broad range of MMP inhibitors. As the protein crystal structures of several MMPs have revealed the binding interactions between the inhibitors and MMPs thus the process of new lead identification for selective MMP inhibitors have been expedited.

Several broad-spectrum and selective MMP inhibitors have been tested in animal models and human clinical trials and hydroxymate MMP inhibitors like CGS-270230, RO-323555 and BAY-129566 have been well studied. The selective collagenase inhibitory activity shown by BAY-129566 and was effective in animal, small and short level clinical trials but failed in large and long-term clinical trials [53]. Succinyl hydroximates are the first generation broad-spectrum MMP inhibitors. British Biotech developed Batimastat (BB-9421) and marimastat (BB-2516) are the two succinyl hydroximates [54]. The inhibitory activity of hydroxymates is due to formation of strong hydrogen bond with carbonyl group of enzyme backbone. The selective MMP-2 activity of ilomastat analogs containing an isobutylidene group illustrated to fit in S1 packet of enzyme and a 2-substituted indole analog nucleus [55].

Some new hydroximates were synthesized and tested for MMP inhibitory activity that also contains phosphonamide zinc-binding group, compounds with an R configuration at phosphorus were found to be potent inhibitors [56]. The piperazine carboxylic acid was novel cyclic MMP inhibitors and the piperazine makes central backbone and provides conformational stability [57]. A series of α-sulfonylhydroxamic acid derivatives as potent MMP inhibitors have synthesized and explained the structure-activity relationship. A dialkyl substituted derivatives displayed potent activity against MMP-9 and MMP–13 while reduced action against MMP-1. These derivatives have also shown to have slighter activity against TACE [58].

NF-Kb: NF-κB is a redox-sensitive transcription factor, heterodimeric protein composed of different transcription factors of the Rel family [59]. NF-κB is composed of homo and heterodimers of five members of the Rel family including NF-κB1 (p50), NF-κB2 (p52), Rel A (p65), Rel B and c-Rel (Rel) [60]. The inhibitor protein called IKappa B (IκB) forms non-covalent bond with NF-κB resides in the cytoplasm of the cell in inactive form. Seven isoforms of IκBs have been identified namely IκBα, IκBβ, I-κBγ, IκBε, BCL3, p100 and p105 containing 30-35 amino acids [61]. NF-κB can be stimulated by LPS or inflammatory cytokines and free radicals which consequence in phosphorylation of IκBs by IKappa B Kinase Complex (IKK) on the conserved serine residue at N-terminal portion of IκB [62, 63].

Activated NF-κB complex translocates into the nucleus and binds DNA at Kappa-B binding motifs such as 5-prime GGGRNNYYCC 3-prime or 5-prime HGGARNYYCC 3-prime and provokes gene expression and further expression of cytokines, chemokine, growth factors, cellular ligands, and adhesion molecules [64, 65]. NF-κB plays a role in several diseases, such as asthma [66], neurodegeneration, ischemia or reperfusion injury, hepatitis, glomerulonephritis and inflammatory bowel disease [67-69].

The potential role played by NF-kB in inflammation opened another feasible approach to control these inflammatory diseases. It was concluded that inflammatory cytokines, including IL-1b, IL-6, and TNF-α are induced by the activation of NF-kB in synoviocytes [70]. Many of the NSAIDs such as aspirin and sodium salicylate have demonstrated to result in NF-kB inhibitory activity followed by inhibition of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [71, 72], which are encoded by NF-kB target genes.

Several heterocyclic compounds have been identified as lead molecules to inhibit IKKb with increased selectivity. Quinazoline analogs have been extensively studied for selective IKKb inhibition, one of most potent compounds in this series SPC-839 with IC_{50} 60 nM having more than 200 times selectivity for IKKb [73]. BMS-345541 an imidazoquinaxaline derivative exhibited ten folds selectivity for IKKb (IC_{50} 0.3 mM) and reported to bind the allosteric center of the kinase instead of regular ATP binding site. Diaryl pyridines have been reported to possess more selectivity for IKKb inhibition, a most potent molecule in this series exhibited in vitro inhibition of LPS induced TNF-a formation with IC_{50} value 0.6 mM and *in-vivo* inhibition with ED_{50} 2 mg/kg body weight [74, 75].

JNK Inhibitors: The c-Jun N-terminal kinases (JNK) are an evolutionarily conserved family of serine or threonine MAP kinases. JNK was acknowledged in 1990 as 54 kDa stress-activated protein kinase [76]. The pro-inflammatory cytokines such as TNF-α and IL-1β as well as environmental stress, such as anisomycin, UV irradiation, hypoxia, and osmotic shock activate JNKs [77]. A wide variety of cellular processes such as proliferation, apoptosis, migration and transcriptional regulation were governed by members of the JNK family [78-82]. NKs are activated by their serine or threonine upstream kinases, mitogen-activated protein kinase (MKK) namely MKK4 and MKK7 [83].

The inhibition of JNK has been reported to be a valuable approach in the development of agents for the treatment of oncological, apoptosis-related and inflammatory diseases [83]. A specific JNK inhibitor, SP 600125 an anthrapyrazole derivative was identified during high throughput screening. SP 600125 is competitive inhibitor of JNK binding at the ATP binding site. It has revealed to be active against all isoforms of JNK having 300 folds selectivity over other MAP kinases [84]. AS-007149 reported as prospective JNK inhibitor by library search and the effect of structural modifications on JNK inhibition. The SAR revealed that the benzothiazol-2-yl acetonitrile pyridine core plays a role in retaining a good level of JNK inhibition [85]. The 3-(4-pyridyl)-imidazole as novel gallows for JNK inhibition identified in high throughput screening with pIC_{50} value 5.8 [86].

Inflammasome: Inflammasome is cytoplasmic caspase-1-activating protein complexes that promote maturation and secretion of the pro-inflammatory cytokines. The activation of inflammasome by different stimuli triggers the proteolytic cleavage of pro-caspase 1 into active caspase 1, which, in turn converts pro-interleukin 1b (pro-IL1b) into the mature IL1b. The nucleotide-binding domain leucine-rich repeat-containing families of receptors are members of the innate immune system and have a critical role in host defense [87-89]. These molecules are key to driving inflammatory responses to abnormal cellular conditions. Many NLRs provide this role on establishment by forming a multiprotein complex called an inflammasome. Nucleotide-binding domain leucine-rich repeat (LRR)-containing receptors (NLRs) are pattern recognition receptors (PRRs) that initiate inflammatory responses to a wide range of stimuli.

The NLPR3 inflammasome is the best characterized and participates in immune responses to infectious and noninfectious agents. It consists of the aforesaid NLRP3 receptor, the adaptor protein ASC and caspases. Martinon *et al*., described, for the first time, an inducible high-molecular-weight complex containing NLRP3, an adaptor protein, and pro-inflammatory caspases, which they called the inflammasome [90]. The activators of NLRP3 are quite varied and include environmental irritants, endogenous danger signals, pathogens, and distinct pathogen-associated molecular patterns (PAMPs) and have been associated with a wide range of diseases including infectious, auto-inflammatory, and autoimmune disorders [91, 92].

Adipokines: White adipose tissue has been recognized to be a true endocrine organ, which is able to secrete a wide variety of factors termed Adipokines [93, 94]. In spite of their metabolic activities, adipokines represent a new family of compounds that could participate in several processes, including inflammation and immunity, and are also involved in the pathophysiology of rheumatic diseases [95-97]. Adipokines consist of a variety of pro-inflammatory factors most of them being increased in obesity and appearing to contribute to the so-called 'low-grade inflammatory state' in obese individuals. Obesity, the condition that stimulates the research on adipokines, has been considered a risk factor for developing osteoarthritis [98, 99].

PPARγ Receptors: PPARγ considered as important target in the development of new drugs and belongs to the nuclear family consisting of a group of approximately 50 transcription factors implicated in many different biological processes [100]. A large number of regulatory genes in lipid metabolism and insulin sensitization, as well as in inflammation and cell proliferation were controlled by PPAR [101, 102]. Its activation requires heterodimerization in the nucleus of the cells with another nuclear receptor, known as the retinoid X receptor α (RXR α), leading to binding of this heterodimer to specific DNA sequence elements termed peroxisome proliferator response elements [103].

It has been established that these two nuclear factors play a central role in the regulation of inflammatory signaling pathways by acting on kinases and transcription factors, such as nuclear factor-kB (NF kB), c-Jun, c-Fos, and nuclear factor of activated T cell [104-106], and inhibiting mucosal production of inflammatory cytokines (interleukin (IL)-1β and tumor necrosis factor α (TNF-α)) and chemokines [107], proliferation of inflammatory cells [108], and expression of some adhesion molecules [109].

Interestingly PPAR- γ was the first reported to undergo agonist-dependent simulation, which promotes binding to nuclear receptor co-repressor-1 protein (NCoR) and stabilizes association with promoter-bound NF-*k*B, thus leading to the transrepression of inflammatory genes in macrophages [110-112].

Other beneficial and inhibitory effects of PPAR- γ agonists on inflammation were reduction in the production of pro-inflammatory molecules in T lymphocytes, promotion of the expression of anti-inflammatory mediators in the innate immune system, reduce cytokines (TNF-α, IL-1, and IL-6) productions by inhibition of genes encoding pro-inflammatory molecules, and reduction of transcriptional activities Nuclear Factor- kB (NF-kB), AP-1, and STAT [113, 114]. PPAR- γ also reduces vascular smooth muscle cell proliferation, increases monocyte apoptosis, and suppresses metalloproteinase-9 expression in atherotic plaques [115-118].

Novel antagonist and partial agonists of PPAR- **γ** have recently been identified; tri-terpenoids 2-cyano- 3, 12- dioxoole-ana-1, 9- dien- 28- oic acid (CDDO) is a partial agonist with anti-inflammatory properties [119] and bisphenol diglycidyl ether (BADGE) and LG-100641 have been identified as antagonists for PPAR- γ [120, 121]. Even though these compounds have little clinical significance, they can be used to understand the physiology of the PPAR- **γ** and for the identification of new ligands. In addition to synthetic chemical methods, research in natural products has also yielded potent PPAR- **γ** agonists from several medicinal plants.

CONCLUSION: In treating the inflammatory diseases, NSAIDs and selective COX-2 inhibitors have been conventionally the most extensively used drugs to date. However, their long-term treatment has been demonstrated to have highly adverse side effects and it has been observed that the use of rofecoxib, selective COX-2 inhibitor might even lead to fatalities due to cardiovascular and thrombotic events. Pro-inflammatory cytokines and components of signal transduction play a central role in the pathology of inflammation, some proteinaceous cytokine inhibitors *viz.* infliximab was effective either as a monotherapy or in combination with other drugs effective in treating RA. Prolonged use of these cytokine inhibitors may lead to post-treatment infections, and therefore there is a quest to obtain small molecules that may inhibit these pro-inflammatory or intracellular signals.

Further, the cost-effectiveness and mode of administration of the cytokine inhibitors are not at

desirable levels. Apart from these pro-inflammatory cytokines as a target for new anti-inflammatory drug discovery, the components of signal transduction like p38 kinase, JNK, and NF-kappaB can be targeted. Some of small molecules that inhibit p38 kinase are in the final stages of clinical trials. The success of these inhibitors depends on how best they pass through the clinical trials for safe use in human beings. Therefore, the present review proposes that there is a paradigm shift in the drug design and discovery attempts towards anti-inflammatory diseases.

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