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NEW IMMUNOMODULATORYAPPROACHES TOALLERGIC INFLAMMATION: BIOLOGICS, SMALL MOLECULES, AND INNOVATIVE VACCINES

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ABSTRACT:

Allergic inflammatory disorders, including asthma, allergic rhinitis, atopic dermatitis, food allergies,andchronicurticaria,representagrowingglobalhealthburdenaffectingmillionsof individualsworldwide.Theincreasingprevalenceoftheseconditionshasbeenlinkedtocomplex interactions among genetic susceptibility, environmental exposures, lifestyle changes, and immunedysregulation.Traditionaltherapeuticapproaches,suchasantihistamines, corticosteroids,andbronchodilators,remainthecornerstoneofallergymanagement;however, these treatments primarily focus on symptom control and often fail to address the underlying immunological mechanisms responsible for disease initiation and progression. Consequently, thereisagrowingneedfortargetedtherapiescapableofprovidingsustaineddiseasecontroland long-term immunological benefits.

Recent advances in immunology and molecular medicine have revolutionized the treatment landscapeofallergicdiseasesthroughthedevelopmentofnovelimmunomodulatorystrategies. Biologicagents,particularly monoclonalantibodiestargetingkeymediatorsoftype2 inflammation,includingimmunoglobulinE(IgE),interleukin(IL)-4,IL-5,IL-13, thymicstromal lymphopoietin (TSLP), and their associated signaling pathways, have demonstrated remarkable efficacy in reducing inflammation, preventing disease exacerbations, and improving clinical outcomesinpatientswithmoderate-to-severeallergicdisorders.Inparallel,small-molecule

therapeutics,suchasJanuskinase(JAK)inhibitorsandotherintracellularsignalingmodulators, offerapromising alternativebyselectivelyinterferingwithinflammatorypathways involvedin allergic responses, while providing the convenience of oral administration. Furthermore,innovativevaccine-basedapproachesareemergingaspotentialdisease-modifying interventions. These include allergen-specific immunotherapy, recombinant allergen vaccines, peptide-basedvaccines,DNAandmRNAvaccines,andnanoparticle-assisteddeliverysystems designed to promote immune tolerance and reshape aberrant immune responses. Unlike conventionalpharmacotherapy,thesestrategiesaimtoinducelong-lastingimmunological changes, thereby reducing allergen sensitivity and preventing disease recurrence. Thisreviewexploresthelatestdevelopmentsinbiologics,smallmolecules,andnext-generation vaccine technologies for allergic inflammation, highlighting their mechanisms of action, therapeuticapplications,clinicalefficacy,safetyconsiderations,andfutureprospects.The integrationoftheseadvancedimmunomodulatoryapproachesintoclinicalpracticerepresentsa significant step toward precision medicine, offering personalized and potentially curative treatmentoptionsforpatientssufferingfromallergicdiseases.Continuedresearchandlarge-scaleclinicalstudiesareessentialtofurtherrefinethesetherapies,improveaccessibility,and establish their long-term effectiveness in allergy management.

KEYWORDS: Allergic inflammation, immunomodulation, biologics, monoclonal antibodies, small-molecule therapeutics,JAKinhibitors,allergenimmunotherapy,recombinantvaccines,mRNAvaccines, immune tolerance, precision medicine, allergic diseases.

INTRODUCTION:

Chronic non-communicable diseases, including allergies and hypersensitivity disorders, are strongly influenced by lifestyle factors and environmental exposures.According to the 2019 GlobalBurdenofDiseasereport,morethan260millionindividualsworldwideareaffectedby asthma, whileapproximately 170 million suffer from atopicdermatitis (AD). Recognizing the growing impact of these conditions, the World Health Organization (WHO) incorporated dedicatedsectionsonallergyandhypersensitivitydisorderswithinChapter3oftheInternational Classification of Diseases, 11th Revision (ICD-11).Allergic and hypersensitivity disorders encompassabroadspectrumofclinicalconditions,includingasthma,urticaria(hives),allergic rhinitis(hayfever),rhinoconjunctivitis,atopicdermatitis(eczema),chronicrhinosinusitiswith

nasal polyps (CRSwNP), food and chemical allergies, and anaphylaxis, which is a potentially life-threatening medical emergency. These disorders are characterized by exaggerated or prolongedtype2(T2)immuneresponsestoenvironmentalstimulithataregenerallyharmless and well tolerated by non-allergic individuals. Persistent allergic inflammation can lead to structuralandfunctionaldamageofaffectedtissuesandorgansifleftuntreated.

Thepathogenesisofallergicinflammation involvesacomplex interactionamongvarious immune cells and is typically initiated by exposure to non-infectious environmental allergens. In sensitized individuals, allergens trigger the cross-linking of immunoglobulin E (IgE) molecules bound to high-affinity FcεRI receptors on mast cells and basophils, leading to cellular activation and the release of inflammatory mediators.Allergic inflammation generally progresses through threesequentialphases.Theearlyphaseoccurswithinsecondstominutesandischaracterizedby the rapid release of preformed mediators and newly synthesized arachidonic acid metabolites. Thisisfollowedbythelatephase,developingseveralhourslater,duringwhicheosinophils, macrophages, lymphocytes, and other immune cells migrate to and infiltrate the site of inflammation.Withcontinuousorrepeatedallergenexposure,achronicinflammatoryphase develops and persists, contributing to long-term tissue damage and disease progression. Interestingly,allergicinflammationsharesseveralimmunologicalfeatureswithinflammation induced by helminth infections and ectoparasites, particularly the involvement of T2 immune responsesandIgE-mediatedmechanisms.Theepithelialbarrier,group2innatelymphoidcells (ILC2s),andThelper2(Th2)cells playessentialroles inorchestratingtheseresponses.While mastcellsandIgEactasprimaryinitiatorsandregulatorsofallergicreactions,eosinophilsserve as major effector cells that sustain and amplify inflammation. Over recent decades, extensive researchhassignificantlyadvancedtheunderstandingofallergicinflammatorymechanisms. Thesediscoverieshaveledtotheidentificationofdistinctdiseaseendotypes,providingvaluable insights into the biological pathways underlying allergic disorders and helping to explain their diverseclinicalphenotypes.

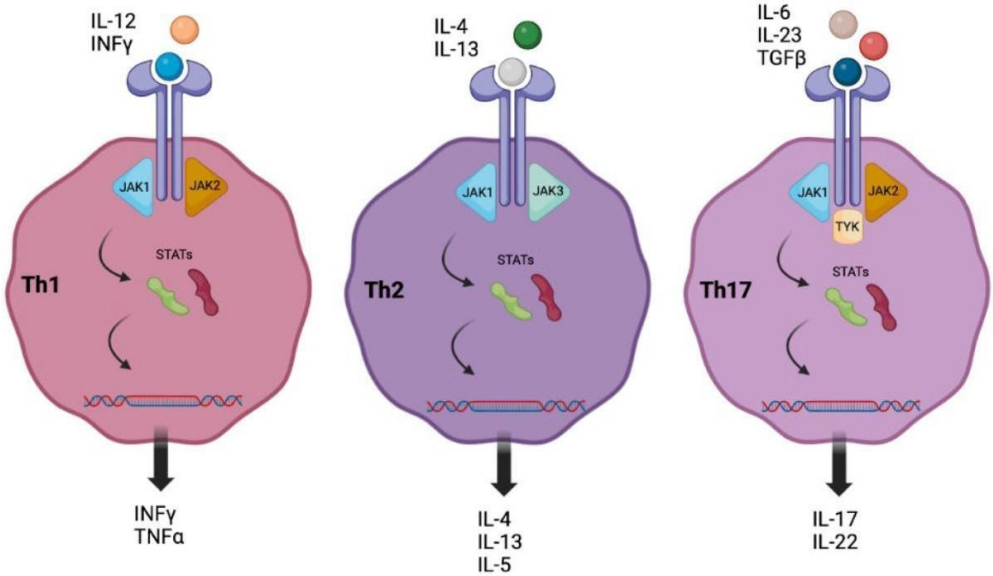
ETIOLOGY:

The high prevalence of allergic diseases in Western countries and their increasing occurrence in developingnationssuggestthatenvironmentaland lifestylefactorsplayasignificantroleintheir development. The adoption of a Western lifestyle across the world may contribute to this trend. Other environmental factors associated with allergy risk include increased air

pollution, greater indoor exposure to allergens, and improvements in living conditions.

One widely accepted explanation is the hygiene hypothesis, which proposes that repeated exposuretoinfectionsduringearlychildhoodhelpsprotectagainstthedevelopmentofallergic diseasessuchasatopicdermatitis(AD).Thistheory issupportedbyobservationsthatchildren in developed countries, who grow up in cleaner and more hygienic environments with reduced exposure to microorganisms, have a higher risk of developing allergies. In contrast, children in developingcountriesaremorefrequentlyexposedtoinfectiousagentsdue to overcrowding, inadequatesanitation,limitedaccesstocleandrinkingwater,andmalnutrition.Theyencounter variousbacterial,viral,andparasiticinfectionsearlyinlife,andintestinalcolonizationbyGram-negative bacteria commonly occurs during infancy. Studies in Europe have demonstrated differencesintheintestinalmicrobiotaofallergicandnon-allergicchildren.

Furthermore,theuseofantibioticsduringthefirsttwoyearsoflifehasbeenassociatedwith anincreased risk of developingAD. Normally, balanced exposure to microbes, parasites, allergens,andotherenvironmentalfactorssupportsthepropermaturation ofimmuneresponses, maintaining equilibrium betweenT-helper 1 (Th1) andT-helper 2 (Th2) cells. However, in genetically susceptible individuals, increased allergen exposure may promote an exaggerated Th2-mediatedimmuneresponse,leadingtoallergicsensitization.RegulatoryTcells(Tregs)play an important role in maintaining immune tolerance by suppressing excessive Th1 and Th2 responsestriggeredthrough activationofbothinnate andadaptiveimmunepathways.

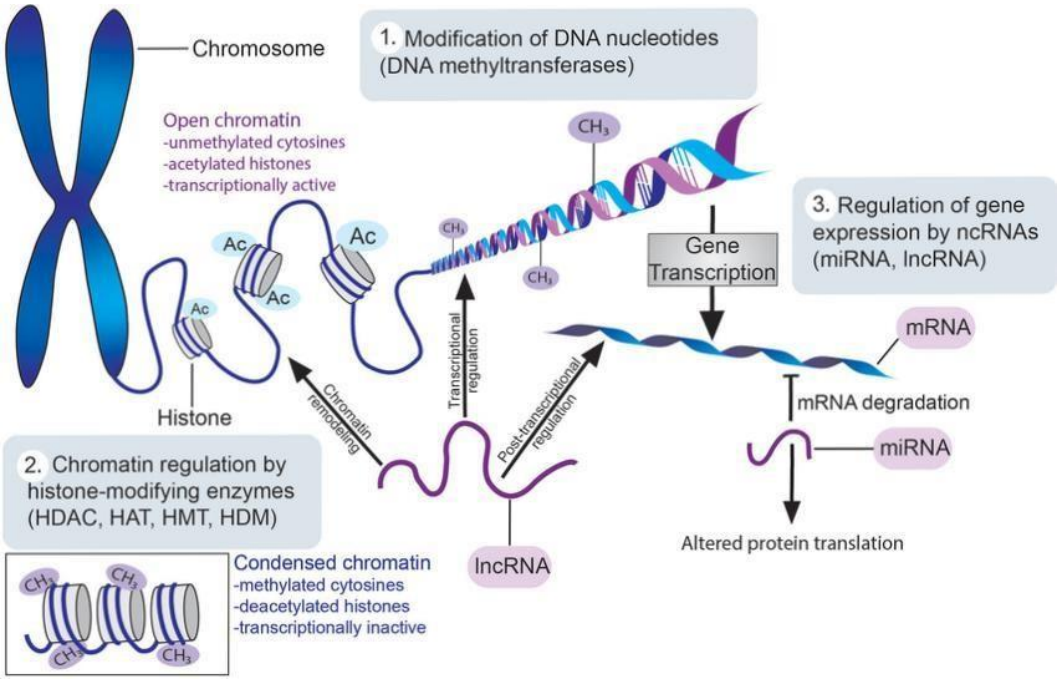


GENETICANDEPIGENETICS:

Geneticpredispositionhaslongbeenrecognizedasoneofthemajoretiologicalfactors contributingtoallergicdiseases.Advancesingenome-wideassociationstudies(GWAS)haveled to the identification of hundreds of genes associated with asthma and other allergic disorders. Althoughadefinitivecausalrelationshiphasnotbeenfullyestablished,thesegeneticfindings havesignificantlyimprovedourunderstandingof the molecularpathways involved inallergy development. The identified genes can broadly be classified into those regulating immune responsesandthoseinfluencingthestructureandfunctionoftissuessuchastheepitheliumand connective tissue, thereby affecting both innate and adaptive immunity.

Inadditiontogeneticsusceptibility,environmentalfactorscaninfluencethedevelopmentof allergic diseases through epigenetic mechanisms, including DNAmethylation and histone modifications . Several genes play critical roles in allergic inflammation and immune regulation. Amongthese,IL-4andIL-13areessentialfor thedifferentiationofT-helper2(Th2)cellsandthe production of immunoglobulin E (IgE), both of which are central to allergic responses. The ADRB2 gene encodes the β2-adrenergic receptor, which mediates relaxation of airway smooth muscles; genetic variations inthis gene may alter airway responsiveness to allergens. HLA-DRB1 is involved in antigen presentation and contributes to immune recognition of allergens, whileCD14participatesininteractionsbetweenenvironmentalexposuresandtheimmune system, influencing allergic susceptibility.

TheFLG(Filaggrin)geneiscrucialformaintainingskinbarrierintegrity.MutationsinFLGcan impair the skin barrier, increasing susceptibility to allergic sensitization, atopic dermatitis, eczema, and food allergies [19,20]. Other important genes include ORMDL3 and GSDMB (formerlyGSDML),bothofwhichhavebeenassociatedwith anincreasedriskofearly-onset asthma. TheADAM33 gene is involved in airway remodeling and may contribute to airway hyperresponsiveness observed in allergic conditions. STAT6 plays a key role inTh2 cell differentiationandtheregulationofallergicinflammation.Additionally,variantsoftheCDHR3 gene, which encodes a protein involved in epithelial cell function, have been linked to severe asthma exacerbations and increased disease severity.



CELLANDCHEMICALMESSANGERS INALLERGY:

Theallergicinflammatoryresponsearisesfromcomplexinteractionsamonginflammatoryand structural cells through the release of chemical mediators, which collectively contribute to the development and progression of allergic symptoms

IGEANDITSRECEPTORS

Immunoglobulin E (IgE) plays a central role in the pathogenesis of allergic inflammation and mediates hypersensitivity reactions through its interaction with specific cell-surface receptors. TwomajorreceptorsforIgEhavebeenidentified:thehigh-affinityreceptorFcεRIandthelow-affinityreceptorFcεRII(CD23).Thesereceptors regulateIgE-mediated immuneresponses and contribute to the initiation and maintenance of allergic diseases.

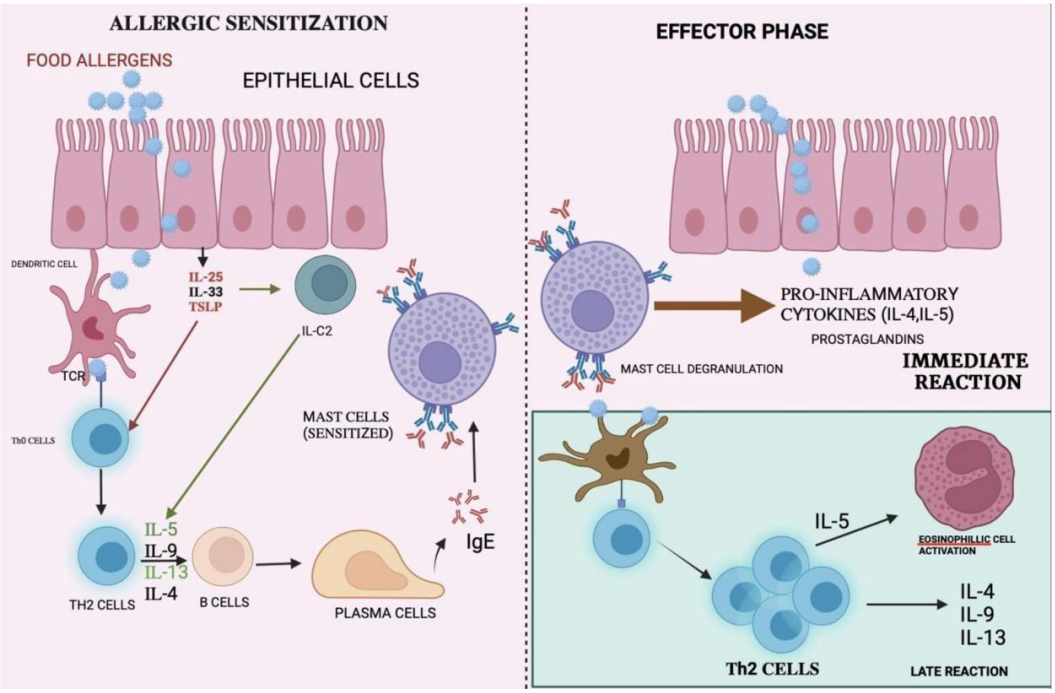
During allergic sensitization, allergen-specific IgE antibodies bind to FcεRI receptors expressed onmastcellsandbasophils.Uponsubsequentexposuretothesameallergen,cross-linkingof the IgE–FcεRI complexes occurs, triggering rapid activation of these cells. This activation leads to degranulationandthereleaseofpreformedmediatorssuchashistamine,proteases,and inflammatorycytokines,whichareresponsiblefortheimmediatesymptomsofallergy,including itching, swelling, bronchoconstriction, mucus secretion, and increased vascular permeability.

Thelow-affinityIgEreceptor,CD23,existsintwoisoforms,CD23aandCD23b.CD23ais

primarily expressed on activated B lymphocytes, whereas CD23b expression is induced on B cells,epithelialcells,andother immunecellsbycytokinessuchasinterleukin-4(IL-4).CD23 plays animportantroleinregulatingIgEsynthesis,allergenuptake, andantigenpresentation, thereby influencing both the magnitude and persistence of allergic responses.

Beyonditsrole inimmediatehypersensitivityreactions,IgEcontributestochronicallergic inflammationbypromotingtherecruitmentandactivationofeosinophils,basophils,andT-helper 2(Th2)cells.Thereleaseof cytokinessuchasIL-4, IL-5,andIL-13further amplifiestheallergic cascade, leading to tissue inflammation and remodeling. Elevated IgE levels are commonly associatedwithallergicconditionssuchasasthma,allergicrhinitis,atopicdermatitis,food allergy, and allergic conjunctivitis .

Recentstudieshavealsohighlightedtheinvolvementof IgEreceptorsondendriticcellsand other antigen-presenting cells, which facilitate allergen capture and presentation to T lymphocytes, thereby enhancing adaptive immune responses.These findings have led to the developmentoftargetedbiologicaltherapies,suchas anti-IgEmonoclonalantibodies,which effectivelyreduce allergic inflammationbypreventingIgEfrombinding toits receptors and interrupting downstream inflammatory signaling pathways .



MASTCELLS:

Uponactivation,mastcellsreleasethreemajorcategoriesofbiologicallyactivemediators:

preformed mediators stored within cytoplasmic granules, newly generated lipid-derived mediators, and newly synthesized cytokines, chemokines, and growth factors. During degranulation,thegranulemembranesfusewiththeplasmamembrane,resultingintherapid release of their contents into the surrounding tissues. Key preformed mediators include histamine,heparin,chondroitinsulfate,tryptase,chymase,carboxypeptidase,andvarious cytokines and growth factors.

Inadditiontothesepreformedsubstances,activatedmastcellsproducelipidmediatorssuchas prostaglandins, leukotrienes, and platelet-activating factor (PAF), which further amplify the inflammatoryresponse.Thesemediatorscontributetovasodilation, increasedvascular permeability, smooth muscle contraction, mucus hypersecretion, and recruitment of inflammatory cellstothesiteofallergenexposure.

Thecombinedeffectsofthesemediatorsleadtothecharacteristicmanifestationsofallergic diseases.Inallergicrhinitis,theycausenasalcongestion,sneezing,itching,andexcessivemucus production,whereasinasthmatheyinducebronchoconstriction,airwayinflammation,wheezing, coughing, and shortness of breath. Histamine is particularly important in triggering immediate

hypersensitivityreactions,whileleukotrienesarepotentmediators ofprolonged bronchoconstriction and airway edema.

Mastcellsalsoreleasecytokinessuchasinterleukin-4(IL-4),IL-5,IL-6,IL-9,IL-13, andtumor necrosis factor-alpha (TNF-α), which promote the differentiation and activation of T-helper 2 (Th2) cells and eosinophils. Chemokines secreted by mastcells attractadditional inflammatory cells, including eosinophils, basophils, and lymphocytes, thereby sustaining and amplifying allergic inflammation. Furthermore, stem cell factor (SCF) and IL-9 support mast cell growth, survival,andpersistencewithintissuesandmucosalsurfaces,contributingto thechronicnature of allergic disorders.

Overall,mastcellsserveascentraleffectorcellsinallergicandhypersensitivityreactions, initiatingboththeimmediateandlate-phaseinflammatoryresponsesthatunderlieconditions such as allergic rhinitis, asthma, atopic dermatitis, and food allergies.

DENDRITICCELLS:

Dendritic cells (DCs)arespecialized antigen-presentingcells thatplaya crucialrole ininitiating and regulating immune responses. Human DCs are broadly classified into two major subsets: $CD11c^{+}$myeloiddendriticcells(mDCs)and$CD11c^{-}$plasmacytoiddendriticcells(pDCs),which arecharacterized by theexpression of CD123, CD303, and CD304. Myeloid DCs can

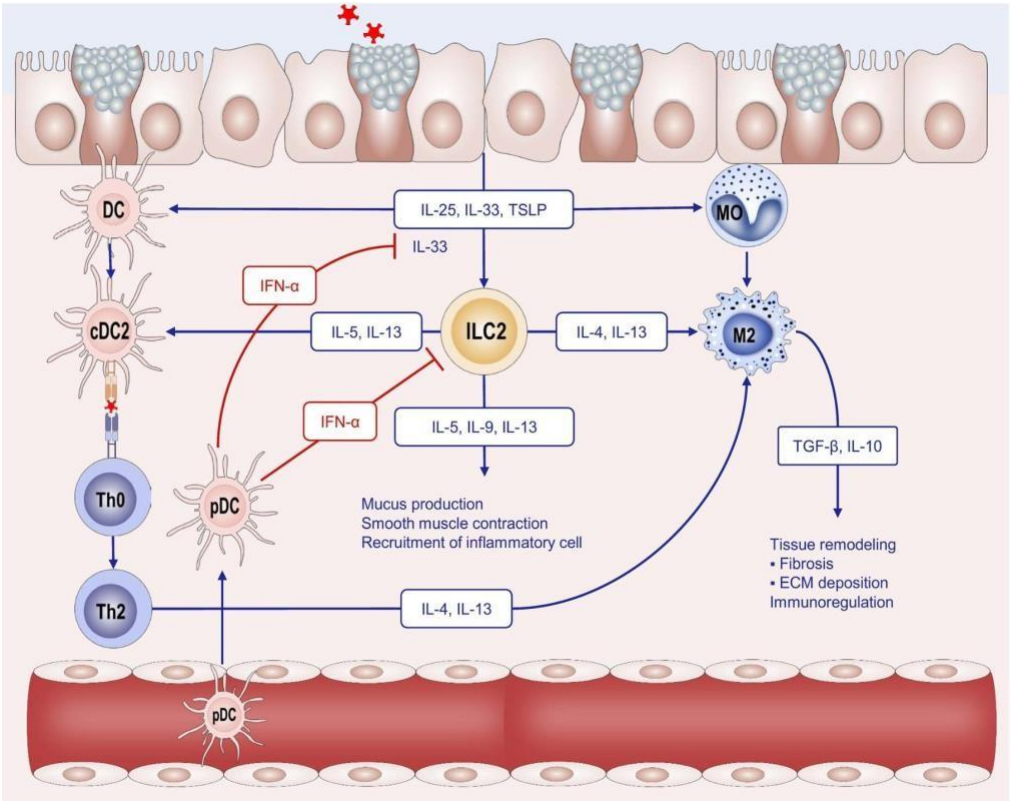
befurther subdivided based on the differential expression of surface markers such as CD1c, CD141, and CD16, each possessing distinct immunological functions.

DCsarestrategicallypositionedbeneathandwithintheairwayepithelium,wheretheyextend dendritic processes between epithelial cells into the airway lumen. This unique arrangement allows them to continuously sample inhaled allergens and pathogens while preserving the integrityoftheepithelialbarrierthroughtheformationoftightjunctionswith neighboring epithelialcells.Uponencounteringallergens,patternrecognitionreceptors,particularlyToll-like receptors (TLRs), recognize pathogen-associated molecular patterns (PAMPs) and damage-associatedmolecularpatterns(DAMPs),triggeringdendriticcellactivationandmaturation. Followingactivation,DCsupregulatechemokinereceptorssuchasCCR7,whichfacilitatestheir migration through lymphatic vessels to the T-cell-rich areas of regional lymph nodes. There, mature DCs process and present allergen-derived peptides on major histocompatibility complex

(MHC)moleculestonaïveTlymphocytes,therebyinitiatingadaptiveimmune responses.MyeloidDCsprimarilyfunctionaspotentantigen-presentingcellsthatpromoteT-cell activation and differentiation, whereas plasmacytoid DCs are important for antiviral immunity through the production of large amounts of type I interferons and contribute to the maintenance of immune tolerance.

Activateddendriticcellssecreteawiderangeofchemokines,includingCCL2,CCL3,CCL4, CCL17,CCL22,andCXCL8,whichrecruiteosinophils,basophils,mastcells,neutrophils,andT lymphocytestothesiteofallergenexposure.Theyalsoproducecytokines suchasIL-12,IL-6, IL-10, and thymicstromallymphopoietin (TSLP)-induced mediators, which influenceT-cell polarization. In allergic diseases, dendritic cells preferentially promote the differentiation of naïveTcellsintoTh2cells,leadingto theproductionofIL-4,IL-5,andIL-13,cytokinesthat drive IgE synthesis, eosinophilic inflammation, and airway hyperresponsiveness.

Thus,dendriticcellsserveasacriticallinkbetweeninnateandadaptiveimmunity,playinga central role in allergen recognition, antigen presentation, immune regulation, and the developmentandpersistenceofallergicinflammation.



TH2 CELLS:

T-helper2(Th2)cellsarekeyregulatorsofallergicinflammationandexerttheireffectsthrough thesecretionofcytokinessuchasinterleukin-4(IL-4),IL-5,IL-9,andIL-13.Duringan allergic response, antigen-presenting cells (APCs), including dendritic cells, process and present allergen-derivedpeptidestonaïveTlymphocytes.In thepresenceofIL-4,releasedbymastcells, eosinophils, or activated T cells, along with chemokines such as CCL17 and CCL22, naïve T cells differentiate into Th2 cells. These Th2 cells promote B-cell activation, proliferation, and class switching, resulting in the production of allergen-specific immunoglobulin E (IgE). Furthermore,Th2-derivedcytokinescontributetoeosinophilrecruitment,mucushypersecretion, airway inflammation, and bronchial hyperresponsiveness, all of which are hallmarks of allergic diseases.

InvariantnaturalkillerT(iNKT)cellsrepresent auniquesubsetoflymphocytesthatshare characteristics of both T cells and natural killer (NK) cells. These cells express a highly conservedT-cellreceptor(TCR),characterizedbytheinvariantvariableregionα-chainVα14–Jα18inmice(correspondingtoVα24–Jα18inhumans).UnlikeconventionalTcells that recognizepeptideantigenspresentedbymajorhistocompatibilitycomplex(MHC)molecules, iNKTcells specificallyrecognizeglycolipid antigens presentedbyCD1d,anon-polymorphic MHC class I-like molecule expressed on antigen-presenting cells.

Upon activation, iNKT cells rapidly produce large amounts of cytokines, including bothTh1-andTh2-type cytokines, thereby influencing immune responses. In allergic disorders, these cells contributetothedevelopmentofairwayinflammation,tissueinjury,andallergen-inducedairway hyperreactivity. They can also promote eosinophilic infiltration, enhance IgE-mediated responses,andamplify inflammatorycascades,makingthemimportantcontributorstothe pathogenesisofasthmaandotherallergicdiseases. Thus,iNKTcellsserveasacriticalbridge between innate and adaptive immunity and play a significant role in the initiation and progressionofallergicinflammation.

INVARIANTNATURALKILLERTCELLS:

InvariantnaturalkillerT(iNKT)cellsexpressacharacteristicinvariantT-cellreceptor(TCR)α-chain known as Vα14–Jα18. These cells are unique because they recognize glycolipid antigens ratherthanpeptideantigens.GlycolipidantigensarepresentedbyCD1d,anon-polymorphic class I MHC-likemoleculeexpressed on antigen-presenting cells (APCs). iNKTcells play a significant role in the development of allergen-induced airway hyperresponsiveness, tissue injury, and cell destruction.

TH17 CELLS:

T-helper 17 (Th17) cells constitute a distinct subset of CD4+ T lymphocytes that develop through a differentiation pathway separatefromthoseofTh1andTh2cells.Their differentiation is driven by cytokines such as transforming growth factor-beta (TGF-β), interleukin-6(IL-6),interleukin-1β(IL-1β),andinterleukin-23(IL-23),whilebeingnegatively regulated by interferon-gamma (IFN-γ) and interleukin-4 (IL-4). Th17 cells have emerged as importantcontributorstobothprotectiveimmunityandinflammatorydiseases,includingallergic disorders.

AprimaryfunctionofTh17 cellsistherecruitmentandactivationofneutrophilsandmonocytes at sites of inflammation. This process enhances the clearance of allergens, pathogens, and damagedtissuethroughphagocytosisandotherinnateimmunemechanisms.However,excessive or persistent Th17 activity can contribute to chronic inflammation and tissue injury, thereby playingasignificantroleinthepathogenesisofallergicdiseases.

Th17 cells are characterized by their production of the cytokines IL-17A, IL-17F, IL-21, IL-22, and,toalesserextent,IL-26.Amongthese,IL-17AandIL-17Farethe mostextensivelystudied

andareconsideredkeymediatorsofinflammatoryresponses.Thesecytokinesstimulateavariety of target cells, including fibroblasts, epithelial cells, endothelial cells, eosinophils, neutrophils, and smooth muscle cells, to produce pro-inflammatory mediators such as IL-6, CXCL8 (IL-8), CXCL1, CXCL10, granulocyte-macrophage colony-stimulating factor (GM-CSF), and matrix metalloproteinases (MMPs). The resulting amplification of inflammatory signaling promotes
leukocyterecruitment,tissueremodeling,andsustainedimmuneactivation.

IL-22, another important Th17-derived cytokine, acts primarily on epithelial tissues and contributestomucosalbarrierintegrity,antimicrobialdefense,andtissuerepair.However, dysregulated IL-22 production may also contribute to epithelial dysfunction and chronic inflammatoryconditions.Inallergicairwaydiseases,Th17-associatedcytokinescanenhance mucussecretion,airwayhyperresponsiveness,andstructuralchangeswithintherespiratorytract. RecentevidencesuggeststhatTh17cellsplayacrucialroleinsevereand corticosteroid-resistant forms of bronchial asthma. Elevated levels of Th17 cells and IL-17 have been detected in patientswithsevereasthmaandareassociatedwithincreasedneutrophilicairwayinflammation, reduced responsiveness to glucocorticoid therapy, and poor clinical outcomes. Furthermore, interactionsbetweenTh17cells,Th2cells,andinnateimmunecellscreateacomplex inflammatory network that contributes to disease progression and chronicity.

Inadditiontoasthma,Th17-mediatedimmuneresponseshavebeenimplicatedinatopic dermatitis, allergic rhinitis, chronic rhinosinusitis, and other inflammatory disorders.

Consequently,therapeuticstrategiestargetingtheIL-17/Th17signalingpathwayarebeing investigatedaspotentialapproachesforcontrollingsevereallergicinflammationandimproving treatment outcomes in patients with refractory allergic diseases.

TH9 CELLS:

Th9cells areaspecializedsubsetofCD4^{+}Thelpercells thatdevelopprimarilyfromTh2cells undertheinfluenceoftransforminggrowthfactor-beta(TGF-β)andinterleukin-4(IL-4).Unlike other T-helper cell populations, Th9 cells are characterized by the absence of the key transcriptionfactorsT-bet,GATA3,RORγt,andFoxp3,whichdistinguishthemfromTh1,Th2, Th17, and regulatory T cells (Tregs). They are recognized mainly for their ability to produce large amounts of IL-9.

During allergen exposure, the expression of IL-9 is significantly increased, highlighting the importantroleofTh9cellsinallergicimmuneresponses.InadditiontoTh9cells,mastcells, basophils, and eosinophils can also secrete IL-9, further amplifying inflammation. IL-9 is

particularly associatedwithallergicdisorderssuchas asthmaand atopicdermatitis.Itcontributes to disease progression by promoting mucus hypersecretion, enhancing mast cell growth and activation,inducingthereleaseofinflammatorymediators,andstimulatingsubepithelialfibrosis. Through these effects, Th9 cells play a crucial role in sustaining allergic inflammation and airway remodeling in chronic allergic diseases.

NATURALKILLERCELLS:

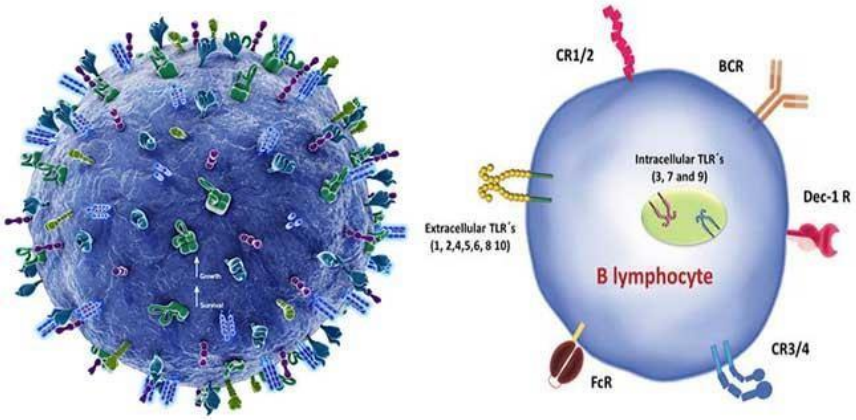
IthasbeenproposedthattheinnateandadaptiveTh2responsesinAD arelinkedbyanewly identifiedcellknownasthenuocyte,aninnateTh2immuneeffectorleukocyte[40].Thesecells proliferate in response to IL-25, IL-33, Notch signaling, and RORγt activation, all of which are derivedfrom epithelialcells[41].NuocytesareconsideredanearlysourceofIL-13,particularly during helminthic infestation. However, their exact role inAD remains to be further defined. TSUPPERSSORCELLS:

Regulatory Tcells (Tregs) play a crucial role in maintainingimmune tolerance and suppressingallergicinflammation.Thesecellsmaybenaturallyderivedfromthethymus (nTregs)orinducedintheperiphery(iTregs/Tr1cells)andarecharacterizedby theexpressionof CD4, CD25, and the transcription factor FoxP3 [42]. Tregs exert their immunosuppressive effects primarily through thesecretion of interleukin-10 (IL-10) and transforming growth factor-beta(TGF-β),whichinhibitdendriticcellactivation andsuppressTh1,Th2,andTh17responses. They also reduce allergen-specific IgE production and limit the activation of mast cells, basophils,andeosinophils,therebypromotingimmunetoleranceandprotectingagainstallergic diseases.

B LYMPHOCYTES:

B lymphocytes play a critical role in the pathogenesis of allergic inflammation by producing allergen-specificIgEantibodiesandfunctioningasantigen-presentingcells.Undertheinfluence of Th2 cytokines, particularly IL-4 and IL-13, activated B cells undergo class-switch recombinationtoproduceIgE,whichbindstohigh-affinityFcεRIreceptorsonmastcellsand basophils,therebysensitizingthesecells toallergens.Uponsubsequentallergenexposure,cross-linking of IgE triggers the release of inflammatory mediators, leading to allergic responses. RecentresearchhashighlightedBlymphocytesasimportanttherapeutictargetsinallergic diseases. Novel immunomodulatory strategies, including biologics that interfere with IgE production or B-cell activation, aim to reduce allergic sensitization and inflammation.

Furthermore,advancesinallergen-specificimmunotherapyandvaccinedevelopmentseekto modulate B-cell responses, promoting immune tolerance while suppressing pathogenic IgE production.Thesefindingsemphasizethesignificantcontributionof Blymphocytestoallergic inflammation and their potential as targets for innovative therapeutic interventions.



EOSINOPHILS:

Eosinophilsareimportanteffector cellsinvolved inthedevelopmentandprogressionofallergic inflammation.Theirgrowth,activation,andsurvivalareprimarilyregulatedbyIL-5,alongwith IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Following allergen exposure, eosinophils are recruited to the site of inflammation, where they release cytotoxic granuleproteins,cytokines,chemokines,andlipidmediatorsthatcontributetotissuedamageand theamplification of allergicresponses. In allergicdiseases such as asthma, atopicdermatitis, and allergic rhinitis, increased eosinophil infiltration is associated with disease severity and chronic inflammation. Recent immunomodulatory approaches have focused on targeting eosinophilic

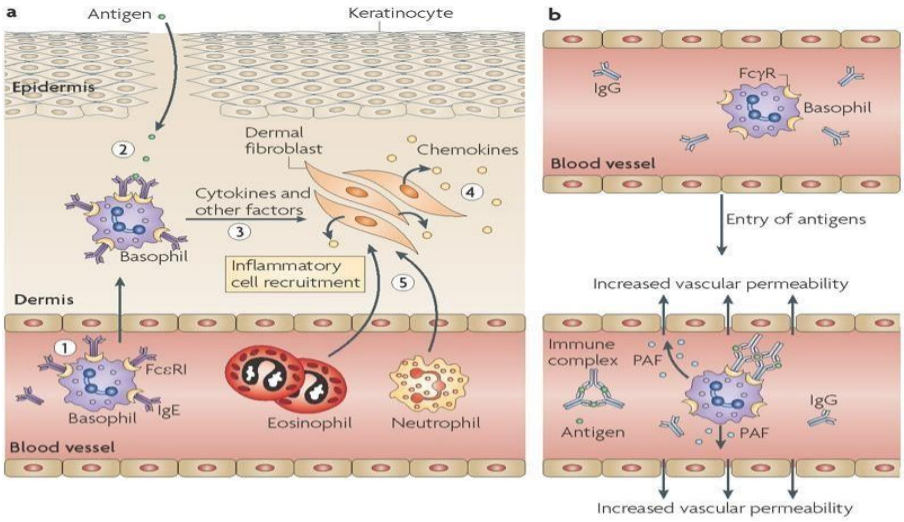
pathways through biologics directed against IL-5 or its receptor, resulting in reduced eosinophil

numbersandimprovedclinicaloutcomes.Thesefindingshighlightthecentralroleofeosinophils in allergic inflammation and support their importance as therapeutic targets in the development of novel treatments.

BASOPHILS:

Basophils are circulating granulocytes that contribute significantly to allergic inflammation and Th2-mediatedimmuneresponses.Althoughtheyrepresentasmallproportionofperipheralblood

leukocytes, basophils are potent producers of IL-4 and IL-13, which promote Th2 cell differentiationandIgEsynthesisbyBlymphocytes.UponactivationthroughIgE-dependent mechanisms, basophils release histamine, leukotrienes, cytokines, and other inflammatory mediatorsthatcontributeto allergicsymptomsandtissueinflammation.Recentstudieshave demonstrated thatbasophils play an importantrolein theinitiation and amplification of allergic responses by interacting with T cells, B cells, and other immune cells. Consequently, novel immunomodulatory approaches targeting IgEsignaling pathways and Th2-associated cytokines may indirectly regulate basophil activation and function. These findings suggest that basophils arekeycontributorstoallergicinflammationandrepresentpotentialtargetsforthedevelopment of innovative therapeutic strategies.



NEUTROPHILS:

Neutrophilsareamongthefirstinflammatorycellsrecruitedtositesoftissueinjuryandinfection and are increasingly recognized for their role in allergic inflammation. These cells contribute to immune responses through the release of proteolytic enzymes, reactive oxygen species, cytokines,andchemokinesthatpromoteinflammationandtissueremodeling.Insevereand chronic forms of allergic diseases, particularly corticosteroid-resistant asthma, increased neutrophilinfiltrationhasbeenassociatedwithpersistentairwayinflammationanddisease severity.Neutrophilsalsointeractwithotherimmunecells,influencingbothinnateandadaptive immune responses. Recent research has highlighted the potential of targeting neutrophil-associatedinflammatorypathwaysthroughsmall-moleculeinhibitorsandbiologictherapiesto reduce chronic inflammation and improve clinical outcomes. These findings indicate that

neutrophilsplayanimportantroleinallergicinflammationandmayserveaspromisingtargets for novel immunomodulatory interventions.

NOVELIMMUNOPHAMACOLOGICALDRUGSANDALLERGYTHEAPY:

SMALLMOLECULESTARGETINGGPROTEINCOUPLEDRECEPTORS:

TheJAK–STATsignalingpathwayisactivatedwhencytokinessuchasgranulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4, IL-5, and IL-3 bind to their respective cell-surface receptors,resultinginreceptorsubunitdimerization.ActivatedJanus kinases(JAKs)associate with the dimerized receptor subunits and undergo transphosphorylation, followed by phosphorylationofintracellulartyrosineresiduesonthereceptor.Thesephosphorylatedresidues serveasdockingsitesforsignaltransducerandactivatoroftranscription(STAT)proteins,which are subsequently phosphorylated by JAKs. The activated STAT proteins then dimerize and translocatetothenucleus,wheretheyfunctionastranscriptionfactorsregulatinggenesinvolved in immune responses, cellular growth, and differentiation. Small-molecule JAK inhibitors interfere with this signaling cascade by blocking JAK activationandpreventingdown stream signal transduction, thereby exerting immunosuppressive and anti-inflammatory effects. The JAKfamilycomprises fourmembers:JAK1,JAK2,JAK3,andtyrosinekinase2(TYK2). IndividualJAKinhibitorsdifferintheiraffinityandselectivityforthesekinases,influencing their therapeutic efficacy and safety profiles.

TLRAGONIST:

Innateimmuneactivationisinitiatedthroughtherecognitionofpathogen-associatedmolecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs). These receptors are expressed on variousskinandimmunecellsandserveascriticalsensorsofmicrobialinvasion andtissue injury. Upon binding of PAMPs or DAMPs to TLRs, intracellular signaling pathways are activated, leading to the production of pro-inflammatory cytokines, chemokines, and other immune mediators.This signaling cascade promotes the recruitment and activation of immune cells, thereby contributing to the initiation and amplification of inflammatory responses. In allergicdiseases,dysregulatedTLR-mediatedsignalinghasbeenimplicatedinthedevelopment and

persistence of chronic inflammation, highlighting its importance as a potential target for novelimmunomodulatorytherapies.

ProductionofCytokines:

ActivationofToll-likereceptor(TLR)signalingstimulatestheproductionofpro-inflammatory cytokines,includingTNF-α,IL-6,andIL-1β,which arecrucialforinitiating inflammationand promotingtissuerepair.Although thesecytokines playanessentialrole inhostdefenseagainst infectionsandinwoundhealing,theirexcessiveproductionmaycontributetothedevelopment of allergic inflammation and skin disorders such as atopic dermatitis and allergic contact dermatitis.Imiquimod, aTLR7/8agonist, isanexampleofatherapeuticagentthatinduceslocal inflammatory responses and is widely used in the treatment of skin cancers and viral infections [52]. Inaddition,TLR9agonistsarecurrentlybeingexploredfortheirpotentialapplicationsin cancer therapy. However, activation of TLR pathways can also intensify allergicresponses by enhancing cytokine release and promoting inflammatory processes, highlighting the complex role of TLR agonists in immune regulation.

TLRAgonistsintheDevelopmentofVaccines:

Toll-likereceptor(TLR)agonistsarewidelyusedasvaccineadjuvantstoenhanceimmune responses against specific antigens. By stimulating innate immune pathways, these agents improve antigen presentation and promote the development of effective adaptive immune responses.Inthecontextofallergicdiseases,the adjuvantpropertiesofTLRagonistsmaybe utilizedtomodulateimmuneresponsestoallergens,potentiallypromotingimmunetoleranceand desensitization. Consequently, TLR agonists have emerged as promising candidates in the developmentofinnovativeallergyvaccinesandimmunotherapeuticstrategiesaimedatreducing allergic sensitization and improving long-term disease control.

TLRANTAGONISTS:

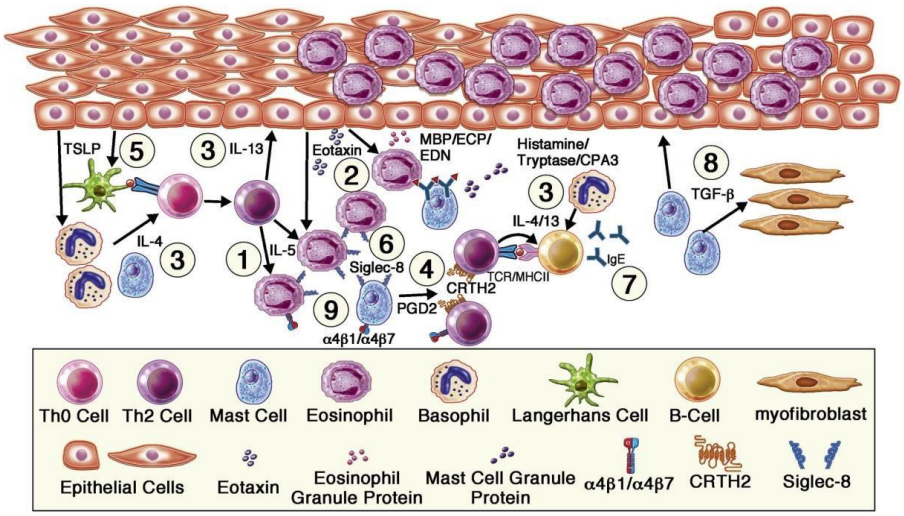
Toll-likereceptor(TLR)antagonistsareemergingimmunomodulatoryagentsthatinhibitthe activation of TLR-mediated signaling pathways involved in innate and adaptive immune responses. TLRs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), leading to the activation of intracellular signaling cascades and the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Whiletheseresponsesareessentialforhostdefense, excessiveordysregulatedTLRactivation can contribute to the development and persistence of allergic and inflammatory diseases.

TLR antagonists act by blocking ligand binding or inhibiting downstream signaling pathways, thereby reducing cytokineproduction, inflammatory cellrecruitment, and tissueinflammation. Bymodulatinginnateimmune activation,theseagentshaveshownpotentialin thetreatmentof allergic disorders, including atopic dermatitis, allergic asthma, and allergic rhinitis. Ongoing researchisfocusedonthedevelopmentofselectiveTLRantagoniststhatcan suppress pathologicalinflammationwhilepreservingprotectiveimmunefunctions.Consequently,TLR antagonists represent a promising class of small-molecule immunomodulators for the managementofallergicinflammation.

H4RECEPTORANTAGONISTS

Histamine receptor antagonists are a class of drugs that block the action of histaminebybindingtohistaminereceptorsandpreventingtheiractivation.

Histamine is a key inflammatory mediator released primarily from mast cells and basophilsduringallergicreactions.Byinhibitinghistaminesignaling,theseagents reduce symptoms such as itching, sneezing, rhinorrhea, urticaria, and inflammation. Histamine receptor antagonists are classified according to the receptor subtype they target, including H1, H2, H3, and H4 receptors.Among these,H1receptorantagonistsarewidelyusedforthetreatmentofallergicrhinitis, urticaria, and other allergic conditions, whereas H4 receptor antagonists have emerged as promising therapeutic candidates due to their ability to regulate immunecellmigrationandinflammatoryresponses.Consequently,histamine receptorantagonistsremainanimportantcomponentofcurrentandemerging strategies for the management of allergic inflammation.



EMERGINGPLANTDERIVEDDRUGS:

Emerging plant-derived drugs are bioactive compounds obtained from medicinal plants that are beinginvestigatedanddevelopedasnoveltherapeuticagentsforthepreventionandtreatmentof various diseases. These compounds possess diverse pharmacological properties, including anti-inflammatory,antioxidant,antimicrobial,and immunomodulatory activities.Recentadvancesin phytochemical research and drug discovery have identified numerous plant-derived molecules with the potential to target specific molecular pathways involved in disease pathogenesis. In the context of allergic and inflammatory disorders, emerging plant-derived drugs offer promising alternativestoconventional therapiesbymodulating immuneresponses,reducinginflammation, andpromotingimmunehomeostasis.Theirnaturalorigin,multitargetmechanismsofaction,and favorable safety profiles have attracted considerable interest for the development of innovative therapeutic strategies.

PHENOLICANDFLAVONOIDCOMPOUND:

Phenolic and flavonoid compounds are naturally occurring phytochemicals widely distributed in fruits, vegetables, medicinal plants, and plant-derived foods. These compounds have attracted considerableattentionduetotheirpotentantioxidant,anti-inflammatory,andimmunomodulatory properties. In allergic diseases, phenolics and flavonoids regulate immune responses by suppressingtheproductionofpro-inflammatorycytokines,inhibitingmastcelldegranulation, reducing histamine release, and modulating signaling pathways such as NF-κB and MAPK. Furthermore,theirantioxidantactivityhelpsneutralizereactiveoxygenspecies,therebylimiting oxidative stress-associated tissue damage.

Severalflavonoids,includingquercetin,kaempferol,luteolin,andcatechins,havedemonstrated significant anti-allergic effects in experimental studies. Similarly, phenolic compounds such as resveratrol and curcumin have been shown to attenuate inflammatory responses and promote immune homeostasis. Through their ability to target multiple inflammatory pathways simultaneously, phenolic and flavonoid compounds represent promising plant-derived immunomodulatorsforthepreventionandtreatmentofallergicandinflammatorydisorders.

ALKALOIDS

Cocaine isanaturallyoccurringalkaloidisolatedfromthecocaplantspeciesErythroxylumcoca and

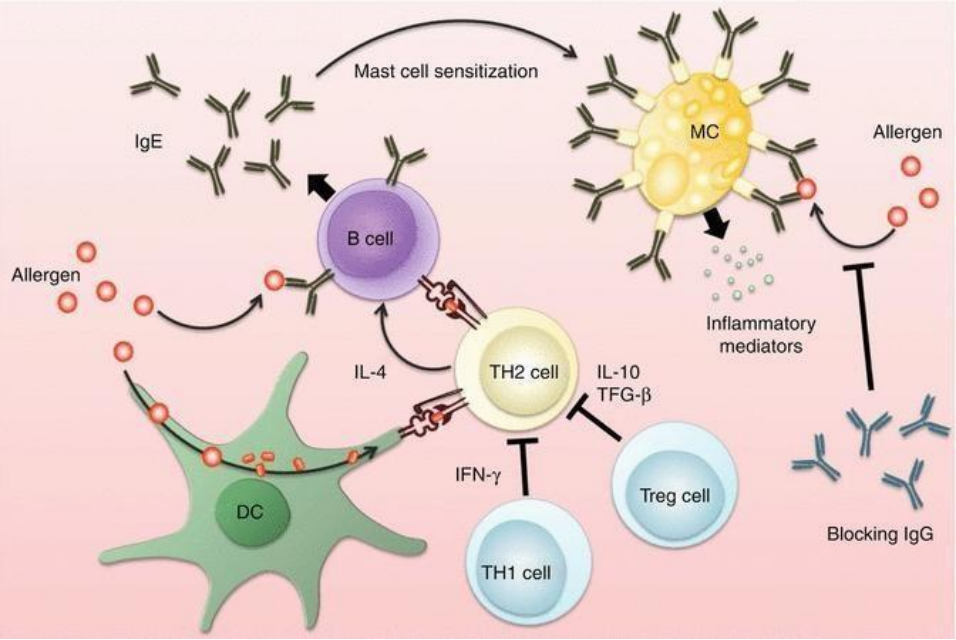
Erythroxylum novogranatense. In addition to its well-known pharmacological effects, cocainehasbeenreportedto influenceimmunefunctionbymodulatingtheproductionofseveral cytokines.Itstimulatesmacrophagesandsplenocytes,leadingto thereleaseofpro-inflammatory cytokines such as IL-1α, IL-6, and TNF-α, as well as immunoregulatory cytokines including IFN-γ, IL-2, IL-4, IL-5, and IL-10 [38]. Through its effects on cytokine secretion and immune cell activation, cocaine demonstrates significant immunomodulatory activity. Furthermore, a varietyofplant-derivedalkaloidshavebeeninvestigatedfortheirabilitytoregulateimmune responses, highlighting their potential as therapeutic agents in immune-mediated and inflammatorydisorders.

VACCINESBASEDONALLERGENDERIVATIVESWITHREDUCEDIGEANDTCELLREACTIVITY:

Theeffectivenessofrecombinantallergen-basedimmunotherapyhasbeendemonstrated in severalclinicalstudies.Inonetrial,patientswithgrasspollenallergyweretreatedwitha mixture ofthefive majorrecombinantTimothygrasspollen allergens(rPhlp1,rPhlp2,rPhlp5a,rPhlp 5b, and rPhl p 6). Treatment resulted in significant clinical improvement, which was associated with modulation of the allergen-specific immune response, characterized by increased allergen-specific IgG levels and reduced IgE production. In another clinical study, patients with birch pollenallergyreceivedeitherrecombinantBetv1(rBetv1),purifiednaturalBetv1extract,or placebo

Thismulticentertrial, involving134patients,demonstratedthatimmunotherapywiththesingle recombinantallergenrBetv1wasaseffectiveastreatmentwiththepurifiednaturalallergen preparationcontainingmultipleisoformsandthecompletebirchpollenextract.Furthermore,the efficacy of sublingual administration of recombinant Bet v 1 has also been investigated and shown promising results.

Despitetheseadvantages,unmodifiedrecombinantallergensretainimmunologicalproperties



Similartotheirnaturalcounterpartsandmaythereforeinduceige-mediatedandT-cell-mediated allergicreactions.Toovercometheselimitationsand improvethesafety andefficacyofspecific immunotherapy (SIT), several strategies have been developed for the design of next-generation allergy vaccines with reduced allergenicity and enhanced immunomodulatory potential.

CONCLUSION

Allergic inflammatory diseases constitute a significant and growing global health burden, driven bycomplexinteractionsamonggeneticsusceptibility,environmentalexposures,epithelialbarrier dysfunction, and immune dysregulation. The increasing prevalence of these disorders, coupled with their substantial impact on patient morbidity and healthcare systems, underscores the need formoreeffectiveandmechanism-basedtherapeuticstrategies.Recentadvancesinimmunology, molecular biology, and biotechnology have substantially enhanced our understanding of the cellular and molecular pathways underlying allergic inflammation, enabling the identification of novel therapeutic targets and the development of next-generation immunomodulatory interventions.

Theadventofbiologictherapieshasrevolutionized themanagementofsevereandrefractory allergic diseases by selectively targeting critical mediators of type 2 immune responses, includingIgE,IL-4,IL-5,IL-13,thymicstromallymphopoietin(TSLP),andtheirassociated receptors.These agents have demonstrated remarkable efficacy in reducing disease activity,

preventingexacerbations,minimizingcorticosteroiddependence,andimprovingoverallclinical outcomes. Concurrently, small-molecule therapeutics, such as Janus kinase (JAK) inhibitors, CRTH2antagonists,phosphodiesterase-4(PDE4)inhibitors,Bruton'styrosinekinase(BTK) inhibitors,Toll-likereceptor(TLR)modulators,andGprotein-coupledreceptor(GPCR)-targeted agents, have emerged as promising approaches for modulating intracellular signaling pathways and immune mechanisms that contribute to allergic inflammation.

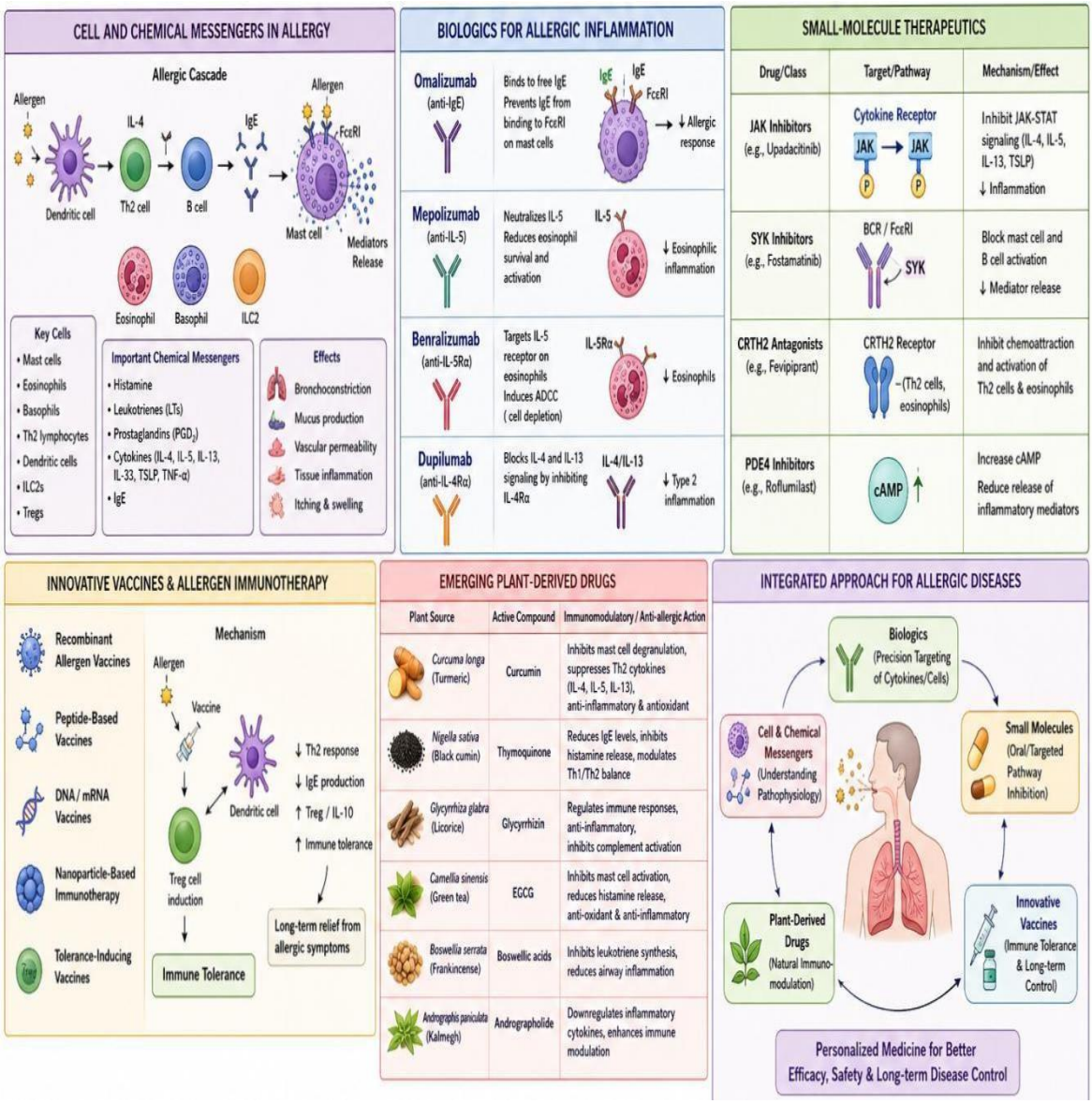
In parallel, significant progress has been achieved in the field of allergen-specific immunotherapythroughthedevelopmentofinnovativevaccineplatforms,including recombinantallergenvaccines,hypoallergenicderivatives,peptide-basedvaccines,DNAand mRNA vaccines, and nanoparticle-mediated delivery systems. These advanced immunotherapeuticstrategies aim to inducedurableimmunetolerance, thereby offering the potentialforlong-termdiseasemodificationratherthantemporarysymptomaticrelief.Such approachesrepresentaparadigmshiftinallergy management,withtheprospectofalteringthe natural history of allergic diseases.

Furthermore, increasing scientific interest in plant-derived immunomodulatory compounds has highlightedthetherapeuticpotentialofnaturallyoccurringphenolics,flavonoids,alkaloids,and other bioactive phytochemicals. Compounds such as curcumin, quercetin, resveratrol, epigallocatechingallate,andberberinehavedemonstrateddiverseanti-inflammatory, antioxidant,andimmunoregulatoryactivities,supportingtheirpotentialroleascomplementary or adjunctive therapeutic agents in allergic disorders.

Despitetheseadvances,severalchallengescontinuetoimpedethewidespreadimplementationof precision immunotherapy, including disease heterogeneity, variability in treatment response, long-term safety considerations, accessibility, and economic constraints. The identification of robust biomarkers, improved characterization of disease endotypes, and optimization of individualizedtreatmentstrategiesremain criticalprioritiesforfutureresearch.Moreover, continuedtranslationalandclinicalinvestigationsareessentialtovalidateemergingtherapeutic targets and establish their long-term efficacy and safety profiles.

Inconclusion,theintegrationofbiologics,targetedsmall-moleculetherapies,innovativevaccine technologies, and emerging plant-derived immunomodulators has transformed the therapeutic landscape of allergic inflammation. These advances collectively support the transition from conventionalsymptom-orientedmanagementtoprecision-based,disease-modifying

interventionsaimedatrestoring immunehomeostasisandachievingsustained clinicalremission. Continuedscientificinnovationandinterdisciplinarycollaborationwillbefundamentalto translatingthesetherapeuticdevelopmentsintoimprovedpatientoutcomesandreducingthe global burden of allergic diseases.



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