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REVIEW ARTICLE

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Eosinophil extracellular traps in respiratory ailment: Pathogenic mechanisms and clinical translation

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Abstract

Background: Eosinophilic extracellular traps (EETs) are reticular complexes comprising deoxyribonucleic-Acid (DNA) fibers and granule proteins.

Aims: EETs play a crucial role in antimicrobial host responses and are pathogenic when overproduced or under degraded. EETs created by eosinophils appear to enable vital immune responses against extra-cellular pathogens, nevertheless, trap overproduction is evident in pathology.

Materials & Methods: As considerably research is performed, new data affirmed that EETs can alter the outcome of respiratory ailment.

Results: We probe into the disclosure and specificity of EETs produced in reaction to various stimuli and propose a role for those frameworks in ailment pathogenesis and the establishment of chronic, unresolved inflammation.

Discussion: Whether EETs can be used as a prospective brand-new target for the diagnosis, treatment and prognosis of respiratory ailments is a scientific theme worth studying.

Conclusion: We probe into the disclosure and specificity of EETs produced in reaction to various stimuli and propose a role for those frameworks in ailment pathogenesis and the establishment of chronic, unresolved inflammation.

KEYWORDS

cytolysis, degranulation, eosinophil extracellular traps, eosinophils, respiratory ailments

Key points

- Under immune stress, eosinophils release intracellular DNA and granular substances, forming large web-like structures known as eosinophilic extracellular traps (EETs).
- In respiratory diseases, the excessive response to microbial stimuli and impaired clearance of secretions may contribute to the formation of EETs. This can lead to heightened inflammatory reactions and exacerbation of the condition.
- Future research should prioritize investigating the mechanisms underlying eosinophil activation and the regulation of EETs. Additionally, the identification of clinical biomarkers for monitoring EETosis is crucial. These research findings

will provide valuable insights into the development of targeted treatment strategies for eosinophil-related diseases.

INTRODUCTION

The immune system is separated into innate and adaptive immunity, which involve immune organs, cells, and molecules and usually play a stable role in immune self-defense, surveillance, and homeostasis in the body. Innate immunity is the foremost line of muniment against infection, but it also has an important impact on noninfectious ailments, such as transplant rejection, tumors, and inflammatory ailments, and is involved in the activation of specific immunoreaction.

Eosinophils are innate immune cells derived from bone and account for only circulating blood cells (1%–6%) at a regular steady state. Eosinophils are 12–17 μM in diameter and are easily identified by bulky particular granules stained with eosin. That bilobed nucleus is easily identifiable under an electron microscope, but a small number of particles are seen under a light microscope and are therefore obscured.[1] Eosinophils are a subcategory of granulocytes featured by multiple specific granules in their cytoplasm. Eosinophils are extensively enlisted as the dominating line of defense against parasites and intensively contain anaphylaxis involving the secretion of preformed Th2 cytokines. A common factor in all those pathologies is the capacity that eosinophils can exude efficacious immunomodulatory elements that are stored in their granules as preformed mediators (growth factors, chemokines, cytokines), as well as de novo, synthesized oxidative metabolites and lipid mediator.[2] Eosinophils are unique in that they contain large crystalline particles that contain preformed proteins, including major-basic-protein (MBP), eosinophilic-peroxidase (EPX), eosinophil-chemotactic-protein (ECP), eosinophil-derived neurotoxin (EDN), and cytokines including interleukin (IL), interferon-ɣ (IFNɣ), tumor necrosis factor-α (TNF-α), and so on (Figure 1).[3]

In 2008, a study first proposed eosinophilic extracellular traps (EETs) comprising DNA released from eosinophils.[4] After eosinophils are activated with IFNɣ or IL-5 and subsequently stimulated with lipopolysaccharide (LPS) or complement component 5a (C5a), extra-cellular DNA fibers are catapulted from the cell. As effector cells, eosinophils form and secrete EETs, which comprise double-stranded DNA (dsDNA) colocalized with particles. That release of intact, membrane-separated granules produced by eosinophil lysis occurs primarily through ETosis, indicating the death of extrusion of DNA extra-cellular traps (ETs) with cytolytic characteristics and nuclear origin. ETosis can affect some eosinophils at the site of inflammation. This suggests that different eosinophil subsets are selectively activated into the ETosis pathway in vivo. The predominantly molecular mechanism of EET formation is still little-known, and a deeper knowledge of EET formation may strengthen the under-standing of nonallergic inflammatory ailments as well as eosinophil-associated allergies.

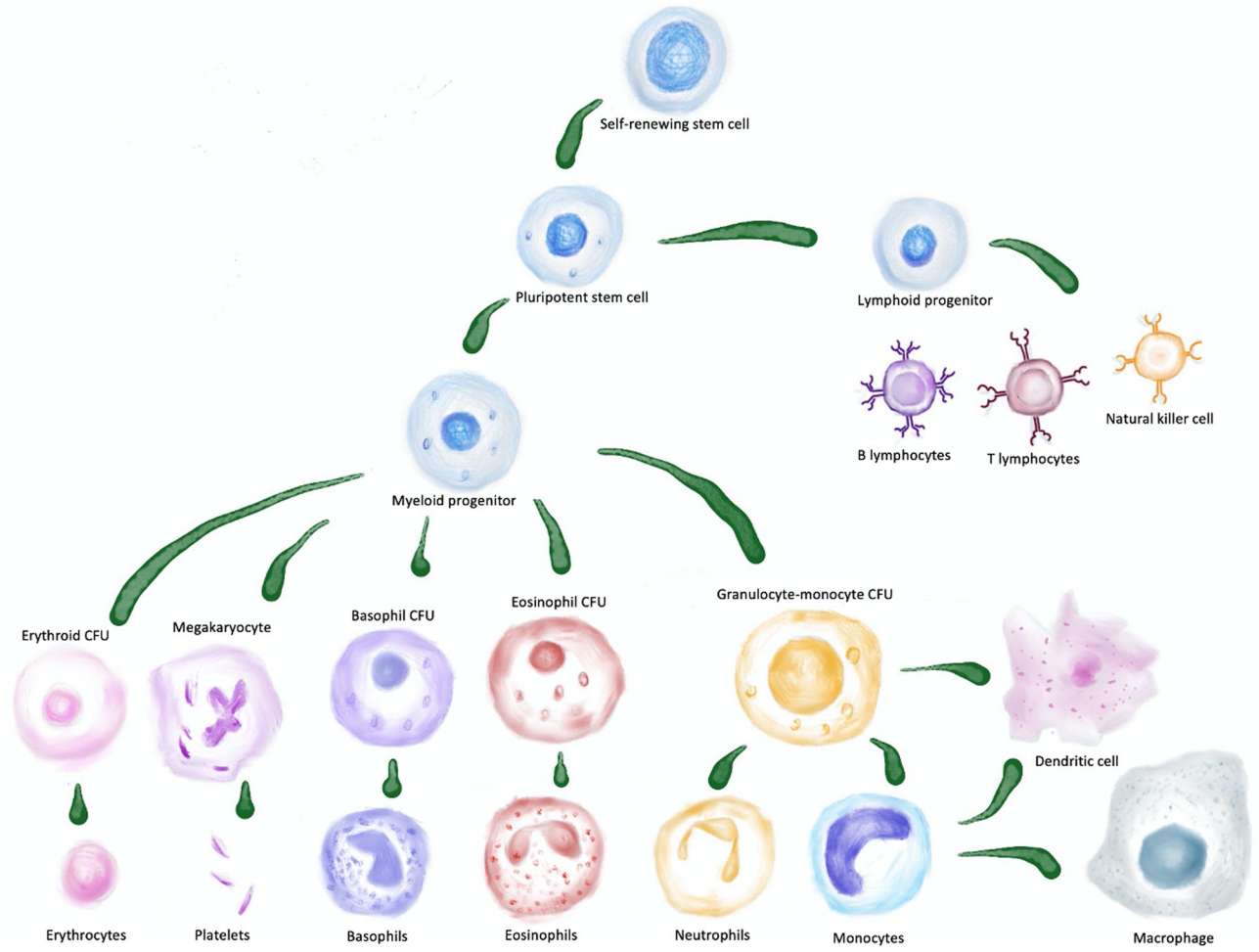
EETS

Degranulation of eosinophils

Because eosinophils derived from bone marrow progenitors are terminal differentiation, the contribution to the biological response of an individual depends mainly on their lifespan, production, activation status, and accumulation. Eosinophils are powerful secretory cells,[5] and in reply to the stimulation of receptors, eosinophils usually transmit the intact granules or granular creations by degranulation. Degranulation, an umbrella term, is used to specify the process of granule release from living cells or the free of intact or ruptured particles from collapsing cells, without involving particular underlying regulatory mecha-nisms.[6] The release of granule proteins is critical to their utility as immune effector cells; these granules include eosinophil-derived cationic granules that can be used by interrupting the intact of the lipid bilayer, exhibiting neurotoxicity and RNase activity, and take part in the generation of active oxidants and free radical species.[7] Four patterns of eosinophil exudation, containing classic exocy-tosis, complex exocytosis, segmented or piecemeal degranulation (PMD), and cell lysis, have been studied using super-resolution microscopy, confocal microscopy, and transmitted electron microscopy (Figure 2).[8]

PMD is the particularly common physiological approach for eosinophil degranulation.[9] During PMD, the contents, eosinophil-specific granules, are gradually depleted and are transmitted to the cell surface via eosinophilic-sombrero-vesicles (EoSVs), alter-ing that variable transmitting of eosinophil-derived mediators.[10] Exocytosis comes along after particle formation and subsequent fusion with the plasma membrane, affecting the framework of opening bypass for the free-of-particle contents.[11] On account of ultrastructural studies, both platelet-activating factor (PAF) and eotaxin induce PMD.[12] That cell surface arrangement and intracellular transport of CD63 within humankind eosinophils occurs in PMD and exocytosis.[13] According to early research, augmentation of the nuclear vesicles/envelope can be perceived in cytolytic eosinophils without signs of ETosis as well. For this reason, the breakdown of the nuclear envelope into vesicles may be related to EETosis but is not the only characteristic of destroyed cell moment.[14]

Cytolysis is the second most commonly observed process of eosinophil degranulation in allergic tissues, following the release of PMD,[15] accounting for 10%–33% of all degranulation patterns.[16] It involves the breakdown of chromatin in the nucleus, obeyed by the disintegration of the cytoplasmic membrane, generating the liberating of free eosinophil granules (FEGs).[17] Research over the past decade has shown that cell lysis of eosinophils resulting in the production of



Eosinophils

Cytotoxic-granule-associated protein	cytokines	chemokines	growth factor	neurotransmitter	lipid mediator	enzyme	adhesion molecule
MBP	IL-1β	CCL-1/ eotaxin-1	VEGF	Substances P	LTD4-LTE4	MMP-9	integrin β1
EPX	IL-1Ra	CCL-1/ MCP-4	PDGF	NGF	PGE1, PGE2	ACP	integrin β2
ECP	IL-2	CCL-2	APRIL			collagenase	CD62L
EDN	IL-3	CCL-3	EGF			histaminase	CD49f
CLC	IL-4	CCL-5	SCF			Phospholipase D	CD49d
	IL-5	CCL-7				catalase	CD11a
	IL-6	CCL-8				ARSB	CD11b
	IL-8	CCL-11					CD11c
	IL-10	CCL-13					
	IL-12	CXCL1					
	IL-13	CXCL10					
	IL-6	CXCL12					
	IL-17						
	IFN-γ						
	GM-CSF						
	TGF-β						
	TNF-α						

FIGURE 1 (See caption on next page).

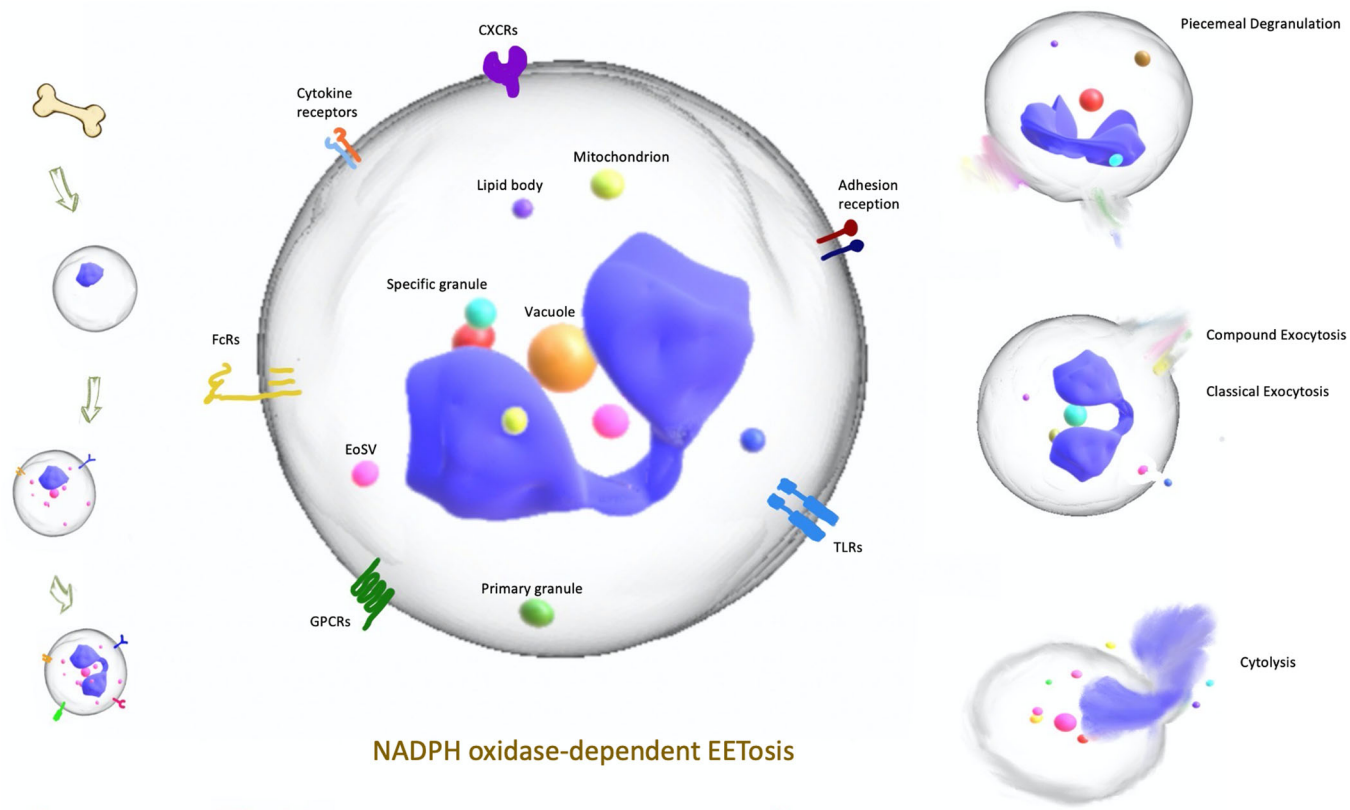


FIGURE 2 Schematic diagram of the mechanism of eosinophil degranulation. The figure exhibits the ephemeral process of the morphological variations possessed by eosinophils experiencing EETosis. Stimulus-induced NADPH-oxidase activation brings on the usual crouse of eosinophil lysis, followed by the typical reduction of bilobed nuclei to a lone round nucleus. Eosinophils are able to release granular contents in response to various stimuli through classical exocytosis, complex exocytosis, PMD, or cytolysis. Classical exocytosis is specified as the free of the complete particle contents by the fusion of the particles to the plasma membrane. Complex exocytosis is specialized by the fusion of intracellular granules with granules before extracellular release. PMD is the ascensive and exclusive free of particle contents mediated by transport vesicles. Cell lysis indicates cell death in the form of nonapoptotic forms specified by the formation of vacuoles within cells and the fragmentation of the nucleus and plasma membrane, reflecting on the free of nuclear DNA and the accretion of intact particles in the outer room. Mature eosinophils mainly include eosinophils and lobulated nucleogranulocytes. The surrounding blood cells mostly contain round or round-like lobulated nuclei, lens-shaped nuclei, coarse nuclear chromatin, and rich cytoplasm containing orange–red coarse, round, tightly arranged eosinophilic granules.

FEGs may be the primary mode of eosinophil manipulation in vivo, rather than the crushing artifacts observed in vitro experiments that release cell granules attributed to mechanical destruction to cells or insufficient release of cell particles.[18] Cell lysis of eosinophils is believed to include the spillage of cell contents, including nuclear material and granule proteins, into the extracellular matrix and occurs in living cells or lysed cells.[4,19] Eosinophils are actively involved in a variety of allergic, infectious, and auto-immune ailments. One pivotal event in the pathology of numerous nonallergic and allergic inflammatory ailments is the moment of eosinophil degranulation, which pictures the free of granular contents into the extracellular room following irritation of eosinophils.[20] In fact, cytolysis has been observed to be the main secretory mechanism involved in eosinophilic esophagitis.[16]

FIGURE 1 Immune cell lineage and its morphology, focusing on eosinophil-related factors. Pluripotent stem cells and colony-forming units (CFUs), which are cells with long lifespans, can complement more functionally and terminally differentiated cells. Eosinophils, neutrophils, basophils, monocytes, and lymphocytes are the five types of white blood cells that are normal and mature in human beings, all derived from hematopoietic stem cells in the bone marrow. White blood cells can be divided into granular and granular free according to morphological differences. Staining granular leukocytes with Reye's dye distinguishes between three types of granular leukocytes, including neutrophils, eosinophils, and basophils. In addition, granule-free leukocytes include monocytes and lymphocytes. Eosinophils release a variety of particles, including crude eosinophils containing peroxidase and acid phosphatase. Eosinophils are mainly used to defend against bacteria and parasites but are also very important during immune and allergic reactions.

Extracellular traps

Occurrence and development of extracellular traps—From NETs to EETs

ETosis is an active category of nicotinamide-adenine-dinucleotide-phosphate (NADPH) oxidase-mediated rapid nonapoptotic cell death that was first observed in neutrophils, called neutrophil ETosis (NETosis).[21] Neutrophils are known to form extracellular frameworks including DNA and granular proteins known as neutrophil extracellular traps (NETs).[22] The newly discovered frameworks are constituted by neutrophils in activated that can terminate invading pathogens prior to their arrival in the host cells, which is a physical process thought to occur after neutrophils engulf and secrete soluble antimicrobial agents and thus serve an antibacterial function. In contrast to what occurs during apoptosis, the nucleus informs the changes of dynamic, containing that reduction of nuclear lobes and chromatin conformation. Eventually, the nuclear membrane disintegrates, followed by the rupture of the plasma membrane, which releases the entire cell contents, including chromatin. DNA traps, which comprise filamentous chromatin frameworks, have been informed to trap and terminate extracellular microorganisms. To date, the formation of DNA traps is thought to be a general mechanism of the innate immune system in vertebrates.[23] Until recently, ETosis has been announced to occur in invertebrate cells, showing an antique and evolutionarily conserved notion.[24]

There is recent evidence that activated eosinophils display similar extracellular frameworks, called EETs, which can bind and terminate bacteria extracellularly.[25] This extracellular network is known to react with reactive-oxygen-species (ROS) after initiation with IFNɣ, C5a, eotaxin, LPS, IL-5, and *Staphylococcus aureus* (*S. aureus*) or thymic stroma-dependent formation of lymphopoietin.[26] Importantly, during ETosis, eosinophils and released particles can evade the rapid clearance of phagocytes.[27] However, the mechanism is still debated.

In early studies, extracellular DNA traps were learned in infectious and autoimmune ailment models. Until recently, they have also been investigated in noninfectious models, just like allergic ailments associated with EETs.[28] However, EETs contain smaller amounts of proteases than NETs. These proteins alter the stability and lofty viscosity of eosinophilic mucins, which in turn impair their interval by inflammatory cells and antibiotics.[29] Thus, EETs may lead to persistent sticky lumen surfaces following their release from cells, leading to further damage to barrier function as well as the possibility of increasing the growth of biofilms and bacterial aggregation in addition to chronic ailment and reinfection.

Eosinophilic extracellular trap formation theory

Currently, there are two theories about the formation of EETs and the fate of the cells that release them. Histones attach to nuclear DNA and make up nucleosomes, the minimum building blocks of chromatin fibers. Extracellular histones, which are dominating components of EETs, are famous for their own pleiotropic effects on the microenvironment, covering and promoting sterile inflammation as well as killing bacteria.[30] Histones, which are not shown in mitochondria, are likely to identify between the formation of EETs depending on mitochondrial-DNA (mtDNA) scaffolds from living cells and those depending on nuclear DNA scaffolds from lysed cells undergoing EETosis.[31]

Yousefi was the first to observe a DNA network structure similar to that of neutrophils that were ejected from live eosinophils. The DNA present in these EETs is derived from mitochondria, and the DNA strands are embedded with granular proteins.[4] Recent studies have shown that degranulation is swift and appears all alone in mtDNA transmission. mtDNA released from eosinophils may encounter the extracellular space and bind to the free EPX. Alternatively, adversely charged mtDNA may be transmitted by formerly fused, emptied particles, and reciprocity interacts with the unexhausted intragranular proteins to make up EETs. This means that these processes have distinct signaling pathways, and given their various free kinetics, it is presumable that the binding between mtDNA and eosinophil proteins during EET formation appears in the extracellular storage.[32]

In 2013, Ueki et al.[19] reported a cleavage mechanism that highlights the release of EETs from nuclear sources. This study was the number one to memorandum human eosinophils undergoing EETosis and revealed the process by which eosinophils undergoing cytolysis release intact cell-free and secretory-competent granules. To study the mechanism of eosinophil lysis, they used immobilized immunoglobulin G (IgG), immunoglobulin A (IgA), and PAF with IL-5 or granulocyte-macrophage colony-stimulating factor (GM-CSF) as well as nonphysiologically stimuli and calcium ionophores. Each of these stimuli causes EETosis, which is a process that is distinct from necrosis or apoptosis. EETosis occurs gradually and is dependent on ROS production, which can be inhibited by DPI. These stimuli are famous for inducing/triggering ROS production by eosinophils.[33,34] The ETosis process in eosinophils is similar to the process in neutrophils, but the important difference is that intact eosinophil granules are free extracellularly and as usual involve most of that protein content. At least some of the particles released by EETosis still have a secretory capacity. Thus, EETosis results in the manufacturing of extracellular reticules and cell-free particles containing nuclear DNA, both of which may exert biological activity against dead eosinophils. The exact mechanism by which EETs are formed is still unknown and requires further study. Knowledge of EET fabrication may intensify the understanding of eosinophil-associated nonallergic and allergic inflammatory complaints.

Features of EETosis

In vitro, activated humankind eosinophils swiftly respond to diverse stimuli after 30–120 min, and EETosis occurs.[35] Most particles remain intact during the EETosis process, leading to the production of free extracellular particles and EETs without granular proteins. Cell

death would be distinguished by emblematic nuclear and cytoplasmic concentrated morphologies, while apoptotic cells undergoing EETosis exhibit disintegration of cell membranes and transmission of free particles.[36] Notably, ETosis is inhibited by NADPH-oxidase and catalase, where hydrogen peroxide changes hydrogen peroxide to extracellular water and molecular oxygen.[21] Serum, albumin, and red blood corpuscle that can clear ROS are also inhibitors of ion-mediated EETosis.[19] These observational experiments show that cell activation is nicely modulated in eosinophils that move through the bloodstream, while EETosis occurs chiefly within inflamed tissues or later eosinophils enter the lumen.[37] Additionally, oxidant-antioxidant imbalances in allergic ailments may favor the expansion of EETosis.[38] Tightening the molecular of ETosis seemingly is essential to minimize sterile inflammation and unnecessary autoimmunity.[39] In view of qualitative and quantitative analyses, cytolytic eosinophils (37%–82%) from inflammatory sites from diverse EADs experience ETosis.[14] The proportion of late and early eosinophils in ETosis is associated with the disease. Moreover, it is not exact that all eosinophils show features of ETosis at the identical site of inflammation. Finally, EETosis is associated with the freeing of FEG, the squeezing of intact EoSVs, and the emergence of CLCs.[14]

EETosis provides eosinophils with a transient, nondividing mechanism that may allow the maintenance of stimulation-dependent secretion in eosinophil-rich organs and tissues even after eosinophils die.[40] DNA traps provide a sizable adhesive surface than the cells themselves and could be at the heart of encapsulation reactions against reagents along with intact particles. The innate action of eosinophil DNA traps warns of the presence of a nonphagocytic parasite or fungal hyphae in the airways, intestinal lumen, or abscesses.[40] In addition, cytolytic ETosis leads to the free of cytokines, granules, damage-associated molecular patterns (DAMPs), viscous chromatin, and lipid mediators and promotes local immune responses, rheological properties of secretions, tissue damage, and sterile inflammation.[16] We found that although chromatin diffuses as EETs at the sites of inflammation, it is not veracious that all cytolytic eosinophils in the identical micro-environment exhibit the ultrastructural variation of ETosis, consequently suggesting that distinct eosinophil collections may be selected for activation in this pathway.[14]

EET functions

When stimulated with immobilized immunoglobulins, calcium ionophores, or platelet-activating factors, eosinophils exudation filamentous nuclear DNA and granule content in NADPH-oxidase-dependent mechanisms, and lipopolysaccharides, CCL11, and C5a, which can induce the noncytolytic free of mitochondrial DNA.[19] EETs stipulate protection against bacteria as well as fungi by capturing pathogens in the gigantic filamentous mesh. In one study, researchers used Il-5 transgenic mice to elicit sepsis through a cecum-ligation-puncture (CLP) model in which eosinophils could swiftly sign up at the site of intestinal inflammation and release EETs.[4] Another study provided conceptual data to show that the enlistment of eosinophils may generate inflammation as well. In inflammatory bowel disease (IBD), eosinophils enable proinflammatory cells that cause diarrhea, leading to histopathological damage, especially in epithelial cells; and strengthen fibrosis.[41] That expression of the released granule proteins was displayed to colocalize with the mtDNA scaffold.[28,42,43] While the accurate role of the various granules in EETs is currently unknown, scientists speculate that EET may allow particles to act centrally near specific pathogen targets to slow tissue damage.

The question of why eosinophils form mtDNA scaffolds after degranulation and exhibit a considerable time delay in EET release remains to be solved. Studies have speculated that the rapid release of granulin represents a nonspecific response to fighting invading pathogens associated with damage to surrounding tissues.[44] Recruiting granules to DNA scaffolds ensures that high concentrations of granules are close to the pathogen, and in this case, tissue damage is likely to be limited.[4] EETs can occur in autoimmune, infectious, as well as noninfectious ailments. EETs are mostly initiated in inflamed tissues or luminal spaces, just like the airways or gastrointestinal mucosa. EETs correlate with ailment intensity and affect the consistency of eosinophil mucin.[45] Since EETs contain toxic granular proteins, they are both beneficial and harmful to the immune defense system of the mucosa of the sinuses. If the body's immune system retrieves fungi or bacteria as pathogens, eosinophils may afflict them by convening and triggering EETs in the airway lumen. In addition to protecting the host, EETs also damage surrounding related tissues, causing dysfunction of the epithelial barrier and exacerbating inflammation of eosinophilic airway disease.[26] In addition, EETs may shelter the host by maintaining impaired epithelial cell barrier function and inhibiting pathogenic invasion.[35]

EOSINOPHIL-ASSOCIATED RESPIRATORY AILMENTS

The foremost effector function of eosinophils in primary inflammatory and allergic ailments comes from the free-of-particle contents. Activated eosinophils excrete proinflammatory components, such as matrix metalloproteinases, leukotrienes, cytokines (IL-5, IL-13, osteopontin), chemokines (CCL22, CCL11, eotaxin), and granular proteins.[46] These negotiators play different roles in the hypersensitivity responses that disrupt all species of microorganisms and in extra-cellular free after the activation of eosinophil.[47] Ailments characterized by eosinophil infiltration, such as severe eosinophilia (SEA), eosinophilitis-chronic-nasosinusitis (ECRS), and eosinophilic-otitis-media (EOM), have been perceived to involve the ample presence of EETs at the site of inflammation. ETosis accounts for a large percentage of cytolytic eosinophils in eosinophil-associated respiratory ailments. There is evidence that EETs considerably increase the viscosity of exudate in patients with ECRS, EOM, and Allergic-Bronchopulmonary-Aspergillosis (ABPA).[48] A reasonable phenomenon of EETs in inflammatory pathology may embrace

overreaction to microbial stimuli and decreased clearance of EET outcomes, such as dsDNA, histones, and peroxidase. The products are known as DAMPs, which activate both the adaptive and innate immune systems. Clinically available markers for monitoring EETosis may be useful in indicating eosinophil-targeted therapy modalities and may provide a detailed understanding of the pathogenesis of the ailment.

ECRS

Chronic sinusitis (CRS) is one of the challenging inflammatory disorders that includes noneosinophilic and eosinophilic phenotypes.[49] The latter is distinguishingly characterized by a larger burden of ailment in terms of the chance of recurrence after the intervention surgery and the risk of comorbidities.[50] Humankinds with ECRS are more prone to have Nasal-Polyps (NPs),[51] and thick colloidal discharge is a notable sign. The secretions that are usually collected during surgery are called allergic mucin or eosinophilic mucin.[52] The presence of eosinophils is related to an increase in ailment intensity.[53] Discharges that are unenviable to transfer can be pathogenic due to the regional concentration of MBP in the secretions far exceeding the standard needed to intervene in epithelial destruction.[54] Immunohistology analysis of CRS specimens has shown an association between extracellular deposition of sinus mucosal injury and MBP.[55] Lytic eosinophil degranulation is more easily observed in mucin than in tissues, so eosinophils within luminal-side mucin and tissue eosinophils may cause epithelial injury.[54] The subsequent epithelial injury may hinder the usefulness of ciliary beats, hence reducing mucus convey and perpetuating cycles of thickening secretions.[56] A large amount of diffuse and aggregated DNA is shown in eosinophils, forming a sticky scaffold that unifies eosinophils and the debris. Immunostaining of eosinophilic mucins shows that they are nucleation-derived chromatin frameworks or DNA traps. EETs exhibit thicker fibers, are covered by more histone molecules, and are slightly vulnerable to proteolytic deterioration. Interestingly, nevertheless, the presence of NPs is not a pivotal factor in the distinction in the number of EETs.[35]

EETosis is not an ailment-specific miracle, although its degree and tissue specialness seem to be vital for ailment evolution. For example, nasal polyposis informs a correlation between eosinophilic degranulation patterns and the degree of tissue eosinophilia depending on different clinical stages and origins.[57] Studies have shown that the existence of lactrin-10 is related with ailment intensity in invalid with ECRS.[58] The presence of antinuclear-antibodies (ANAs) in nasal effusions has also been reported in patients with sinus ailment and the Samter triad, as well as proof of exhaustive histone-coated EETs in nasal tissues.[35,59] The medical features of EETs may stem from their utilitarian properties. DNA traps are produced when the nasal mucosa is inflamed and impaired with hyper viscous eosinophilic mucin clearance, leading to persistent inflammation and secondary epithelial barrier defects.[48] In addition, odor molecules may interfere with the passage of the olfactory nerve from the nasal hollow into the olfactory epithelium. Decreased olfactory capability associated with EET emergence may indicate that tissue eosinophilia or eosinophil-associated mucus cytokines may generate cellular injury at the neuronal level, possibly due to inflammatory infiltration in ECRS-related olfactory dysfunction.[60] After elucidation of the involved mechanism, the implementation of an exact drug in the field of ECRS will be more efficient. This is because it involves multiple inflammatory ailments and exhibits a high degree of heterogeneity, leading to different treatment feedback. Despite eosinophil activation in inflamed lesions is associated with the pathogenesis of ECRS. Those elements, that contribute to persistent inflammation, are fully in incomprehension. A recent clinical finding suggested that tissue eosinophils and EET numbers are the most pivotal prognostic elements for refractory sinusitis. Furthermore, tissue eosinophil and EET calculations appear to possess analogous correlations with clinical indicators. The investigators explored the clinical duty of citrulline histone H3-positive EETosis in refractory CRSwNP and hypothesized that eminently active eosinophils and EETosis play a key role in tissues and are contained in the pathogenesis of ailment and tissue damage.[61] Overall, tissue eosinophilia and EETosis mainly impress refractoriness in the sick with CRSwNP.

Eosinophilic asthma

Among humankind with eosinophilic asthma, a subcategory of invalid with recurrent infectious bronchitis and low pulmonary utility exhibit autoantibodies in the sputum specimen.[62] Bronchoscopy often shows mucus plugs blocking the subsegmental bronchi, and histological analysis indicates many eosinophils in the mucus plugs. Cell-lysogenic eosinophils as well as CLC formation and deposition of chief alkaline proteins were sighted as well, demonstrating the presence of EETosis.[63] CLC is common at the site of inflammation of eosinophils associated with EETosis. Galectin-10 is the component protein of CLCs and is considered to make up the nongranular moiety (10%).[64] According to proteomic analysis of peripheral eosinophils, galactolectin-10 proved to be the all-important protein among the component proteins.[65] Galectin-10, assigned in the peripheral cytoplasm of eosinophils, is uniformly redistributed in the cytoplasm during ETosis, and CLCs are sporadically formed in the cytoplasm.[66] The response of EETs to bacterial infection may be related to the breakdown of local tolerance and the source of potential autoantigens. SNARE proteins establish a super-family of proteins involved in membrane fusion. Several studies have shown the intracellular presence of SNARE proteins in humankind eosinophils. Decreased airway-hyperresponsiveness (AHR) was discerned in synaptic Vesicle-associated Membrane Protein 7 (VAMP-7)-deficient eosinophils, implying that eosinophil degranulation is similarly crucial for asthma attacks.[67] The finding contrasts with new experimental research revealing that a lack of EPX or MPB in eosinophils does not improve AHR.[68] However, free particles in sputum may be a helpful biomarker of asthma activity.[69] Therefore, it is essential to deeply

study the right role of eosinophil proteins and eosinophil degranulation in the pathogenesis of asthma.

Peripheral blood eosinophils isolated from patients with intense eosinophilic asthma showed a considerable possibility for EET formation in vitro as stimulated with LPS and IL-5, and the proportion of EETs was uncorrelated with pulmonary function. EETs have been confirmed to possess an autocrine influence on containing subsequent degranulation of eosinophils as well as have been informed to activate epithelial cells to release proinflammatory cytokines.[70] In another research, EETs were informed to be released under excitation by thymic-stromal-lymphopoietin (TSLP), a well-known T helper 2 (Th2) cell signal.[71] Therefore, in the environment of Th2, EETs may be a latent source of autoantigens. Strangely, in vitro research has shown that pharmacologically pertinent concentrations of dexamethasone do not reduce autoantibody-activated eosinophil formation of EETs, suggesting the involvement of a persistent inflammatory environment in patients with steroid-resistant asthma. Furthermore, a study showed the presence of IgG-type autoantibodies in the airways of humankind with intense eosinophilic asthma, which may be caused by EET release. Due to this persistent inflammatory environment, interrupted resolution of EET-induced inflammation might activate an auto-response and the creation of autoantibodies against EET production.[72]

Studies have shown that ovalbumin sensitization and excitation in mice lead to EETs and EPX incrementation in eosinophils in pulmonary tissue and induce an increase in extracellular DNA levels in bronchoalveolar irrigation fluid.[73] In subsequent periods of time, the identical subgroup affirmed a significant reduction in airway resistance with recombinant DNase treatment, accompanied by decreased goblet cell hyperplasia and the formation of EETs.[74] EET secretions enlarged the mucin or airway secretions of these naïve mice after the allergen attack.[75] Mucosal thrombosis in humans with asthma is associated with eosinophilia as well as increased EPX levels in the airways and is associated with decreased lung function. Patients lose immune tolerance and exhibit increased production of local autoantibodies, leading to goblet cell hyperplasia and EET overproduction in associated mucin, both of which reflect on the creation of incredibly viscous, airway-obstructing mucus plugs, which are characteristic of eosinophilic ailment.

Chronic-obstructive-pulmonary-diseases (COPD)

Despite extensive research into COPD, the molecular and cellular foundation for the ailment's alteration remains uncertain. There is limited knowledge about EETosis and its utility in the pathogenesis of COPD. ANAs are an effective trigger for EET formation in vitro.[72] In earlier studies, ANAs would be discovered in sputum from humans with severe COPD, and an autoimmune pathology of COPD has been introduced.[76] Nevertheless, the chief function of EETs or NETs in COPD pathogenesis and any feasible intrinsic autoinflammation has not been demonstrated. Research has confirmed that eosinophils are a common cause of persistent cough in middle-aged individuals. They are also associated with increased AHR and can contribute to the obstruction of airflow or a decline in Forced Expiratory Volume in the first second (FEV1), ultimately leading to the development of COPD.[77]

Induction of EETosis in patients with COPD may be a secondary feature of the presence of eosinophils in the airways in genetically inclined humankind. According to the researchers' observations, eosinophils are very sensitive to smoke toxins, which trigger a widespread EETosis response when evaluated in sputum.[78] In addition, the increment of EET-associated debris and subsequent phagocytosis by neutrophils may initiate and pioneer NETosis, an incident that was very pronounced in the severe COPD exacerbation subgroup.[78] The cytotoxic impacts of eosinophils may be of greater prominence in patients with more severely symptomatic ailments and may exacerbate the ailment. Freely destroyed eosinophil-secreting granules may aggressively damage the epithelium and endothelium because the proteins they include can cause tissue harm and dysfunction.[48] The airway microenvironment of COPD caused by smoking may explain this difference because it triggers cell death. Collectively, EETosis helps explain the role of eosinophils in COPD pathophysiology, particularly at the onset as well as during progression and helps prevent COPD in young smokers at risk.

ABPA

ABPA is one of the pulmonary ailments caused by excessive allergy to *Aspergillus fumigatus*. Currently, imaging features of ABPA include bud shadow, mucus impaction, bronchiectasis, pulmonary opacity, pleural pulmonary fibrosis, and central lobular nodules.[79] It is specialized by bronchiectasis, recurrent pulmonary infiltrates, and poorly controlled asthma, often accompanied by thick eosinophilic mucus blockage.[79] The severity of this mucus blockage is associated with recurrence.[80] Scholars have demonstrated the presence of many EETs in mucus secretions acquired from the pulmonary of humankind with ABPA.[81] Mechanistically, EETosis induced in vitro by Aspergillus fumigatus is a tyrosine kinase pathway and involves the adhesion molecule CD11b β-integrin.[82] Airway eosinophils exhibit an enhanced response to multiple ligands and are further activated for degranulation.[82] Human eosinophils develop ETosis in response to immobilized IgG or IgA, IL-5/GM-CSF, and calcium ion carriers with platelet activators that release EETs. Besides a direct reaction to Aspergillus fumigatus, it is practicable that regionally created cytokines, immunoglobulins, and other mediators can trigger eosinophils to bring forth EETosis.

Notably, biomolecules associated with fungal cell walls trigger eosinophilic Th2 inflammation in mouse respiratory organs.[83] With Th2 conditions, blood eosinophils purposefully accumulate in airway mucosa. Eosinophils are frequently mitigated by migrating into the airway cavity and then removing the mucus cilia.[84] Except apoptosis, which creates fragmented DNA, ETosis occurs in luminal eosinophils by interacting directly with fungi or regional stimuli, releasing adhesive chromatin structures. EETs increase the consistency of

mucus rather than eliminating fungi directly. Eosinophil cell lysis transmits unimpaired granules and a wide extent of molecular patterns associated with nuclear and cytosolic damage.[85] Free particles can be used as repositories for toxic granular proteins and extracellular organelles with secretory capacity.[19] Persistent epithelial injury may hinder the applicability of cilia beats, hence reducing mucus transmission and lead to the eosinophil-induced inflammation. Therefore, EETosis may stimulate a continuous period of the production of thick secretions.[48] Further study of the pathophysiology of ETosis-derived DNA traps in allergic ailments may favor upcoming treatments for eosinophil inflammation.

Other eosinophil-related respiratory ailments

EOM is a previously cognized refractory middle ear ailment that has been a concern in foreign countries.[86] EOM is specialized by high-viscosity ear effusions and strong eosinophil infiltration in the mucous membranes of the middle ear.[87] Unlike chronic otitis media, EOM is closely related to allergic conditions. Corticosteroids are the only efficient drug treatment at the moment, and patients usually require the intervention of surgery. Mucosal eosinophils extensively infiltrate the middle ear cavity and are stimulated by regionally created activators. Removal of obstructive eosinophil mucin usually requires surgical measures to improve drainage pathways. Conductive hearing loss is predisposed to in the early stages of EOM, with half of humankind having an elevated bone conduction threshold, resulting in deafness (6%).[29] The unusual levels of toxic eosinophilic granule proteins discerned in eosinophilic mucin are considered pathogenic and cause epithelial injury. EETs have been reported in middle ear exudations obtained from a small number of humans with EOM.[35] To elucidate the presence or absence of cytolysis and ETs in EOM, researchers initiated a case series examination. ETosis-derived DNA traps were found to symbolize leading extracellular structural sections that support eosinophils and increase their consistency. The development of EETosis is most probably ordinary in humans with EOM as well as contributes to its pathogenesis. Neutrophil elastases and lysates can degrade the structure of EET. Surprisingly, the consistency of secretions in patients with EOM is decreased by bacterial infections. The finding permits us to meditate that the existence of neutrophils may reduce consistency.[88]

Antineutrophil cytoplasmic antibody titers are detectable in sputum in humans with eosinophilic granulomas as well as polyangiitis, triggering a wide degree of EET formation in vitro. Therefore, autoantibodies are an effective trigger for in vitro EET.[72] EETs, which have been confirmed in biopsies, are used for systemic autoimmune ailments such as bullous pemphigoid and Wegner granulomas, as well as inflamed intestinal tissue from autoimmune ailments just like Crohn's ailment.[4,42] Scholars have reported a higher number of eosinophils infiltrating the intestinal wall in IL-5-treated animals than in wild-type animals and transgenic mice after cecal ligation and puncture. Tissue eosinophilia is related with enlarged levels of discernible EETs accumulated in tissues, which may be the result of an overreaction to gut bacteria.[4]

CONCLUSION

Eosinophils are mysterious white blood cells with immune functions that are still being investigated. Traditionally, eosinophils have been thought to protect against parasitic infections, mainly sizable multicellular worms. Recent evidence suggests that a role for eosinophils, which are primarily involved in parasitic infections, also mediate immunity to viral, bacterial, and fungal infections. One of the proposed chemical processes by which eosinophils utilize their shielded impacts is a generation of DNA-based ETs. Notably, the role of DNA in encoding RNA and protein sequences extends beyond its biochemical function. As an incredibly efficient physical entity, it is mainly used for capturing bacteria and other extracellular pathogens, while serving as a precious scaffold for antimicrobial mediators, just like granule proteins from immune cells.

Eosinophils are thought to be terminal effector cells included in the host to safeguard from parasitic infection and Th2-type inflammation. Eosinophilia, an activated phenotype that has been shown in biological specimens from patients with complaints, is easily observed accumulation of FEG in the corresponding tissues or exudation of humankind.[7] Subsequently research studies are required to clear up the precise pathophysiological role in vivo; besides the models of mice may possess some restrictions in analyzing eosinophil lysis.[89] Nevertheless, the clinical significance of eosinophilia has been underestimated, in part due to a scarcity of comprehension of pathogenic mechanisms and etiologies. The existing thought of EETosis triggers a brand-new orientation on eosinophilic inflammation. Blood-derived eosinophils accumulating in inflamed tissues have two directions, some of which form FEG through EETosis, while others migrate subsequent to the sinus cavity and free DNA traps that form the agglomeration framework of eosinophil mucin. EETosis releases unscathed cellular contents that are perdurability, unlike apoptosis. Therefore, new therapeutic targets for eosinophilic respiratory diseases may focus on dysregulation or overactivated EETosis and DNA traps. Clinically available markers for monitoring EETosis may help indicate eosinophil-targeted therapy.

AUTHOR CONTRIBUTIONS

Shun-Yu Wu: reviewed the relevant literature and wrote the manuscript. **Bo-Yu Cai**, **Tian-Yu Wang**, **Zhi-Wen Cao**, and **Hu Peng**: participated in proofreading. **Huan-Hai Liu**: proofread the article.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors have nothing to report.

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