International Journal of Ecophysiology
Journal homepage: https://ijoep.usu.ac.id

Differences And Different Responses In Inflamation And Pneumonia (A Mini Review)

Yulia Putri[1], Dina Keumala Sari[2]*, Yunita Sari Pane[3], Ririe Fachrina Malisie[4], Nuraiza Meutia[5], M. Ichwan[3]

1 Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

2 Departement of Nutrition, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

3 Department of Pharmacology and therapeutic, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

4 Department of Pediatric, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

5 Department of Physiologi, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

*Corresponding Author: dina@usu.ac.id

ARTICLE INFO

Article history:
Received 23 Desember 2023
Revised 14 January 2024
Accepted 18 February 2024
Available online
https://talenta.usu.ac.id/ijoep

E-ISSN: 2656-0674

How to cite:
Putri Y, Sari DK, Pane YS, Malisie RF, Meutia N, Ichwan M. 2024. Differences And Different Responses In Inflamation And Pneumonia (A Mini Review). *International Journal of Ecophysiology*. 6(1), 43-49

10.32734/ijoep.v6i1.15779

ABSTRACT

A major public health issue with high morbidity and short and long term mortality in all age groups worldwide, pneumonia is a typical acute respiratory infection that affects the alveoli and distal airways. Community-acquired pneumonia and hospital-acquired pneumonia are the two main categories of pneumonia. Pneumonia can be brought on by a wide range of microbes, including bacteria, respiratory viruses, and fungus. The incidence of these microbes varies greatly geographically. Pneumonia affects susceptible people more frequently, such as young children under the age of five and older persons with a history of chronic illnesses. Pathogen features play a less important influence in disease development than does the host immune response. Patients with pneumonia frequently exhibit respiratory and systemic symptoms, and radiological findings as well as clinical presentation are used to make the diagnosis. It is essential to identify the microorganisms that are causing the disease because delayed or ineffective antimicrobial therapy can have negative effects. The treatment of pneumonia will be enhanced by new antibiotic and non-antibiotic medicines, as well as quick and precise diagnostic tools that can identify bacteria and drug resistance.

Keyword: Pneumonia, lung, inflammation, bacteria, respiratory

ABSTRAK

Pneumonia merupakan masalah kesehatan masyarakat yang besar dengan morbiditas dan mortalitas yang tinggi dalam jangka pendek dan jangka panjang pada semua kelompok umur di seluruh dunia. Pneumonia adalah infeksi saluran pernapasan akut yang umum menyerang alveoli dan saluran napas bagian distal. Pneumonia yang didapat dari komunitas dan pneumonia yang didapat di rumah sakit adalah dua kategori utama pneumonia. Pneumonia dapat disebabkan oleh berbagai macam mikroba, termasuk bakteri, virus pernapasan, dan jamur. Insiden mikroba ini sangat bervariasi secara geografis. Pneumonia lebih sering menyerang orang-orang yang rentan, misalnya anak-anak di bawah usia lima tahun dan orang lanjut usia dengan riwayat penyakit kronis. Ciri-ciri patogen memainkan pengaruh yang kurang penting dalam perkembangan penyakit dibandingkan respon imun pejamu. Pasien dengan pneumonia sering kali menunjukkan gejala pernafasan dan gejala sistemik, dan temuan radiologis serta gambaran klinis digunakan untuk membuat diagnosis. Penting untuk mengidentifikasi mikroorganisme penyebab penyakit karena terapi antimikroba yang tertunda atau tidak efektif dapat menimbulkan efek negatif. Pengobatan pneumonia akan ditingkatkan dengan obat-obatan antibiotik dan non-antibiotik baru, serta alat diagnostik yang cepat dan tepat yang dapat mengidentifikasi bakteri dan resistensi obat.

Keyword: Pneumonia, paru-paru, peradangan, bakteri, pernafasan

1. Introduction

A fairly uncommon result of frequently occurring host-microbe interactions is pneumonia.Numerous common and unavoidable microorganisms, including the rhinovirus, influenza virus, pneumococcus, Staphylococcus aureus, and many others, are responsible for pneumonias. Most people routinely come into con-tact with these microorganisms, yet pneu-monia seldom happens. What vari-ations in host-microbe interactions control the development of pneumonia?

The very young, the elderly, and individuals with a variety of ailments or diseases, such as stress, poverty, poor air quality, obesity, diabetes, atherosclerosis, and more, tend to be more susceptible to pneumonia. The mechanisms that make these people more vulnerable to pneu- monia are largely theoretical. Variations in the inflammatory response during res-piratory infection are among the many factors at play [1].

More than a little portion of pneumonia cases are not caused by any one species of bacteria. The biology of the microbe is important, even though it may not be as crucial as the host's reaction to the germ. Microbe characteristics can affect the likelihood and severity of pneumonia. The interaction between bacteria and the host's inflammatory pathways is at the heart of some of the microbial differences linked to pneumonia development. For instance, more virulent pneumococci are more likely to induce pneumonia than those that stimulate macrophage inflammatory resp-onses. In the US, Pneumococcus is the most frequent bacterial cause of both pediatric and adult community-acquired pneumonia (CAP) [2].

Pneumococcal isolates discovered in children that were studied and taken from patients' blood or empyema fluid or from the nasal passages of carriers without pneumococcal illness showed a significant variance in macrophage NF-kB activation. An important transcription factor for the production of many pro-inflammatory cytokines is NF-kB. Compared to isolates from other children, children with complex pneumonia have a higher like-lihood of having low NF-kB activators in their pneumococcal isolates. Both in vitro and in vivo, these pneumococci cause macrophages to express pro-inflam-matory cytokines in a lower and slower manner, and they clear mice's lungs of the pathogen less successfully [3,4]. These results imply that pneumococcus has the viru-lence trait of not inducing inflammation.

2. Biomarker of Pneumonia related infec-tion, inflammation and immune system

Various non-infectious forms can deliver respiratory indications and unused aspir-atory penetrates with systemic in-cen-diary signs and side effects with fever, leukocytosis and intense stage reactants that can be easily befuddled with bac-terial pneumonia. Ordinarily, Gram stains of respiratory discharges are frequently inaccessible or are troubl-esome to asse-ss, and microbi-ological culture reports take 24 to 48 hours. A negative sputum culture in a persistent suspected of hav-ing community-acquired pneu- monia (CAP) does not run the show out the plausibility of extreme bacterial conta-mination [5].

The standard strategies utilized nowadays to analyze CAP have not changed obviously since Pasteur and Sternberg to begin with refined pneum-ococci from sputum in 1881 and Christian Gram to begin with connected his presently popular recolor to look at sputum examples 5 a long time after-ward. Procuring tall quality sputum tests for culture and translating these culture comes about stay tricky clinical chall-enges. There are no unequivocal clinical indicators of infection serio-usness, in spite of the fact that numerous clinical scoring frameworks right now exist for this reason. No by and large concurred criteria exist for discourage mining whichh patients ought to be conceded to the clinic therapeutic benefit or to the seriously care unit (ICU). Given these regions of vulnerability in clinical dec-ision-making, a concerted exertion has been embraced to create dependable and commonsense biomarkers for the determination, hazard expectation and administration of CAP [5,6].

To be accommodating in schedule clinical hone, a biomarker ought to give extra noteworthy data not as of now accessible by standard strategies – that finishes at slightest one or more of the taking after: helps in set up- ing a quick and solid determination; gives an sign of guess; chooses those patients most likely to advantage from a particular interce-ssion; reflects the viability or need of adequacy of particular intercessions; cau-tions in development of disease mov-ement; shows a expansive suff-iciency of variety and does not appear an fatigue or weariness marvel, meaning that amid drawn out and progressive conta-minations its levels stay raised and conti-nuously responsive to the irresistible jolt [7].

Table 1. Biomarker of Pneumonia

	Widely available biomarkers	**Potential future biomarkers**
Biomarkers of inflammation	Tumor necrosis factor alpha	IL-1β
	Lactate	IL-6
		IL-10

Biomarkers of coagulation	Activated partial thromboplastin time	Protein C
	Platelets	D-dimer
	Fibrinogen	Thrombin–antithrombin complexes
	Disseminated intravascular coagulation scores	Prothrombin fragment 1.2
		Activated partial thromboplastin time waveform analysis
Biomarkers of infection	C-reactive protein	Adrenomedullin
	Procalcitonin	Pro-adrenomedullin
	Blood urea nitrogen	B-type natriuretic peptide
	Leukocytes	Triggering receptor expressed on myeloid cells-1 (soluble triggering receptor expressed on myeloid cells-1)
	Endotoxin	High mobility group box-1
	PCR	
Biomarkers of stress	Cortisol	Copeptin

3. Constitutive immune defense of the lung

Numerous continually active defen-ses that cooperate to safeguard the respir-atory tract. Inhaled creatures are more likely to be impaction by the branching system of conducting airways before they enter the deep lung. Impacted bacteria are captured by the mucociliary escalator in the conducting airways, which propels them into the glottis where they are ingested for digestion and/or excretion. By limiting vital nutrients and containing elements toxic to microo-rganisms, the surface-lining fluids of the respiratory system, from the nose to the alveoli, are unfriendly to microbes. Microbes that manage to get past these aforementioned defenses are phag-ocytosed by alveolar macrophages, whi-ch patrol the lung surface [6,7]. These inherent defenses frequently enough to stop clinically significant microbial accum-ulations when lung-penetrating mi-croorganisms are few and not particularly aggressive [7].

Even though the lungs have experienced a lot of microbial exposure and are not completely sterile, they normally do not become infected. People who have weaknesses in these funda-mental defenses may be more susceptible to pneumonia. Although specifically addressing inflammation is outside the purview of this manuscript, it is important to note that pneumonia risk is frequently exacerbated by airway structural changes (such as those caused by chronic respiratory diseases), muco-ciliary escalator dysfunction (such as primary ciliary dyskinesia), altered surface lining properties (such as those caused by changes in salts, carbo-hydrates, or other metabolites), or other flaws in constitutive lung defenses [8].

4. Constitutive immune defense of the lung

When a population of virulent or numerous bacteria overwhelms the body's natural defenses, it becomes required to mobilize an additional defe-nse (inflammation). Effective micro-organism eradication, in particular, depends on rapid neutrophil accum-ulation. By phagocytosis, degranulation, and the release of neutrophil extracellular traps, these inflammatory cells eliminate microorganisms. Monocytes, dendritic cells, natural killer (NK) cells, invariant natural killer T (iNKT) cells, gd-T cells, mucosa-associated invariant T (MAIT) cells, and innate lymphoid cells (ILCs) of various types are some of the leukocytes recruited in addition to neutrophils to help with antimicrobial lung defense. Beyond these cell accumulations, extra-vascular plasma also builds up, resulting in the radiological infiltrate that is used to diagnose pneumonia [9].

While pulmonary edema directly causes lung damage, this fluid exudate's antimicrobial components, including complement and antibodies, are crucial to immune defense. Coordination between these inflammatory processes aids in the removal of many and/or virulent microorganisms from the lungs [10].

While rapidly escalating inflam-mation aids in the battle against infe-ction, putting the breaks on the inflammatory response is also essential. The inflammation in the infected or previously infected lung is slowed or reversed by a variety of processes. Using gap junction connections, alveolar macr-ophages control the inflammatory reactions of epithelial cells. Ion transport proteins in epithelial cells remove infla-mmatory

exudate fluid by pumping it from the air gaps into the interstitial spaces, where it can be eliminated by lymphatics [11].

Efferocytosis, which is triggered by specialized pro-resolving mediators including Lipoxin A4 and Resolvin D1, eliminates dead and dying inflammatory cells like apoptotic neutrophils. The infected lung is populated by cells that are trained to control inflammation and injury, such as regulatory T cells and myeloid-derived suppressor cells. These anti-inflammatory and inflammation-resolving systems work together to lessen and avoid the clinical severity of pneumonia [7.12,13].

5. Mechanism of Infection to activated Immune response

Safe resistance points to annihilate microorganisms that attack the aviation routes. Respiratory epithelial cells are secured by cell-associated and discharged mucins that frame a layer of polymeric glycoconjugates that expel pathogens from the aviation routes. The epithelium can moreover expel pathogens through phagocytosis and intracellular murdering. The tranquil alveolar space contains numerous alveolar macrophages that, upon actuation, can phagocytose and murder pathogens, which is moved forward by apoptosis. Natural lymphoid cells (ILCs) are tissue-resident cells populating the aspiratory mucosa. Along with common executioner cells, ILCs boost have resistance amid aviation route disease[11,12,13]. Neutrophils move to the aviation routes pulled in by chemotactic proteins discharged by respiratory epithelial cells and alveolar macrophages; these chemotactic proteins too advance the enlistment of other leukocyte subsets. The lung contains a marginated pool of neutrophils fastened to the vasculature, empowering quick neutrophil enrollment into tissue upon disease. Satisfactory pneumonic resistance involves neutrophil- intervened slaughtering of attacking organisms by a few effector components, counting the discharge of neutrophil extracellular traps (NETs)[3,7,8]. Platelets can frame complexes with leukocytes, encouraging NET arrangement and the discharge of microbicidal specialists. Inhabitant memory T (T RM) cells are created after introduction to pathogens and dwell within the tranquil lung. ATI, alveolar sort I cell; ATII, alveolar sort II cell; BASC, bronchioalveolar stem cell; CXCs, CXC chemokines; DAMPs, damage-associated atomic designs; NF-κB, atomic factor-κB; RBC, ruddy blood cell; SP, surfactant protein; T1R, G-protein-coupled sweet taste receptor; T2R, G-protein-coupled biting taste receptor; TLR, Toll-like receptor (Fig1).

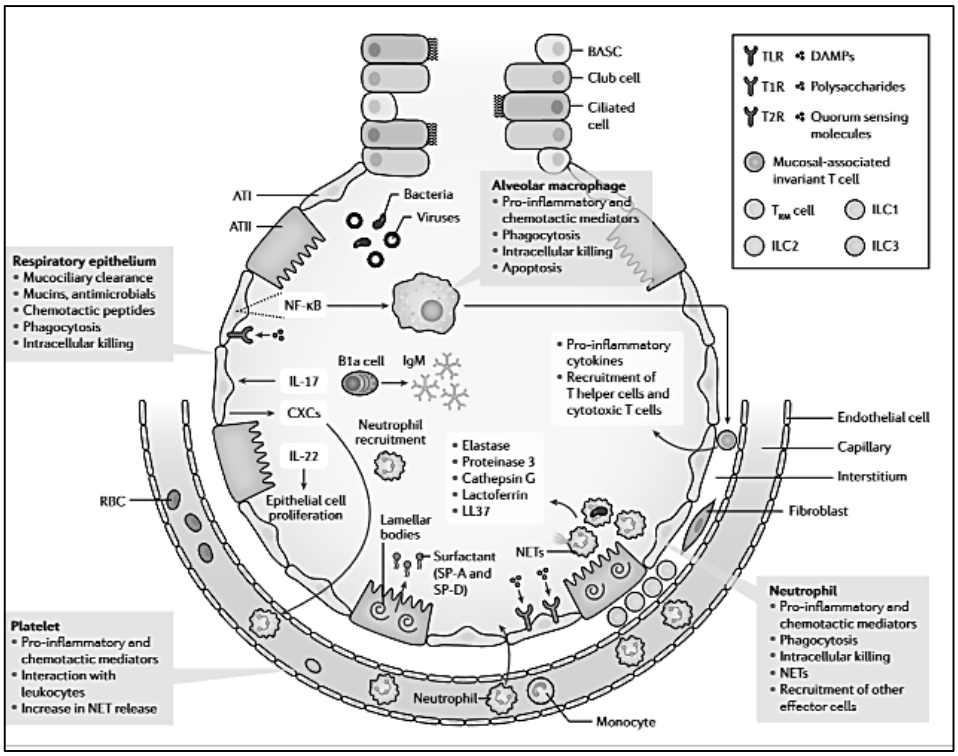

Figure 1. Immune resistence and response of Bacterian and antigen infection to induce pneumonia [34].

Anatomical obstructions display the primary line of guard against pneumonia. Mucociliary clearance, interceded by mucous and fluid layers and cilia on the surface of respiratory epithelial cells, is considered the essential intrinsic resistance mechanism. The respiratory epithelium professional duces a vigorous obstruction composed of secretory items, surface glycocalyces and films, and intercellular junctional proteins connected to the actin cytoskeleton. Cell-associated and emitted mucins shape a polymeric glycoconjugate layer that can tie and transport way ogens from the airways. The branching bronchial tree gives an extra protection

component by avoid- ing particles of >3 μm in distance across from entering the lower airways. On the off chance that organisms do reach the lower respiratory tract, the have protection gets to be molded by an connect play between inhabitant and enlisted resistant cells and components [10].

5. Mechanism of Infection to activated innate immunity

The intrinsic safe framework is antiquated, and numerous angles are moderated over vertebrates, spineless creatures, and plants. In one sense, it can be characterized as those angles of have defense encoded within the germline that do not require the quality modification central to versatile insusceptibility. Practically, individuals of the natural safe reaction recognize moderated atomic designs, raise prompt cautious instruments, alarm and enlist other individuals of the safe reaction to the location of infection, and arrange reactions with the versatile safe reaction. This framework incorporates physical boun-daries, design acknowledgment instru-ments, cell murdering by resistant cells and antimicrobial proteins, and coordin-ation through cytokine signaling [11,12].

Different safe and non-immune cell sorts take part within the pneumonic natural resistant reaction. Aviation route epithelial cells create bodily fluid and antimicrobial peptides, which traps and neutralizes flotsam and jetsam and pathogens, and expels them from the lung by means of the mucociliary lift. Inhabitant resistant cells, counting macr-ophages and lymphocytes, and alveolar epithelial cells surveil the aviation route and alveolar spaces for potential patho-gens, emitting chemokines, and cytokines to enroll extra effector cells such as neutrophils and monocytes [15]. Movement of these cells to the alveolar space through the extracellular network is encouraged by vascular endothelium, fibroblasts, and alveolar epithelial cells (Figure 2).

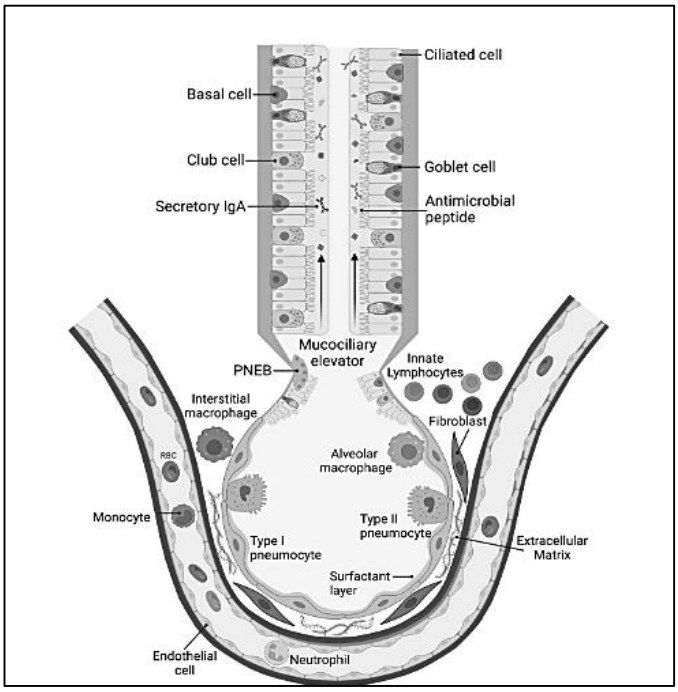

Figure 2. Innate Immune and response of Bacteria and antigen infection to induce pneumonia [33].

The normal human lung motivates roughly 11,000 L of discuss every day, containing a blend of gasses, fine standardticulates (e.g., dust and flotsam and jetsam) and microorganisms. As such, the lung has a few anatomical boundaries which onstitute the primary line of defense against lung pathogens. The epithelial cells of the conducting aviation routes frame a con- tinuous physical and chemical obstruction of pseudostratified epithelium within the proximal aviation routes with basic cuboidal epithelium in more distal bronchioles. Whereas their work is heterogenous, all epithelial cells of the lung share in their capacity to direct paracellular permeability through tight and adherens intersections [16]. These proteins, checked on broadly somewhere else, give a physical obstruction between the airspace and interstitium through their associations with neighboring cell cytoskeletal proteins. These paracellular intelligent avoid dissemination of microorganisms and vascular spill, which may be disturbed amid provocative damage by have components such as TNF-α (tumor rot figure alpha) and pathogen-derived poisons, such as pneumolysin and lipopolysaccharide [17,18]. The facilitate activity of ciliated and challis cells of the upper aviation routes too gives a essential work for anatomical defense: mucociliary clearance [19]. The upper aviation routeis lined with a complex aviation route surface fluid, comprised of a gel-like upper layer made of bodily fluid that physically traps organisms and

particles from the environment and a more fluid-like lower layer that encourages the beating of cilia. Whereas containing more than 200 proteins, the bodily fluid layer is fundamentally made up of mucins, especially MUC5AC and MUC5B (mucin 5AC and 5B), discharged by cup cells and submucosal organs [20,21,22]. As of late reviewed in detail, these polymeric glycoproteins help within the physical composition of the aviation route lining liquid that Fig. 2 Outline of highlights of the natural immune response within the lungs. Different safe and non-immune cell sorts take an interest within the aspiratory intrinsic resistant reaction [23,24].

Aviation route epithelial cells create bodily fluid and antimicrobial peptides, which traps and neutralizes flotsam and jetsam and pathogens, and evacuates them from the lung through the mucociliary lift[25,26]. Inhabitant resistant cells, counting macrophages and lymphocytes, and alveolar epithelial cells surveil the aviation route and alveolar spaces for potential pathogens, discharging chemokines, and cytokines to select extra effector cells such as neutrophils and monocytes. Movement of these cells to the alveolar space through the extracellular network is encouraged by vascular endothelium, fibroblasts, and alveolar epithelial cells [27,28,29].

Besides, mucins are known to have coordinate against microbial work. MUC5B is particularly basic for homeostatic direction of mucociliary clearance, the need of which leads to persistent disease and a decrease in macrophage work and interleukin-23 (IL-23) professional duction [30,31]. In the interim, MUC5AC is vital in have defense against flu infection, possibly through its intuitive with α2,3-linked sialic corrosive. Interests, MUC1 (mucin 1), a transmembrane mucin communicated by both epithelial and resistant cells, has an immunomodulatory part to hose fiery signaling amid respiratory contamination through coordinate interaction with toll- like receptors (TLRs) [32,33]. Increased mucin discharge after either flu or Streptococcus pneumoniae infec- tion was as of late appeared to be mostly subordinate on sort I intergalactic signaling, the generation of which was too related with in expanded microbial shedding and transmission [9,34].

5. Conclusion

Long run may lie in combining data from sev- eral markers, each reflecting a different angle of illness. Such a board might incorporate one marker of bacterial infec- tion, one marker reflecting cluttered coagulation, one hormone, and one proinflammatory cytokine. This professional- posal draws credibility from prove for the incremental esteem of combining markers of cleared out ventricular dysfunc- tion, myocardial cell harm, renal disappointment and inflamma- tion in anticipating cardiovascular passings among more seasoned men. Consolidating the four biomarkers significantly progressed the prognostic esteem of a show based as it were on built up chance variables such as age, blood weight and hyperlipidemia. Interests, two of the four check- ers included in predicting cardiovascular hazard (pro-brain natriuretic peptide and CRP) cover with those examined over within the setting of serious CAP.

REFERENCE

[1] Peteranderl C, Morales-Nebreda L, Selvakumar B, et al. Macrophage-epi-thelial paracrine crosstalk inhibits lung edema clearance during influenza infe- ction. J Clin Invest. 2016; 126 (4):156 6–1580. [PubMed: 26999599

[2] Nikolich-Zugich J The twilight of immunity: emerging concepts in aging of the immune system. Nat Immunol. 2018;19(1):10–19. [PubMed: 2924254 3]

[3] Dela Cruz CS, Wunderink RG, Christiani DC, et al. Future research directions in pneumonia: NHLBI wor king group report. Am J Respir Crit Care Med. 2018;(in press)

[4] Tseng, Y. W., Chang, C. C., and Chang, Y. C. Novel virulence role of pneumococcal NanA in host inflam mation and cell death through the activ ation of inflammasome and the caspase pathway. *Front. Cell Infect. Microbiol*. 2021.11, 613195. doi:10. 3389/fcimb. 2021.613195

[5] Sharapova, Y., Svedas, V., and Suplat ov, D. Catalytic and lectin domains in neuraminidase a from Streptococcus pn eumoniae are capable of an interm olecular assembly: Implications for bio film formation. FEBS J. 2022. 288, 3217–3230. doi: 10.1111/febs.15610

[6] Justiz Vaillant, A. A., Sabir, S., and Jan, A. Physiology, immune response. In: StatPearls [Internet]. 2022. Treasure Island (FL): StatPearls Publishing.

[7] Dalia, A. B., Standish, A. J., and Wei ser, J. N. Three surface exoglycosidases from Streptococcus pneu moniae, NanA, BgaA, and StrH, promote resis tance to opsono phagocytic killing by human neutrophils. Infect. Immun. 2010. 78, 2108–2116. doi:10.112 8/IAI. 01125-09

[8] Blanchette, K. A., Shenoy, A. T., Milner, J., Gilley, R. P., Mcclure, E., Hinojosa, C. A., et al. Neuraminidase a-exposed galactose promotes Streptoc occus pneum oniae biofilm formation during colonization. Infect. Immun. 84, 2922–2932. 2016. doi: 10.1128/ IAI. 00277-16

[9] Tang BM, McLean AS, Dawes IW, Huang SJ, Cowley MJ, Lin RC: Gene-expression profiling of gram-positive and gram-negative sepsis in critically ill patients. Crit Care Med 2008, 36:1125-1128.
[10] von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, Chrabieh M, Musta pha IB, Ghandil P, Camcioglu Y, Vasc oncelos J, Sirvent N, Guedes M, Vitor AB, Herrero-Mata MJ, Arostegui JI, Rodrigo C, Alsina L, Ruiz-Ortiz E, Juan M,Fortuny C, Yague J, Anton J, Pascal M, Chang HH, Janniere L, Rose Y, Garty BZ, Chapel H, Issekutz A, et al.:Pyogenic bacterial infections in hum ans with MyD88 deficiency. Science 2008, 321:691-696.
[11] Amour J, Birenbaum A, Langeron O, Le Manach Y, Bertrand M, Coriat P, Riou B, Bernard M, Hausfater P: Influence of renal dysfunction on the accuracy of procalcitonin for the diag nosis of postoperative infection after vascular surgery. Crit Care Med 2008, 36:1147-1154
[12] Wattanathum A, Manocha S, Groshaus H, Russell JA, Walley KR: Interleukin-10 haplotype associated with increased mortality in critically ill patients with sepsis from pneumonia but not in patients with extrapulmonary sepsis. Chest 2005, 128:1690-1698.
[13] Ku CL, von Bernuth H, Picard C, Zhang SY, Chang HH, Yang K, Chrabieh M, Issekutz AC, Cunningham CK, Gallin J, Holland SM, Roifman C, Ehl S, Smart J, Tang M, Barrat FJ, Levy O, McDonald D, Day-Good NK, Miller R, Takada H, Hara T, Al-Hajjar S, Al-Ghonaium A, Speert D,Sanlaville D, Li X, Geissmann F, Vivier E,Marodi L, et al.: Selective predisposition to ba cterial infections in IRAK- 4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in prot ective immunity. J Exp Med 2007, 204:2407-2422.
[14] Guillon A, Arafa EI, Barker KA, Belkina AC, Martin I, Shenoy AT, et al. Pneumonia recovery reprograms the alveolar macrophage pool. JCI Insight. 2020;5(4):e133042
[15] Aberdein JD, Cole J, Bewley MA, Marriott HM, Dockrell DH. Alveolar macrophages in pulmonary host defe nce the unrecognized role of apoptosis as a mechanism of intracellular bacte rial killing. Clin Exp Immu nol. 2013; 174(2):193–202.
[16] Schneider C, Nobs SP, Kurrer M, Rehrauer H, Thiele C, Kopf M. Indu ction of the nuclear receptor PPAR-gamma by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages. Nat Immunol. 2014;15(11):1026–37.
[17] Sanchez-Moral L, Rafols N, Martori C, Paul T, Tellez E, Sarrias MR. Multi- faceted Roles of CD5L in Infectious and Sterile Inflammation. Int J Mol Sci. 2021;22(8):4076.
[18] Kelley JL, Ozment TR, Li C, Schw eitzer JB, Williams DL. Scave nger receptor-A (CD204): a two-edged swo rd in health and disease. Crit Rev Immunol. 2014;34(3):241–61
[19] Gonzalez-Juarbe N, Gilley RP, Hinojosa CA, Bradley KM, Kamei A, Gao G, et al. Pore-Forming Toxins Ind uce Macrophage Necroptosis during Acute Bacterial Pneumonia. PLoS Path og. 2015;11(12):e1005337
[20] Roquilly A, Jacqueline C, Davieau M, Molle A, Sadek A, Fourgeux C, et al. Alveolar macrophages are epigen etically altered after inflam- mation, leading to long-term lung immun oparalysis. Nat Immunol.2020;21(6):63 6–48.
[21] Gowdy KM, Madenspacher JH, Azzam KM, Gabor KA, Janardhan KS, Aloor JJ, et al. Key role for scavenger receptor B-I in the integrative phys iology of host defense during bact erial pneumonia. Mucosal Immunol. 2015;8 (3):559–71.
[22] Hollifield M, Bou Ghanem E, de Villiers WJ, Garvy BA. Scavenger receptor A dampens induction of inflam mation in response to the fungal patho- gen Pneumocystis carinii. Infect Immun .2007;75(8):3999–4005.
[23] Gopal R, Lee B, McHugh KJ, Rich HE, Ramanan K, Mandalapu S, et al. STAT2 Signaling Regulates Macrop hage Phenotype During Influenza and Bacterial Super-Infection. Front Immu nol. 2018;9:2151
[24] Xiong H, Carter RA, Leiner IM, Tang YW, Chen L, Kreiswirth BN, et al. Distinct Contributions of Neutrophils and CCR2+ Monocytes to Pulmonary Clearance of Different Klebsiella pneumoniae Strains. Infect Immun. 2015;83(9):3418–27.
[25] Peiro T, Patel DF, Akthar S, Gregory LG, Pyle CJ, Harker JA, et al. Neutro-phils drive alveolar macrophage IL-1beta release during respiratory viral infection. Thorax. 2018;73(6):546–56.
[26] Ziltener P, Reinheckel T, Oxenius A. Neutrophil and Alveolar Mac- rophage Mediated Innate Immune Control of Legionella pneumophila Lung Infection via TNF and ROS. PLoS Pathog. 2016;12(4):e1005591

[27] Magnen M, Gueugnon F, Petit-Courty A, Baranek T, Sizaret D, Brewah YA, et al. Tissue kallikrein regulates alveolar macrophage apoptosis early in influenza virus infection. Am J Physiol Lung Cell Mol Physiol. 2019;316(6):L1127–40.
[28] Behar SM, Martin CJ, Booty MG, Nishimura T, Zhao X, Gan HX, et al. Apoptosis is an innate defense function of macrophages against Myco- bact erium tuberculosis. Mucosal Immunol. 2011;4(3):279–87
[29] Minutti CM, Modak RV, Macdonald F, Li F, Smyth DJ, Dorward DA, et al. A Macrophage-Pericyte Axis Directs Tissue Restoration via Amphireg- ulin-Induced Transforming Growth Factor Beta Activation. Immunity .2019; 50(3):645-54 e6
[30] Sabatel C, Radermecker C, Fievez L, Paulissen G, Chakarov S, Fernandes C, et al. Exposure to Bacterial CpG DNA Protects from Airway Allergic Inflam mation by Expanding Regulatory Lung Interstitial Macrophages. Immu nity. 2017;46(3):457–73.
[31] Zimmermann M, Aguilera FB, Castellucci M, Rossato M, Costa S, Lunardi C, et al. Chromatin remodell ing and autocrine TNFalpha are requi red for optimal interleukin-6 expression in activated human neutrophils. Nat Co mmun. 2015;6:6061
[32] Kormaz and Traber. Innate Immune respone in pneumonia.2023. pp: 1-26. https://doi.org/10.1186/s41479-023 001 06-8
[33] Torrez T, Cilloniz C, Niederman MS, Menendez R, Chalmers JD, Wunderink RG and Poll TV. Pneumonia Primer Nature. 2021. Article citation ID: 2021 7:25.