

7. CONCLUSÃO

Como conclusões do presente trabalho, temos:

- Os fosfolipídios potencializaram a resposta de macrófagos M0 e polarizados para M1 na produção de NO, porém não mudam as características fenotípicas dos M2.
- POPC e *Paldo*PC apresentaram efeito sinérgico na função inflamatória dos M0 e M1 (citocinas e quimiocinas), mas não são agentes inflamatórios naturais. Para o perfil M2 os fosfolipídios modificaram o estado basal inflamatório, porém esse efeito não foi somatório ao estímulo inflamatório do LPS.
- Os macrófagos AMJ2-C11 apresentaram plasticidade, sendo polarizados para M1 ou M2 dependendo do estímulo.
- Os fosfolipídios apresentaram efeito sinérgico na resposta inflamatória dos M0, devido ao aumento da expressão de receptores da imunidade inata e moléculas adaptadoras, e de modo independente da polarização dos macrófagos.
- POPC aumentou a produção de PGD₂ e está correlacionado ao aumento da fagocitose de *Klebsiella pneumoniae*.

8. REFERÊNCIAS

- AJUEBOR, M. N.; SINGH, A.; WALLACE, J. L. Cyclooxygenase-2-derived prostaglandin D(2) is an early anti-inflammatory signal in experimental colitis. **American Journal of Physiology Gastrointestinal and Liver Physiology**, v. 279, n. 1, p. G238-44, jul. 2000.
- AKIRA, S.; TAKEDA, K. Toll-like receptor signalling. **Nature**, v. 4, n. July, p. 88–88, 2004.
- ALBIGER, B. et al. Role of the innate immune system in host defence against bacterial infections: Focus on the Toll-like receptors. **Journal of Internal Medicine**, v. 261, n. 6, p. 511–528, 2007.
- ALMSTRAND, A.-C.; VOELKER, D.; MURPHY, R. C. Identification of oxidized phospholipids in bronchoalveolar lavage exposed to low ozone levels using multivariate analysis. **Analytical biochemistry**, v. 474, p. 50–8, 1 abr. 2015.
- ARONOFF, D. M. et al. E-prostanoid 2 receptor signaling suppresses lung innate immunity against *Streptococcus pneumoniae*. **Prostaglandins & Other Lipid Mediators**, v. 98, n. 1–2, p. 23–30, maio 2012.
- ARONOFF, D. M.; CANETTI, C.; PETERS-GOLDEN, M. Prostaglandin E2 inhibits alveolar macrophage phagocytosis through an E-prostanoid 2 receptor-mediated increase in intracellular cyclic AMP. **Journal of immunology (Baltimore, Md. : 1950)**, v. 173, n. 1, p. 559–65, 1 jul. 2004.
- BAILEY, P. The reactions of ozone with organic compounds. **Chemical Reviews**, v. 58, n. 5, p. 925–1010, 1958.
- BAILIE, M. B. et al. Leukotriene-deficient mice manifest enhanced lethality from *Klebsiella pneumonia* in association with decreased alveolar macrophage phagocytic and bactericidal activities. **Journal of immunology (Baltimore, Md. : 1950)**, v. 157, n. 12, p. 5221–4, 15 dez. 1996.
- BALHARA, J.; GOUNNI, A S. The alveolar macrophages in asthma: a double-edged sword. **Mucosal immunology**, v. 5, n. 6, p. 605–9, 2012.
- BENOIT, M.; DESNUES, B.; MEGE, J.-L. Macrophage Polarization in Bacterial Infections. **The Journal of Immunology**, v. 181, n. 6, p. 3733–3739, 15 set. 2008.

- BETTELLI, E.; KORN, T.; KUCHROO, V. K. Th17: the third member of the effector T cell trilogy. **Current Opinion in Immunology**, v. 19, n. 6, p. 652–657, dez. 2007.
- BHAN, U. et al. Cooperative interactions between TLR4 and TLR9 regulate interleukin 23 and 17 production in a murine model of Gram negative bacterial pneumonia. **PLoS ONE**, v. 5, n. 3, p. 1-11, 2010.
- BOWERS, D. R.; HUANG, V. Emerging Issues and Treatment Strategies in Carbapenem-Resistant Enterobacteriaceae (CRE). **Current Infectious Disease Reports**, v. 18, n. 12, p. 48, 2016.
- BROUG-HOLUB, E. et al. Alveolar macrophages are required for protective pulmonary defenses in murine *Klebsiella pneumonia*: elimination of alveolar macrophages increases neutrophil recruitment but decreases bacterial clearance and survival. **Infection and immunity**, v. 65, n. 4, p. 1139–46, abr. 1997.
- CAI, S. et al. Both TRIF- and MyD88-dependent signaling contribute to host defense against pulmonary *Klebsiella* infection. **Journal of immunology (Baltimore, Md. : 1950)**, v. 183, n. 10, p. 6629–38, 2009.
- CAI, S. et al. NLR4 Inflammasome-Mediated Production of IL-1 Modulates Mucosal Immunity in the Lung against Gram-Negative Bacterial Infection. **The Journal of Immunology**, v. 188, n. 11, p. 5623–5635, 1 jun. 2012.
- CANETTI, C. et al. Syk activation is a leukotriene B4-regulated event involved in macrophage phagocytosis of IgG-coated targets but not apoptotic cells. **Blood**, v. 102, n. 5, p. 1877- 1883, 2003.
- CARNEIRO, A. B. et al. Lysophosphatidylcholine Triggers TLR2- and TLR4-Mediated Signaling Pathways but Counteracts LPS-Induced NO Synthesis in Peritoneal Macrophages by Inhibiting NF- κ B Translocation and MAPK/ERK Phosphorylation. **PLoS ONE**, v. 8, n. 9, p. 1–9, 2013.
- CHACON-SALINAS, R. et al. Differential pattern of cytokine expression by macrophages infected in vitro with different *Mycobacterium tuberculosis* genotypes. **Clinical and Experimental Immunology**, v. 140, n. 3, p. 443–449, jun. 2005.
- CHIEN, H.-Y. et al. Attenuation of LPS-induced cyclooxygenase-2 and inducible NO synthase expression by lysophosphatidic acid in macrophages. **Innate immunity**, v. 21, n. 6, p. 635–46, ago. 2015.

- CRIEGEE, R. Mechanism of Ozonolysis. **Angewandte Chemie International Edition in English**, v. 14, n. 11, p. 745–752, 1975.
- DAVICINO, R. C. et al. Coupling pathogen recognition to innate immunity through glycan-dependent mechanisms. **International Immunopharmacology**, v. 11, n. 10, p. 1457-1463, 2011.
- DAVIES, S. S. et al. Oxidized Alkyl Phospholipids are Specific, High Affinity Peroxisome Proliferator-activated Receptor γ Ligands and Agonists. **Journal of Biological Chemistry**, v. 276, n. 19, p. 16015-23, 2001.
- DEMITSU, T. et al. Dmitsu et al, 1989 Phagocytosis and bactericidal action. **International journal of immunopharmacology**, v. 11, n. 7, p. 801–8, 1989.
- DENG, J. C. et al. STAT4 is a critical mediator of early innate immune responses against pulmonary Klebsiella infection. **Journal of immunology (Baltimore, Md. : 1950)**, v. 173, n. 6, p. 4075–83, 15 set. 2004.
- DOORDUIJN, D. J. et al. Complement resistance mechanisms of Klebsiella pneumoniae. **Immunobiology**, v. 221, n. 10, p. 1102–1109, 2016.
- DRAIJER, C. et al. Characterization of macrophage phenotypes in three murine models of house-dust-mite-induced asthma. **Mediators of Inflammation**, v. 2013, p. 1–11, 2013.
- DUBOIS, R. N. et al. Cyclooxygenase in biology and disease. **FASEB journal : official publication of the Federation of American Societies for Experimental Biology**, v. 12, n. 12, p. 1063–73, set. 1998.
- EDWARDS, C. K. et al. Edwards et al, 1986 Chronic infection due to *Mycobacterium intracellulare*. **Journal of immunology (Baltimore, Md. : 1950)**, v. 136, n. 5, p. 1820–7, 1 mar. 1986.
- ENHORNING, G.; HOLM, B. A. Disruption of pulmonary surfactant's ability to maintain openness of a narrow tube. **J Appl Physiol**, v. 74, n. 6, p. 2922–2927, 1 jun. 1993.
- EPELMAN, S.; LAVINE, K. J.; RANDOLPH, G. J. Origin and Functions of Tissue Macrophages. **Immunity**, v. 41, n. 1, p. 21–35, jul. 2014.
- ESCRIBÁ, P. V. Membrane-lipid therapy: A new approach in molecular medicine. **Trends in Molecular Medicine**, v. 12, n. 1, p. 34-43, 2006.

- ESCRIBÁ, P. V. et al. Membrane lipid therapy: Modulation of the cell membrane composition and structure as a molecular base for drug discovery and new disease treatment. **Progress in Lipid Research**, v. 59, p. 38–53, 2015.
- ESCRIBÁ, P. V et al. Role of lipid polymorphism in G protein-membrane interactions: Nonlamellar-prone phospholipids and peripheral protein binding to membranes. **Proceedings of the National Academy of Sciences**, v. 94, n. 21, p. 11375–11380, 1997.
- FACCIOLI, L. H. et al. The accumulation of ¹¹¹In-eosinophils induced by inflammatory mediators, in vivo. **Immunology**, v. 73, n. 2, p. 222–7, jun. 1991.
- FAN, H. et al. Lysophosphatidic acid inhibits bacterial endotoxin-induced pro-inflammatory response: potential anti-inflammatory signaling pathways. **Molecular medicine (Cambridge, Mass.)**, v. 14, n. 7–8, p. 422–8, 2008.
- FLAMAND, L. et al. Release of anti-HIV mediators after administration of leukotriene B4 to humans. **The Journal of infectious diseases**, v. 189, n. 11, p. 2001–9, 1 jun. 2004.
- FREEMAN, S. A.; GRINSTEIN, S. Phagocytosis: Receptors, signal integration, and the cytoskeleton. **Immunological Reviews**, v. 262, n. 1, p. 193–215, 2014.
- FU, P.; BIRUKOV, K. G. Oxidized phospholipids in control of inflammation and endothelial barrier. **Translational Research**, v. 153, n. 4, p. 166–176, abr. 2009.
- FUNK, C. D. Prostaglandins and Leukotrienes: Advances in Eicosanoid Biology. **Science**, v. 294, n. 5548, p. 1871–1875, 30 nov. 2001.
- GAUVREAU, G. M.; WATSON, R. M.; O'BYRNE, P. M. Protective effects of inhaled PGE2 on allergen-induced airway responses and airway inflammation. **American journal of respiratory and critical care medicine**, v. 159, n. 1, p. 31–6, jan. 1999.
- GILROY, D. W. et al. Inducible cyclooxygenase may have anti-inflammatory properties. **Nature medicine**, v. 5, n. 6, p. 698–701, 1999.
- GISKE, C. G. et al. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. **Antimicrobial Agents and Chemotherapy**, v. 52, n. 3, p. 813–21, 2008.
- GORDON, S.; MARTINEZ, F. O. Alternative activation of macrophages: Mechanism and functions. **Immunity**, v. 32, n. 5, p. 593–604, 2010.

- GREEN, L. C.; TANNENBAUM, S. R.; GOLDMAN, P. Nitrate synthesis in the germfree and conventional rat. **Science (New York, N.Y.)**, v. 212, n. 4490, p. 56–8, 3 abr. 1981.
- HANADA, T.; YOSHIMURA, A. Regulation of cytokine signaling and inflammation. **Cytokine & Growth Factor Reviews**, v. 13, n. 4, p. 413–421, 2002.
- HAPPEL, K. I. et al. Divergent roles of IL-23 and IL-12 in host defense against *Klebsiella pneumoniae*. **The Journal of experimental medicine**, v. 202, n. 6, p. 761–769, 2005.
- HASHIMOTO, M.; ASAI, Y.; OGAWA, T. Treponemal Phospholipids Inhibit Innate Immune Responses Induced by Pathogen-associated Molecular Patterns. **Journal of Biological Chemistry**, v. 278, n. 45, p. 44205–44213, 2003.
- ISHII, M. et al. Epigenetic regulation of the alternatively activated macrophage phenotype. **Blood**, v. 114, n. 15, p. 3244–3254, 8 out. 2009.
- ITO, N. Ito et al, 2002 Requirement of Phosphatidylinositol. **Journal of Biological Chemistry**, v. 277, n. 47, p. 44898–44904, 15 nov. 2002.
- JANDA, J. M. The Genus *Klebsiella*: An Ever-Expanding Panorama of Infections, Disease-Associated Syndromes, and Problems for Clinical Microbiologists. **Clinical Microbiology & Case Reports**, v. 1, n. 4, p. 1–7, 2015.
- JIANG, Z.; ZHU, L. Update on the role of alternatively activated macrophages in asthma. **Journal of asthma and allergy**, v. 9, p. 101–7, 2016.
- JOO, M. et al. Induction and Function of Lipocalin Prostaglandin D Synthase in Host Immunity. **The Journal of Immunology**, v. 179, n. 4, p. 2565–2575, 15 ago. 2007.
- JOO, M.; SADIKOT, R. T. PGD synthase and PGD2 in immune response. **Mediators of inflammation**, v. 2012, p. 503128, 2012.
- KAFOURY, R. M. et al. Lipid ozonation products activate phospholipases A2, C, and D. **Toxicology and applied pharmacology**, v. 150, n. 2, p. 338–49, jun. 1998.
- KAFOURY, R. M. et al. Induction of inflammatory mediators in human airway epithelial cells by lipid ozonation products. **American Journal of Respiratory and Critical Care Medicine**, v. 160, n. 6, p. 1934–42, 1999.
- KANDASAMY, P. et al. Pulmonary surfactant phosphatidylglycerol inhibits *Mycoplasma pneumoniae*-stimulated eicosanoid production from human and mouse macrophages. **Journal of Biological Chemistry**, v. 286, n. 10, p. 7841–53, 2011.

- KISZEWSKI, A. E. et al. The local immune response in ulcerative lesions of Buruli disease. **Clinical and Experimental Immunology**, v. 143, n. 3, p. 445-51, 2006.
- KOVACH, M. A. et al. IL-36 γ is a crucial proximal component of protective type-1-mediated lung mucosal immunity in Gram-positive and -negative bacterial pneumonia. **Mucosal Immunology**, n. February, p. 1–15, 2017.
- KURONUMA, K. et al. Anionic pulmonary surfactant phospholipids inhibit inflammatory responses from alveolar macrophages and U937 cells by binding the lipopolysaccharide-interacting proteins CD14 and MD-2. **Journal of Biological Chemistry**, v. 284, n. 38, p. 25488-500, 2009.
- LANDMAN, D. et al. Evolution of antimicrobial resistance among *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* in Brooklyn, NY. **The Journal of antimicrobial chemotherapy**, v. 60, n. 1, p. 78–82, 1 jul. 2007.
- LÄRFARS, G. et al. Larfars et, 1999 Activation of Nitric Oxide Release and Oxidative Metabolism. **Blood**, v. 93, n. 4, p. 1399–405, 15 fev. 1999.
- LAWRENCE, T.; NATOLI, G. Transcriptional regulation of macrophage polarization: enabling diversity with identity. **Nature Reviews Immunology**, v. 11, n. 11, p. 750–761, 2011.
- LEE, A. G. How lipids affect the activities of integral membrane proteins. **Biochim. Biophys. Acta**, v. 1666, n. (1-2), p. 62-87. 2004.
- LEE, W. L.; DOWNEY, G. P. Neutrophil activation and acute lung injury. **Current opinion in critical care**, v. 7, n. 1, p. 1–7, fev. 2001.
- LEWIS, J. F.; JOBE, A. H. Surfactant and the adult respiratory distress syndrome. **The American review of respiratory disease**, v. 147, n. 1, p. 218–33, 1993.
- LINDSAY, M. A. et al. Lindsay et al, 1998 Leukotriene B4 activates the NADPH oxidase. **Journal of immunology (Baltimore, Md. : 1950)**, v. 160, n. 9, p. 4526–34, 1 maio 1998.
- LIU, G.; YANG, H. Modulation of macrophage activation and programming in immunity. **Journal of Cellular Physiology**, v. 228, n. 3, p. 502–512, mar. 2013.
- LPSN. **List of prokaryotic names with standing in nomenclature**. Disponível em: <http://www.bacterio.net/klebsiella.html>. Acessado: 17 de novembro de 2015.
- MANCUSO, P. et al. 5-lipoxygenase reaction products modulate alveolar macrophage phagocytosis of *Klebsiella pneumoniae*. **Infection and Immunity**, 1998.

- MANCUSO, P.; PETERS-GOLDEN, M. Mancuso e Peters, 2000 Modulation of alveolar macrophage phagocytosis by leukotrienes. **American journal of respiratory cell and molecular biology**, v. 23, n. 6, p. 727–33, dez. 2000.
- MANGAN, P. R. et al. Transforming growth factor-beta induces development of the T(H)17 lineage. **Nature**, v. 441, n. 7090, p. 231–234, 2006.
- MARATHE, G. K. et al. Inflammatory platelet-activating factor-like phospholipids in oxidized low density lipoproteins are fragmented alkyl phosphatidylcholines. **Journal of Biological Chemistry**, v. 274, n. 40, p. 28395-404, 1999.
- MARTINEZ, F. O. et al. Macrophage activation and polarization. **Frontiers in bioscience : a journal and virtual library**, v. 13, p. 453–61, 1 jan. 2008.
- MARTINEZ, F. O.; HELMING, L.; GORDON, S. Alternative Activation of Macrophages: An Immunologic Functional Perspective. **Annual Review of Immunology**, v. 27, n. 1, p. 451–483, abr. 2009.
- MARTÍNEZ, J. et al. Membrane structure modulation, protein kinase C alpha activation, and anticancer activity of Minerval. **Molecular pharmacology**, v. 67, n. 2, p. 531–40, 2005.
- MATSUOKA, T. et al. Prostaglandin D2 as a mediator of allergic asthma. **Science (New York, N.Y.)**, v. 287, n. 5460, p. 2013–7, 17 mar. 2000.
- MOORE, T. A et al. Divergent Role of Gamma Interferon in a Murine Model of Pulmonary versus Systemic *Klebsiella pneumoniae* Infection. **Infection and Immunity**, v. 70, n. 11, p. 6310–6318, 2002.
- MOORE, T. A. et al. Increased mortality and dysregulated cytokine production in tumor necrosis factor receptor 1-deficient mice following systemic *Klebsiella pneumoniae* infection. **Infection and Immunity**, v. 71, n. 9, p. 4891-4900, 2003.
- MORENO, J. R. et al. The role of prostaglandin E2 in the immunopathogenesis of experimental pulmonary tuberculosis. **Immunology**, v. 106, n. 2, p. 257-66, 2002.
- MORRISSETTE, N.; GOLD, E.; ADEREM, A. The macrophage – a cell for all seasons. **Trends in Cell Biology**, v. 9, n. 5, p. 199–201, maio 1999.
- MOSMANN, T. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. **Journal of Immunological Methods**, v. 65, n. 1–2, p. 55–63, 1983.

MOTA, L. A. M. **Macrófagos peritoneais de camundongo cultivados com soro homólogo apresentam grande número de corpos lipídicos e ação microbida reduzida contra o *Toxoplasma gondii***. 2009. 57 f. *Dissertação* (Mestre em Biociências e Biotecnologia) - Universidade Estadual do Norte Fluminense Darcy Ribeiro, Campos dos Goytacazes – RJ.

MURATA, T. et al. Anti-inflammatory role of PGD2 in acute lung inflammation and therapeutic application of its signal enhancement. **Proceedings of the National Academy of Sciences**, v. 110, n. 13, p. 5205–5210, 2013.

NAIR, M. G. et al. Alternatively activated macrophage-derived RELM- α is a negative regulator of type 2 inflammation in the lung. **The Journal of Experimental Medicine**, v. 206, n. 4, p. 937–952, 2009.

NAIR, M. G.; COCHRANE, D. W.; ALLEN, J. E. Macrophages in chronic type 2 inflammation have a novel phenotype characterized by the abundant expression of Ym1 and Fizz1 that can be partly replicated in vitro. **Immunology Letters**, v. 85, n. 2, p. 173–180, 2003.

NIEMAN, G. F. et al. Alveolar function following surfactant deactivation. **Journal of applied physiology: respiratory, environmental and exercise physiology**, v. 51, n. 4, p. 895–904, out. 1981.

NUMATA, M. et al. Phosphatidylglycerol suppresses influenza A virus infection. **American Journal of Respiratory Cell and Molecular Biology**, v. 46, n. 4, p. 479–87, 2012.

NUMATA, M. et al. Phosphatidylglycerol provides short-term prophylaxis against respiratory syncytial virus infection. **The Journal of Lipid Research**, v. 54, n. 8, p. 2133–2143, 2013.

NUMATA, M. et al. Phosphatidylinositol inhibits respiratory syncytial virus infection. **Journal of Lipid Research**, v. 56, n. 3, p. 578–587, 2015.

NUMATA, M.; KANDASAMY, P.; VOELKER, D. R. Anionic pulmonary surfactant lipid regulation of innate immunity. **Expert review of respiratory medicine**, v. 6, n. 3, p. 243–6, 2012.

PACZOSA, M. K.; MECSAS, J. *Klebsiella pneumoniae*: Going on the Offense with a Strong Defense. **Microbiology and Molecular Biology Reviews**, v. 80, n. 3, p. 629–61. 2016.

- PALESTINI, P. et al. Compositional changes in lipid microdomains of air-blood barrier plasma membranes in pulmonary interstitial edema. **J Appl Physiol**, v. 95, n. 10, p. 1446–1452, 2003.
- PATERSON, D. L. Resistance in gram-negative bacteria: Enterobacteriaceae. **American Journal of Infection Control**, v. 34, n. 5 SUPPL., p. 20–28, 2006.
- PETERS-GOLDEN, M. et al. Leukotrienes: Underappreciated Mediators of Innate Immune Responses. **The Journal of Immunology**, v. 174, n. 2, p. 589–594, 15 jan. 2005.
- PFEFFER, K. et al. Mice deficient for the 55 kd tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to *L. monocytogenes* infection. **Cell**, v. 73, n. 3, p. 457–467, maio 1993.
- PINOT, F. et al. Curosurf modulates cAMP accumulation in human monocytes through a membrane-controlled mechanism. **Am J Physiol Lung Cell Mol Physiol**, v. 278, n. 1, p. L99–L104, 2000.
- PODSCHUN, R. et al. Incidence of Klebsiella Species in Surface Waters and Their Expression of Virulence Factors. **Applied and Environmental Microbiology**, v. 67, n. 7, p. 1–4, 2001.
- PORCHERAY, F. et al. Macrophage activation switching: An asset for the resolution of inflammation. **Clinical and Experimental Immunology**, v. 142, n. 3, p. 481–489, 2005.
- RAES, G. et al. FIZZ1 and Ym as Tools to Discriminate between Differentially Activated Macrophages. **Developmental Immunology**, v. 9, n. 3, p. 151–159, 2002.
- RODRIGUEZ, M. et al. Polarization of the Innate Immune Response by Prostaglandin E2: A Puzzle of Receptors and Signals. **Molecular Pharmacology**, v. 85, n. 1, p. 187–197, 2013.
- ROSSI, F. The challenges of antimicrobial resistance in Brazil. **Clinical infectious diseases : an official publication of the Infectious Diseases Society of America**, v. 52, n. 9, p. 1138–43, 1 maio 2011.
- SAMUELSSON, B.; FUNK, C. D. Enzymes Involved in the biosynthesis of leukotriene b4. **Thejournal of biological chemistry**, v. 254, n. 33, p. 19469–19472, 1989.

SANTROCK, J.; GORSKI, R. A.; O'GARA, J. F. Products and mechanism of the reaction of ozone with phospholipids in unilamellar phospholipid vesicles. **Chem. Res. Toxicol**, v. 5, n. 1, p. 134-141, 1992.

SAVOV, J. D. et al. Neutrophils play a critical role in development of LPS-induced airway disease. **American Journal of Physiology - Lung Cellular and Molecular Physiology**, v. 283, n. 5, p. L952–L962, 1 nov. 2002.

SCHER, J. U.; PILLINGER, M. H. The anti-inflammatory effects of prostaglandins. **J Investig Med**, v. 57, n. 6, p. 703–708, 2009.

SCHMIDT, R. et al. Altered fatty acid composition of lung surfactant phospholipids in interstitial lung disease. **American Journal of Physiology - Lung Cellular and Molecular Physiology**, v. 283, n. 5, p. L1079–L1085, 2002.

SCHURR, J. R. et al. Central role of toll-like receptor 4 signaling and host defense in experimental pneumonia caused by gram-negative bacteria. **Infection and Immunity**, v. 73, n. 1, p. 532-45, 2005.

SEREZANI, C. H. et al. Prostaglandin E2 suppresses bacterial killing in alveolar macrophages by inhibiting NADPH oxidase. **American Journal of Respiratory Cell and Molecular Biology**, v. 37, n. 5, p. 562-70, 2007.

SHAUGHNESSY, L. M.; SWANSON, J. A. The role of the activated macrophage in clearing *Listeria monocytogenes* infection. **Frontiers in bioscience : a journal and virtual library**, v. 12, n. 1, p. 2683–2692, 2007.

SIBILLE, Y.; REYNOLDS, H. Y. Macrophages and polymorphonuclear neutrophils in lung defense and injury. **The American review of respiratory disease**, v. 141, n. 2, p. 471–501, mar. 1990.

SOARES, A. C. et al. Dual function of the long pentraxin PTX3 in resistance against pulmonary infection with *Klebsiella pneumoniae* in transgenic mice. **Microbes and Infection**, v. 8, n. 5, p. 1321–1329, abr. 2006.

SOARES, E. M. et al. Leukotriene B4 Enhances Innate Immune Defense against the Puerperal Sepsis Agent *Streptococcus pyogenes*. **The Journal of Immunology**, v. 190, n. 4, p. 1614–1622, 15 fev. 2013.

SQUADRITO, G. L.; SALGO, M. G.; FRONCZEK, F. R.; Pryor, W. Synthesis of inflammatory signal transduction species formed during ozonation and/or peroxidation of tissue lipids. **Methods Enzymol**, 319, p. 570-582, 2000.

STABLES, M. J.; GILROY, D. W. Old and new generation lipid mediators in acute inflammation and resolution. **Progress in Lipid Research**, v. 50, n. 1, p. 35–51, jan. 2011.

TAKAO, S. et al. Role of reactive oxygen metabolites in murine peritoneal macrophage phagocytosis and phagocytic killing. **The American journal of physiology**, v. 271, n. 4 Pt 1, p. C1278-84, 1 out. 1996.

TALVANI, A. et al. Leukotriene B4 induces nitric oxide synthesis in *Trypanosoma cruzi*-infected murine macrophages and mediates resistance to infection. **Infection and Immunity**, v. 70, n. 8, p. 4247-53, 2002.

TAUBER, A. I. Timeline: Metchnikoff and the phagocytosis theory. **Nature Reviews Molecular Cell Biology**, v. 4, n. 11, p. 897–901, 2003.

TORTORA, G. J.; FUNKE, B. R.; CASE, C. L. **Microbiologia**. Artmed. 10° Ed. 2012.

TOSHCHAKOV, V. et al. TLR4, but not TLR2, mediates IFN- β –induced STAT1 α/β –dependent gene expression in macrophages. **Nature Immunology**, v. 3, n. 4, p. 392–398, 2002.

TSATSANIS, C. et al. Signalling networks regulating cyclooxygenase-2. **The International Journal of Biochemistry & Cell Biology**, v. 38, n. 10, p. 1654–1661, jan. 2006.

UHLSON, C. et al. Oxidized Phospholipids Derived from Ozone-Treated Lung Surfactant Extract Reduce Macrophage and Epithelial Cell Viability. **Chemical Research in Toxicology**, v. 15, n. 7, p. 896–906, jul. 2002.

VAZQUEZ-TORRES, A. et al. Antimicrobial actions of the NADPH phagocyte oxidase and inducible nitric oxide synthase in experimental salmonellosis. I. Effects on microbial killing by activated peritoneal macrophages in vitro. **The Journal of experimental medicine**, v. 192, n. 2, p. 227–36, 17 jul. 2000.

VIEIRA, A. T. et al. Control of *Klebsiella pneumoniae* pulmonary infection and immunomodulation by oral treatment with the commensal probiotic *Bifidobacterium longum* 51A. **Microbes and Infection**, v. 18, n. 3, p. 180–189, mar. 2016.

VOGLER, O. et al. The G $\beta\gamma$ dimer drives the interaction of heterotrimeric G proteins with nonlamellar membrane structures. **J. Biol. Chem**, v. 279, n. 35, p. 36540–36545. 2004.

- WARE, L. B.; MATTHAY, M. A. The acute respiratory distress syndrome. **The New England journal of medicine**, v. 342, n. 18, p. 1334–49, 4 maio 2000.
- WEAVER, C. T. et al. Th17: An Effector CD4 T Cell Lineage with Regulatory T Cell Ties. **Immunity**, v. 24, n. 6, p. 677-88, 2006.
- WEAVER, C. T. et al. IL-17 Family Cytokines and the Expanding Diversity of Effector T Cell Lineages. **Annual Review of Immunology**, v. 25, n. 1, p. 821–852, abr. 2007.
- WEBSTER, S. J. et al. Distinct Cell Death Programs in Monocytes Regulate Innate Responses Following Challenge with Common Causes of Invasive Bacterial Disease. **The Journal of Immunology**, v. 185, n. 5, p. 2968–2979, 1 set. 2010.
- WHO. World Health Organization. **Antimicrobial resistance global report on surveillance**. 2014.
- WILLINGHAM, S. B. et al. NLRP3 (NALP3, Cryopyrin) Facilitates In Vivo Caspase-1 Activation, Necrosis, and HMGB1 Release via Inflammasome-Dependent and -Independent Pathways. **The Journal of Immunology**, v. 183, n. 3, p. 2008–2015, 1 ago. 2009.
- WIRTH, J. J.; KIERSZENBAUM, F. Stimulatory effects of leukotriene B4 on macrophage association with and intracellular destruction of *Trypanosoma cruzi*. **Journal of immunology (Baltimore, Md. : 1950)**, v. 134, n. 3, p. 1989–93, mar. 1985a.
- WIRTH, J. J.; KIERSZENBAUM, F. Effects of leukotriene C4 on macrophage association with and intracellular fate of *Trypanosoma cruzi*. **Molecular and Biochemical Parasitology**, v. 15, n. 1, p. 1–10, abr. 1985b.
- WRIGHT, J. R. Immunoregulatory functions of surfactant proteins. **Nature reviews. Immunology**, v. 5, n. 1, p. 58–68, 2005.
- WRIGHT, S. M. et al. Altered airway surfactant phospholipid composition and reduced lung function in asthma. **Journal of applied physiology (Bethesda, Md. : 1985)**, v. 89, n. 4, p. 1283–1292, 2000.
- YANG, Q. et al. Influence of the Membrane Lipid Structure on Signal Processing via G Protein-Coupled Receptors. **Molecular Pharmacology**, v. 68, n. 1, p. 210–217, 2005.
- YANG, Y. et al. Macrophage polarization in experimental and clinical choroidal neovascularization. **Scientific Reports**, v. 6, n. 1, p. 30933, 4 nov. 2016.

YE, P. et al. Interleukin-17 and Lung Host Defense against *Klebsiella pneumoniae* Infection. **American Journal of Respiratory Cell and Molecular Biology**, v. 25, n. 3, p. 335–340, set. 2001.

ZENG, X. et al. Interferon-Inducible Protein 10, but Not Monokine Induced by Gamma Interferon, Promotes Protective Type 1 Immunity in Murine *Klebsiella pneumoniae* Pneumonia. **Infection and Immunity**, v. 73, n. 12, p. 8226–8236, 1 dez. 2005.