Respiratory symptoms associated with different macrophage states; M1, M2, M2c

Overview of the inflammation pathway

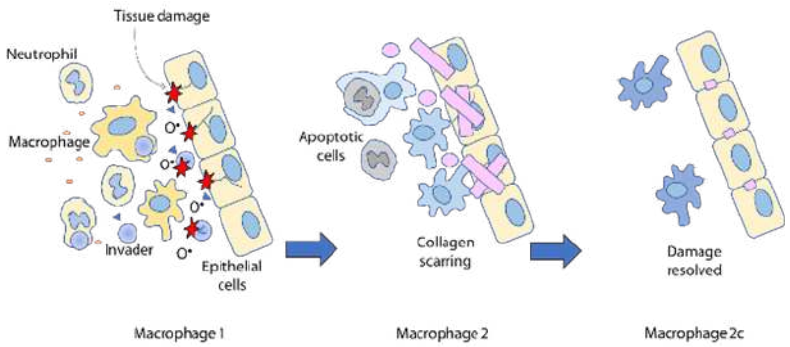
Respiratory illnesses typically follow a predictable trajectory: a pathogen invades, the body's immune system reacts which causes us to experience acute symptoms such as fatigue, body aches, loss of appetite, and fever. As the infection is brought under control by the immune system, collateral damage often occurs in the nearby tissues. Using immune activating products can help the immune system during this fight to reduce the duration of the infection, but their benefits are limited to the very first phase of fighting an infection. Once the infection is under control, the spent immune cells and dead pathogens are cleared through mucous leading to symptoms such as coughing and stuffy or runny nose. These are the symptoms that can linger for weeks or months beyond the actual infection because it can be difficult for the immune system to calm down and return to baseline.

This is where BerriQi is useful: BerriQi calms an activated immune system back to baseline, helping to shorten the duration of lingering symptoms.

Macrophages and their classes

Alveolar macrophages constitue 90% of the pulmonary macrophage population

Macrophages are a type of immune cell which patrol our tissues and organs for foreign/invading particles or our own dead tissue to consume through a process called phagocytosis. Phagocytosis involves surrounding and engulfing the target and then destroying it within the macrophage. In addition to patrolling and phagocytosing, macrophages signal and recruit other cells of the immune system to the site of activity. This signalling and recruiting happens by the macrophages releasing cytokines and chemokines. These are protein or chemical messengers which stimulate other immune cells - including more macrophages - to migrate to the site of invasion or injury. Finally, macrophages release protein-degrading protease enzymes and reactive oxygen species to remodel tissue and destroy invading cells. These three processes, phagocytosis, immune signalling and releasing destructive compounds, makes macrophages essential components in infection and wound defence and repair. **Macrophage activity can change based on environmental cues.** Macrophages can exist in two different activation states (M1 and M2). M1 refers to the classically activated macrophages and inhibits cell proliferation and causes tissue damage[1]. The alternatively activated macrophages (AAM) exist in the M2 state and can further differentiated into M2a, M2b, M2c, and M2d states.



BerriQi

Anagenix.

M1
Macrophages and Symptoms

Pro-inflammatory

M1 activated macrophages detect and fight pathogens while recruiting other immune cells to help. The role of M1 macrophages is to secrete pro-inflammatory cytokines and chemokines, present antigens, and thus participate in the positive immune response and function as an immune monitor[2]. The macrophage M1 phenotype is involved in the acute phase where they respond to microbial factors and Th1 proinflammatory cytokines to exhibit glycolytic metabolism that is associated with inflammatory cytokine release, enhanced bacterial killing, and the recruitment of immune cells into the lung parenchyma and alveolus[3]. Macrophages and other recruited immune cells, such as neutrophils and eosinophils, then clear away damaged tissue and any invading microorganisms. This process can be lifesaving but may result in substantial collateral tissue damage. As a result, the symptoms associated with M1 classical activation are a result of inflammation such as:

Fever	**Lack of energy**	**Aches**
Lack of Appetite	**Sore throat**	**Runny nose**

M2
Macrophages and Symptoms

Anti-inflammatory

Following an infection or damage to the alveolar tissue, lung macrophages express an increase in M2-associated genes[4,5]. Once the source of damage/infection has been cleared away during the lung repair process, macrophages are polarized to the M2 phenotype in the presence of cytokines, accelerating the resolution of inflammation. M2 macrophages have been shown to reduce inflammation [6]. M2 macrophages promote epithelial cells to produce collagen like a band-aid. Collagen can provide structural support in the short term, but becomes stiff scar tissue when left too long, in a process called airway remodelling[7]. Airway remodelling leads to reduced lung capacity, shortness of breath, and wheezing. M2 macrophages may also secrete too much TGF-β (transforming growth factor-beta) to promote the proliferation and differentiation of lung fibroblasts and aggravate the progression of pulmonary fibrosis[2]. Symptoms when macrophages are in this state are linked to:

Scratchy throat	**Slight mucus production**	**Coughing**	**Shortness of breath**

M2c
Macrophages and Symptoms

Pro-healing

Apoptotic cells signal the macrophages to switch to an anti-inflammatory state, which send further anti-inflammatory signals, and promote tissue regeneration. However, inappropriate collagen may be deposited by fibrotic macrophages and other cells called fibroblasts. Ultimately this will result in scar tissue devoid of protein messengers or chemical messengers, which signals macrophages to enter a fibrolytic, collagen-degrading, fully M2 phase. M2c activated macrophages clean up any mess left behind from healing, such as removing collagen that is no longer needed.

M2c macrophages express anti-inflammatory cytokines, leading to reduced inflammatory infiltration locally[3]. M2c can maintain the immunosuppressive function of regulatory T cells unimpaired, thereby contributing to the resolution of inflammation and tissue repair[4]. Symptoms whilst macrophages are in this final stage often present as:

Breathing clearly	**Reduction of all prior symptoms**	**Return to baseline**

Macrophage State	Symptoms of Infection	State of Infection	How it helps	Typical no. of days
M1	Fever, Lack of Appetite, Lack of energy, Sore throat, Aches, Runny nose	Beginning	Fights the infection	1-2
M2	Scratchy throat, Slight mucus production, Coughing, Shortness of breath	Middle	Clears the infection away	3-5
M2c	Breathing clearly, Reduction of all prior symptoms, Return to baseline	End	Helps heal damaged tissue	6-10

BerriQi

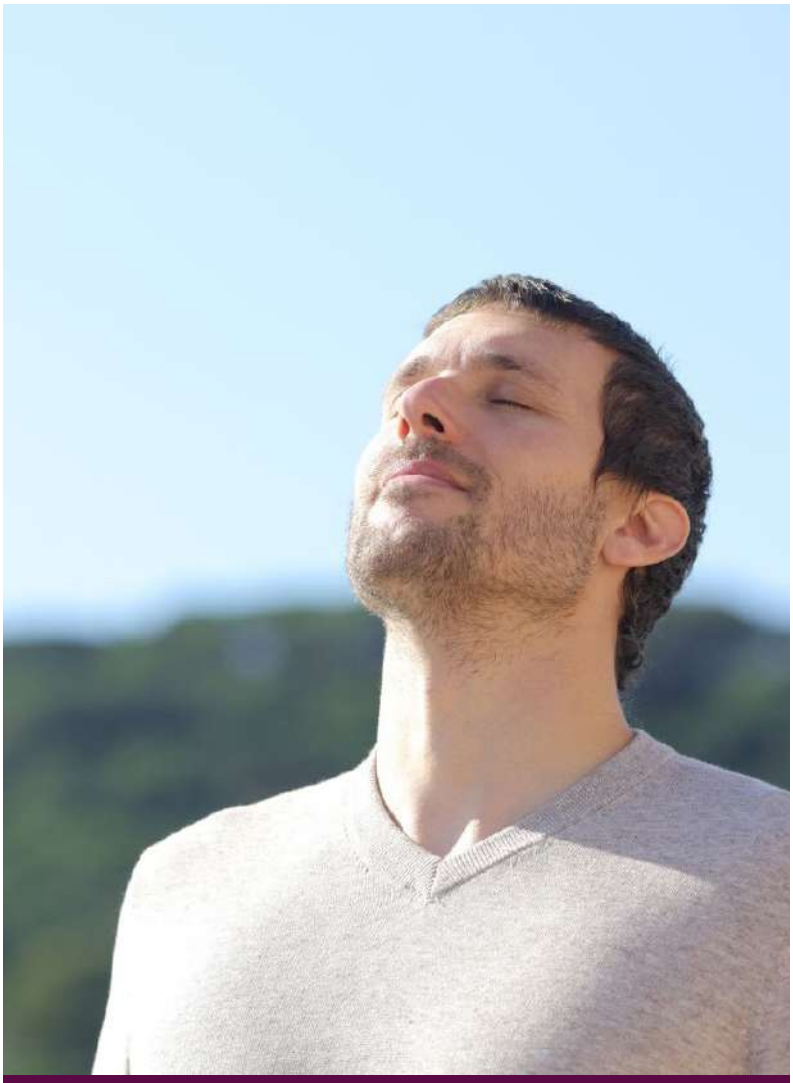
Anagenix.

BerriQi shortens sick days by activating the healing phase (M2c)

Specific types of anthocyanins in BerriQi have the unique ability to bind to a receptor activating progression from M1 pro-inflammatory mode to M2 anti-inflammatory mode[5,6]. It is in our best interests to resolve chronic lung inflammation and the associated collateral tissue damage and scarring by having our macrophages in the M2 state. BerriQi consumption has been shown to consistently improve airway inflammation and mucus production in in vivo models of acute inflammation and chronic inflammation[5,6]. BerriQi has been shown to help with lung inflammation by restoring the total number of immune cells in the lungs to normal pre-inflammatory levels.

At the high dose, BerriQi reverses scarring in the lungs by removing collagen that has been deposited under chronic inflammatory conditions. The unique anthocyanins in BerriQi help to promote the M2 state and this activity restores the stretchiness of the lung tissue and lung capacity.

- **Reduces lung inflammation**
- **Reduces mucus overproduction**
- **Reduces wheeze, cough and phlegm**
- **Reduces collagen scarring of lung tissue**
- **Supports lung tissue repair**



NEW BerriQi clinical supporting the results of the preclinical is now available.

Contact us info@anagenix.com for more details.

REFERENCES

1. Mills CD. M1 and M2 Macrophages: Oracles of Health and Disease. Crit Rev Immunol. 2012;32(6):463-88. doi: 10.1615/critrevimmunol.v32.i6.10. PMID: 23428224.
2. Cheng P, Li S, Chen H. Macrophages in Lung Injury, Repair, and Fibrosis. Cells. 2021 Feb 18;10(2):436. doi: 10.3390/cells10020436. PMID: 33670759; PMCID: PMC7923175.
3. Hu G, Christman JW. Editorial: Alveolar Macrophages in Lung Inflammation and Resolution. Front Immunol. 2019 Sep 24;10:2275. doi: 10.3389/fimmu.2019.02275. PMID: 31616438; PMCID: PMC6768960.
4. Tu G.-W., Shi Y., Zheng Y.-J., Yi-Jun Z., He H.-Y., Ma G.-G., Hao G.-W., Luo Z. Glucocorticoid attenuates acute lung injury through induction of type 2 macrophage. *J. Transl. Med.* 2017;15:1–11. doi: 10.1186/s12967-017-1284-7.
5. Shaw, O. M., Hurst, R. D., & Harper, J. L. (2016). Boysenberry ingestion supports fibrolytic macrophages with the capacity to ameliorate chronic lung remodeling. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, 311(3), L628-L638.
6. Shaw, O. M., Hurst, R. D., Cooney, J., Sawyer, G. M., Dinnan, H., & Martell, S. (2021). Boysenberry and apple juice concentrate reduced acute lung inflammation and increased M2 macrophage- associated cytokines in an acute mouse model of allergic airways disease. *Food science & nutrition*, 9(3), 1491-1503.
7. Nieuwenhuizen NE, et al. Allergic airway disease is unaffected by the absence of IL-4Ralpha-dependent alternatively activated macrophages. *The Journal of allergy and clinical immunology*. 2012

For more information contact info@anagenix.com

Anagenix.