Review Article

Microbial Pathogenesis, Recently Developed Inflammatory Markers, Microbial Resistance against Different Drugs

Saba Mobeen[1], Fariha ur Rehman[1], Bakhtawar Maqbool[1], Tariq Jamil[2*], Samia Bashir[3], Afsheen Fazil[4], Sadia Zafar[5], Amal Haleem[6]

[1]Institute of Microbiology, University of Agriculture Faisalabad, Pakistan
[2]Faculty of Veterinary Science, University of Agriculture Faisalabad, Pakistan
[3]Department of Biochemistry, University of Agriculture Faisalabad, Pakistan
[4]Department of Pathology, Faculty of Veterinary Science, University of Agriculture Faisalabad, Pakistan
[5]Department of Life Sciences, University of Management and Technology, Lahore, Pakistan
[6]Cancer Genetics and Epigenetics Lab, Department of Biosciences, COMSATS University, Islamabad, Pakistan

Abstract

Microbes playing important role in progression of infectious diseases. Bacterial attack on the nervous and respiratory cells undergoes metabolic pool. Different types of fungi also causing the infections once the attack on the human body. These pathogenic fungi are *Blastomyces dermatitidis* and *Histoplasma capsulatum* sense an increase in temperature. Gut microbiome also playing important roles in the brain function and behavior by causing the several neurological disorders. These symptoms can be seen in epilepsy and in response to seizure interventions. Different amino acids have been used as a source of bacterial nutrition for example, tryptophan as one of the essential amino acid playing important role in catalyzing the different reactions in body. Riboswitches are the regulatory sequences that can bind to the active target molecules in order to regulate the gene expression of most of gens causing the abnormal response. Chloramphenicol is the drug that is used to control the infections caused by bacteria as it the broad spectrum antibiotic and can target broad range of bacterial strains.
Keywords: Antibiotics, mechanism of action, bacterial pathogens, microbial pathogenesis.

INTRODUCTION

Microbes playing important role in progression of infectious diseases. Once the particular microbe attack on the body cells, then series of events occurred in order to produce the immune reposes. Body cells produce the antibodies and other chemical proinflammtory cytokines to elicit the immune response. Genomic editing is facilitated by a selection of transformable cells and a small induction of recombination in the target site by Cas9 cleavage. There are different aspects of microbial attack on body cells such as nervous system in the form of Alzheimer disorder, respiratory damage in the form of tuberculosis [1-3]. Bacterial attack on the nervous and respiratory cells undergoes metabolic pools. Bacterial pathogens express a wide range of molecules that bind host cell targets to facilitate a variety of different host responses. Different antibiotics and chemical compounds are used con control the attack on body cells. The ultimate goals to target the bacterial membrane so that bacterial cells won't able to enter directly to surface membrane. bacterial genome editing is carried out to knock-out genes, knock-in genes or introduce mutations in the bacterial genome. Genomic modifications drugs have been proposed to kills the bacteria in the form of genome editing. These genetic engineering features helpful to control the growth of different bacteria. One of the example of bacterial metabolism in human brain is the Alzheimer disorder [1, 2, 9].

Citation: Saba Mobeen *et al* (2021). Microbial Pathogenesis, Recently Developed Inflammatory Markers, Microbial Resistance against Different Drugs. *Saudi J Med Pharm Sci, 7*(11): 551-556.

551

Table-1: Shows the different aspects of microbial metabolism, action and drugs

Microbial/action/drugs	Biological Role	Action of potential agent	References
Bacteria mode of action	*P. gingivali*is that is the most pathogenic form of bacteria that produces toxins in the form of gingipains cause the large severe inflammation in the brain.	It resulted the infections may trigger the severe neurodegeneration associated with Alzheimer disease and patients suffering form that disease has high serum levels of beta-amyloid peptide.	[4, 5]
Fungal mode of action	Pathogenic fungi are *Blastomyces dermatitidis* and *Histoplasma capsulatum*	Can sense an increase in temperature. These fungi promoted the immune responses by attacking on the lungs cells and undergo to the phase transition.	[7, 8]
Gut microbiome	They are also playing important roles in the brain function and behavior, pro- and anti-inflammatory responses	By causing the several neurological disorders.	[11, 12, 13]
Aptamers	Biochemical role and nucleic acid sequences	That can inhibit the growth of bacteria by binding to their nuclear region.	[26, 27, 28]
Ampicillin, Chloramphenicol, Amoxicillin	Control the infections such as respiratory tract infections, urinary tract infections, meningitis, salmonellosis, and endocarditis, bacteria superficial eye infections such as bacterial conjunctivitis, chest infections including pneumonia, dental abscesses and urinary tract infections.	Biochemical and immunological responses.	[29, 30, 31, 33]
Bacterial metabolism in human brain	Alzheimer disorder.	Neuroinflammation	[1, 2]

Mechanisms of Microbial pathogenesis and inflammatory markers

Alzheimer disease is the most complicated if not treated at early stages of infections as progression of inflammation into the brain tissues leads to severe damage to the different parts of brain [1, 2]. As a result of this, metabolism of microbes reflects the reactions occurring in the different regions of brain. *P. gingivali,* is the most pathogenic form of bacteria that produces toxins in the form of gingipains cause the large severe inflammation in the brain of Bacterial and viral infections may trigger the severe neurodegeneration associated with Alzheimer disease and patients suffering form that disease has high serum levels of beta-amyloid peptide. Sometimes, it may also due to the attack of viral infections such as cytomegalovirus that has been linked to the cognitive dysfunction [3-5]. Researchers have proposed that continues attack of bacteria and viruses to the brain tissues leads to degeneration of neuron. But diagnosis and proper medical treatments in the right time may helpful to control the pathogenesis of other neurological disorders and Vision problems, such as blurred vision, double vision or loss of peripheral vision. There are different approaches to control the attack of microbes via therapeutic treatments [6].
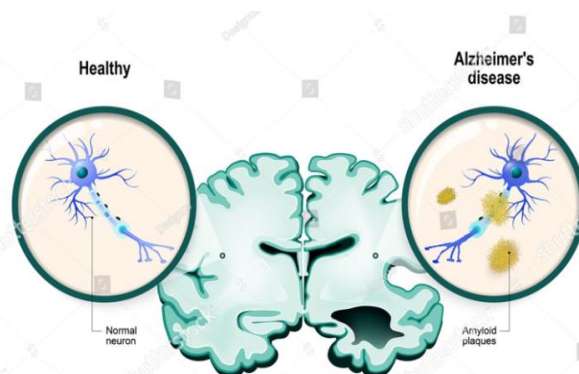

Fig-1: Shows the comparisons of normal and tumorous tissues with Alzheimer diseases

Different types of fungi also causing the infections once the attack on the human body. These pathogenic fungi are *Blastomyces dermatitidis* and *Histoplasma capsulatum* sense an increase in temperature. These fungi promoted the immune responses by attacking on the lungs cells and undergo to the phase transition. The persistence attack of these

fungi leads to poor functioning of lungs and sometimes cause lung cancer. Different drugs are used to target the fungi that causing the infectious diseases and mechanism focused on the targeting the genes responsible for particular disease [7, 8]. Autotransporters are the biologically active proteins across the outer membranes of gram-negative bacteria such as *Y. pestis* genome comprised twelve genes as yaps encode by the autotransporters. These yaps causing the different infections in human body as expressed increased at the certain level. These genes are activating the transcription of genes involved in cell proliferation and suppressing apoptotic genes and causing the cancers as they playing important role as oncogenes [8, 9].

Each microprobe has its own mode of action of attacking to the body cells. Not all microbes have the maximum capacity for latency that depends upon on the prolonged incubation periods between infection and disease differ from microbes. Sometimes, stress to the body organs stimulating the microprobes providing the toxins that accusing the anxiety and depression. Stress-induced changes to the microbiome may in turn affect the brain and behavior. Bacteria such as *encephalitis* and *meningitis* can result the severe damage to the neurons of the brains. Microbes probably influence the brain via multiple mechanisms. Serotonin, dopamine and GABA are affected the mode and sometimes leads to excessive secretions of these chemical compounds causes the alterations in the brain functions [10-12]. Gut microbiome also playing important roles in the brain function and behavior by causing the several neurological disorders. These symptoms can be seen in epilepsy and in response to seizure interventions. Sometimes, colonization of the bacteria in the gut causing the abnormal responses and sufficed the production of different chemicals or hormones affecting the functioning of the neurons and excessive damaging to brains tissues causes brain hemorrhage. These conditions are imitate to the medical emergency and due to the resistance caused by the bacterial and other microbes, molecular based drugs needed to be design to act on the microbes surfaces and kills them directly from the body [11-13].

Different amino acids have been used as a source of bacterial nutrition for example , tryptophan as one of the essential amino acid playing important role in catalyzing the different reactions in body. This enzyme also important for tryptophan metabolism and lots of enzymes have been playing significant role converting the tryptophan into the indole compounds. Tryptophan has a multitude of metabolic functions as incorporation into polypeptide chains of bacterial enzymes and serves as a precursor of the cofactor. The biochemical mechanism of each bacteria as follows. *Peptostreptococcus russellii* playing important role in converting the tryptophan into the indole-3-acid-acetic.

Clostridium sporogenes also playing important role in converting the tryptophan into the indole-3-propionic acid. Lactobacillus spp another class of the bacteria that playing important role in converting the tryptophan into the indoleacrylic acid. Tryptophan and tyrosine residues play special roles in "anchoring" membrane proteins within the cell membrane. Deficiency of the tryptophan for the bacterial growth leads to inhibition of biochemical proces and stop the process of translation as amino acids playing important role in protein metabolism. Deficiency also leads to poor growth [14-16].

There are different aspects of the inflammatory makers released by body in response to bacterial attack. One of these kind of response is the inhibiting the inflammation by pharmacological interventions, such as inhibitors of inflammatory kinases and agonists of relevant transcription factors/cytokines, prevents insulin resistant. Gut microbiota is playing important role in balancing pro- and anti-inflammatory responses in various disease conditions and in relation to nutritional status. Few studies showed that mechanism remains unclear of gut microbes–host interactions may influence about the nutritional supplementations of amino acids and activation of inflammatory cytokines. Chronic inflammation that is associated with metabolic implications of low-grade immunity processes. There are few gaps in literature that how bacteria can use metabolic pool in order to attack on the human body and causes inflammatory responses. The analysis of the toxic metabolites in relation to inflammatory markers such as hsCRP, WBC, or fibrinogen helpful for the identification of alterations at the molecular level. These events and medical diagnosis through appropriate manner can leads to dehisces the attack of bacteria on exposed areas. Moreover, molecular targeting of bacterial species can be also useful approach to discover the innovative antibiotics that can be used for large scale treatment [17-20].

One of the example of insulin that have been artificially synthesized by the biological scientists in order to check the insulin resistance in dogs. Diabetes in the metabolic syndrome arises due to the defect in the insulin production of the pancreas. It also influxes on the liver cells that unable to secret the normal insulin. The increasing incidence of metabolic syndrome and its highly morbid, chronic, and exceptionally costly downstream diseases threatens to overwhelm the world's health care systems and economies. Metabolic risks arise due to the cardiovascular diseases that affected the world all around the world. Biochemical alterations in the composition of the gut microbiota have been reported in individuals with obesity. Sometimes chemical agents accumulation leads to borne of cardiovascular diseases One of such example id the trimethylamine-N-oxide as metabolite of the gut microbiota. It causes the

promotion of the atherosclerosis as increase the biochemical events occurring in the cells [21, 22].

Action of different chemicals drugs

Riboswitches are the regulatory sequences that can bind to the active target molecules in order to regulate the gene expression of most of gens causing the abnormal response. Aptamers are nucleic acid sequences that can inhibit the growth of bacteria by binding to their nuclear region. Antibiotics target ribosomes to inhibit the growth of bacteria by binding to their nuclear region in the 30S or 50S ribosomal subunit. Each antibiotic has its own function to oncogenes of bacterial strains either binding to the membrane of the bacteria or binding to specific region that can activate the molecular transcription process [23-25].

There are different natural chemical compounds that possess the bioactivities that inhibit the growth of bacteria and other pathogens. Kaempferol as the natural compound that is used to increase the antimicrobial potential of ciprofloxacin in a NorA overexpressed *S.aureus.* Chalcones and catechin gallates are group of the natural compounds functions to efflux pump inhibitory activities. There are also many other compounds such as epigallocatechin gallate from green tea target the genetic material of most of bacterial strains. Natural compounds are the most important for the treatment of against bacteria, viruses, fungus, and most of pathogens as they can reduced the level of oxidants induced by microorganisms [26-28].

Ampicillin is the chemical class of drugs that is used to control the infections such as respiratory tract infections, urinary tract infections, meningitis, salmonellosis, and endocarditis. As it the broad spectrum antibiotic and can target broad range of bacterial strains. It also used to prevent group B streptococcal infection in the newly born Childs. It has different mode of action on severity of patients. It may be used as single dose or combinations in order to control the growth of bacteria superficial eye infections such as bacterial conjunctivitis. It also can be given in the normal concentrations according to the patient history and immunity against the specific disease [29, 30].

Chloramphenicol is the drug that is used to control the infections caused by bacteria as it the broad spectrum antibiotic and can target broad range of bacterial strains. It may be used as single dose or combinations in order to control the growth of bacteria superficial eye infections such as bacterial conjunctivitis. It has also been used for the treatment of typhoid and cholera. It has only the target the bacterial strains as it comprised the chemical compounds that can treat the eye infections. It can be given in the normal concentrations according to the patient history and

immunity against the specific disease. Floxin is the drugs that is used to control the infections caused by bacteria and related strains. It may be used as single dose or combinations in order to control the growth of bacteria. It is given to those patients suffering from the bacterial infections of the skin, lungs, prostate, or urinary tract such as bladder and kidneys. Floxin is also used to treat pelvic inflammatory disease and chlamydia and gonorrhea. The main target infections are the pneumonia, skin infections, bronchitis and acute pelvic inflammatory disease. It has only the target the bacterial strains while on the other hand; it has no activity against the viruses and other pathogens as it is specific to only bacteria [30-32].

Amoxicillin is also another class of the drugs that is used to control the infections caused by bacteria and related strains such as bacterial infections, such as chest infections including pneumonia, dental abscesses and urinary tract infections. It is used also for children, often to treat ear infections and chest infections in the form of single dose or combinations in order to control the growth of bacteria. It is given to those patients suffering from the bacterial infections of the skin, lungs, prostate, or urinary tract such as bladder and kidneys [33, 34].

CONCLUSION

Although, different antibiotics can target only the target the specific bacterial strains while on the other hand; it has no activity against the viruses and other pathogens. Some chemical modifications needed to make in order to improve the efficacy of different antibiotics and chemicals compounds such as riboswitches can bind to the active target molecules in order to regulate the gene expression of most of gens causing the abnormal response. Biochemical alterations in the composition of the gut microbiota can be improved with cardiovascular diseases.

REFERENCE

1. Kim, K. S. (2008). Mechanisms of microbial traversal of the blood–brain barrier. *Nature Reviews Microbiology*, *6*(8), 625-634.
2. Huang, S. H., & Jong, A. Y. (2001). Cellular mechanisms of microbial proteins contributing to invasion of the blood–brain barrier: Micro Review. *Cellular microbiology*, *3*(5), 277-287.
3. Hanke, M. L., & Kielian, T. (2011). Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. *Clinical science*, *121*(9), 367-387.
4. Sherwin, E., Bordenstein, S. R., Quinn, J. L., Dinan, T. G., & Cryan, J. F. (2019). Microbiota and the social brain. *Science*, *366*(6465).
5. Das, S., Owen, K. A., Ly, K. T., Park, D., Black, S. G., Wilson, J. M., ... & Casanova, J. E. (2011). Brain angiogenesis inhibitor 1 (BAI1) is a pattern

recognition receptor that mediates macrophage binding and engulfment of Gram-negative bacteria. *Proceedings of the National Academy of Sciences*, *108*(5), 2136-2141.

6. Berer, K., & Krishnamoorthy, G. (2012). Commensal gut flora and brain autoimmunity: a love or hate affair?. *Acta neuropathologica*, *123*(5), 639-651.

7. Kennedy, D. O. (2014). Polyphenols and the human brain: Plant "secondary metabolite" ecologic roles and endogenous signaling functions drive benefits. *Advances in Nutrition*, *5*(5), 515-533.

8. Prasad, K. N., Mishra, A. M., Gupta, D., Husain, N., Husain, M., & Gupta, R. K. (2006). Analysis of microbial etiology and mortality in patients with brain abscess. *Journal of Infection*, *53*(4), 221-227.

9. Rivest, S. (2003). Molecular insights on the cerebral innate immune system. *Brain, behavior, and immunity*, *17*(1), 13-19.

10. Singamsetty, V. K., Wang, Y., Shimada, H., & Prasadarao, N. V. (2008). Outer membrane protein A expression in Enterobacter sakazakii is required to induce microtubule condensation in human brain microvascular endothelial cells for invasion. *Microbial pathogenesis*, *45*(3), 181-191.

11. Sanwal, P. (2021). Nanoparticle: Role in Chemical Industries, Potential Sources and Chemical Catalysis Applications. *Sch Int J Chem Mater Sci*, 4(4), 40-45.

12. Sanwal, P. (2021). A Review on Nanoparticles, Synthesis, Characterization, Current Applications and Future Perspectives. *Sch Bull*, 7(4), 118-122.

13. Muhammad, K. Q. (2021). Inductively Coupled Plasma Spectroscopy as Instrumental Tool for Detection of Nanoparticles. *Sch Bull*, 7(8), 220-224.

14. Le Guennec, L., Coureuil, M., Nassif, X., & Bourdoulous, S. (2020). Strategies used by bacterial pathogens to cross the blood–brain barrier. *Cellular microbiology*, *22*(1), e13132.

15. Hyland, N. P., Quigley, E. M., & Brint, E. (2014). Microbiota-host interactions in irritable bowel syndrome: epithelial barrier, immune regulation and brain-gut interactions. *World journal of gastroenterology: WJG*, *20*(27), 8859.

16. Brüssow, H. (2020). Problems with the concept of gut microbiota dysbiosis. *Microbial biotechnology*, *13*(2), 423-434.

17. Hasain, Z., Mokhtar, N. M., Kamaruddin, N. A., Mohamed Ismail, N. A., Razalli, N. H., Gnanou, J. V., & Raja Ali, R. A. (2020). Gut microbiota and gestational diabetes mellitus: a review of host-gut microbiota interactions and their therapeutic potential. *Frontiers in cellular and infection microbiology*, *10*, 188.

18. Witkowski, M., Weeks, T. L., & Hazen, S. L. (2020). Gut microbiota and cardiovascular disease. *Circulation research*, *127*(4), 553-570.

19. Michaudel, C., & Sokol, H. (2020). The gut microbiota at the service of immunometabolism. *Cell metabolism*. Verhaar, B. J., Prodan, A., Nieuwdorp, M., & Muller, M. (2020). Gut microbiota in hypertension and atherosclerosis: a review. *Nutrients*, *12*(10), 2982.

20. Kavčič, B., Tkačik, G., & Bollenbach, T. (2020). Mechanisms of drug interactions between translation-inhibiting antibiotics. *Nature communications*, *11*(1), 1-14.

21. AlSheikh, H. M. A., Sultan, I., Kumar, V., Rather, I. A., Al-Sheikh, H., Tasleem Jan, A., & Haq, Q. M. R. (2020). Plant-based phytochemicals as possible alternative to antibiotics in combating bacterial drug resistance. *Antibiotics*, *9*(8), 480.

22. Kovalakova, P., Cizmas, L., McDonald, T. J., Marsalek, B., Feng, M., & Sharma, V. K. (2020). Occurrence and toxicity of antibiotics in the aquatic environment: A review. *Chemosphere*, *251*, 126351.

23. Theuretzbacher, U. (2020). Dual-mechanism antibiotics. *Nature Microbiology*, *5*(8), 984-985.

24. Cheng, D., Ngo, H. H., Guo, W., Chang, S. W., Nguyen, D. D., Liu, Y., ... & Wei, D. (2020). A critical review on antibiotics and hormones in swine wastewater: Water pollution problems and control approaches. *Journal of hazardous materials*, *387*, 121682.

25. Thorpe, A., Sirota, M., Juanchich, M., & Orbell, S. (2020). Action bias in the public's clinically inappropriate expectations for antibiotics. *Journal of Experimental Psychology: Applied*, *26*(3), 422.

26. Gupta, V., Kant, V., Sharma, A. K., & Sharma, M. (2020). Comparative assessment of antibacterial efficacy for cobalt nanoparticles, bulk cobalt and standard antibiotics: A concentration dependant study. *Наносистемы: физика, химия, математика*, *11*(1), 78-85.

27. Wang, J., Chu, L., Wojnárovits, L., & Takács, E. (2020). Occurrence and fate of antibiotics, antibiotic resistant genes (ARGs) and antibiotic resistant bacteria (ARB) in municipal wastewater treatment plant: an overview. *Science of The Total Environment*, 140997.

28. Ashfaq, M., Hashmi, M. Z., Mumtaz, A., Javed, D., Ain, N. U., Shifaqat, S., & Rehman, M. S. U. (2020). Environmental risk assessment of antibiotics and AMR/ARGs. In *Antibiotics and Antimicrobial Resistance Genes in the Environment* (pp. 331-349). Elsevier.

29. Pulingam, T., Thong, K. L., Appaturi, J. N., Nordin, N. I., Dinshaw, I. J., Lai, C. W., & Leo, B. F. (2020). Synergistic antibacterial actions of graphene oxide and antibiotics towards bacteria and the toxicological effects of graphene oxide on human epidermal keratinocytes. *European Journal of Pharmaceutical Sciences*, *142*, 105087.

30. Eduardo-Correia, B., Morales-Filloy, H., & Abad, J. P. (2020). Bacteria from the multi-contaminated

tinto river estuary (SW, Spain) show high multi-resistance to antibiotics and point to Paenibacillus spp. as antibiotic-resistance-dissemination players. *Frontiers in microbiology*, *10*, 3071.

31. Udaondo, Z., & Matilla, M. A. (2020). Mining for novel antibiotics in the age of antimicrobial resistance. *Microbial Biotechnology*, *13*(6), 1702-1704.

32. Anh, H. Q., Le, T. P. Q., Da Le, N., Lu, X. X., Duong, T. T., Garnier, J., ... & Nguyen, T. A. H. (2021). Antibiotics in surface water of East and Southeast Asian countries: A focused review on contamination status, pollution sources, potential risks, and future perspectives. *Science of The Total Environment*, *764*, 142865.

33. Roope, L. S., Tonkin-Crine, S., Herd, N., Michie, S., Pouwels, K. B., Castro-Sanchez, E., ... & Wordsworth, S. (2020). Reducing expectations for antibiotics in primary care: a randomised experiment to test the response to fear-based messages about antimicrobial resistance. *BMC medicine*, *18*(1), 1-11.

34. Soni, H., Kumar-M, P., Sharma, V., Bellam, B. L., Mishra, S., Mahendru, D., ... & Singh, V. (2020). Antibiotics for prophylaxis of spontaneous bacterial peritonitis: systematic review & Bayesian network meta-analysis. *Hepatology international*, *14*(3), 399-413.