A Cholesterol and Actinide Dependent Shadow Biosphere of Archaea And Viroids in Pulmonary Diseases

Ravikumar Kurup A.[1,*]; Parameswara Achutha Kurup[1]

[1]Professor of Metabolic Medicine and Neurology
The Metabolic Disorders Research Centre, TC 4/1525, Gouri Sadan, Kattu Road, North of Cliff House, Kowdiar PO, Trivandrum, Kerala, India
*Corresponding author.
Email: ravikurup13@yahoo.in

Abstract

Objective: Endogenous digoxin has been related to the pathogenesis of lung diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. The possibility of endogenous digoxin synthesis by archaea with a mevalonate pathway and cholesterol catabolism was considered.

Methods: 10 cases each of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma before starting treatment and 10 age and sex matched healthy controls from general population were chosen for the study. Cholesterol substrate was added to the plasma of the patients and the generation of cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA redutase, digoxin and bile acids were studied. The changes with the addition of antibiotics and rutile to the patient's plasma were also studied. The statistical analysis was done by ANOVA.

Results: The parameters mentioned above were increased the patient's plasma with addition of cholesterol substrate. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels.

Conclusions: An actinide dependent shadow biosphere of archaea and viroids is described in interstitial lung disease, chronic bronchitis emphysema, bronchial asthma contributing to their pathogenesis.

Key words: Archaea; Viroids; Interstitial lung disease; Chronic bronchitis emphysema; Bronchial asthma

INTRODUCTION

Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF.[1] Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.[2] Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.[3,4] Endogenous digoxin has been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[2] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5,6,7] Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.[8] An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.[6]

METHODS

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The

following groups were included in the study:- interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[9] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37°C for 1 hour. The following estimations were carried out:- Cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA redutase, digoxin and bile acids. [10,11,12,13] Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

RESULTS

The parameters checked as indicated above were:- cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA redutase, digoxin and bile acids. Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

Table 1
Effect of rutile and antibiotics on muramic acid and serotonin

Group	Muramic acid % change (Increase with Rutile)		Muramic acid % change (Decrease with Doxy+Cipro)		5 HT % (Increase without Doxy)		5 HT % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
ASTH	23.45	1.79	66.32	3.63	22.56	2.46	62.70	4.53
CBE	23.20	1.57	66.65	4.26	22.12	2.44	63.69	5.14
ILD	22.95	1.61	65.76	4.01	22.92	1.99	66.55	4.55
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2
Effect of rutile and antibiotics on free DNA and RNA

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy)	
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
ASTH	23.17	1.49	63.96	5.72	23.21	1.72	66.40	3.69
CBE	22.98	1.50	65.13	4.87	23.15	1.62	66.48	4.17
ILD	22.79	2.20	64.26	6.02	22.60	1.64	66.86	4.21
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3
Effect of rutile and antibiotics on HMG CoA reductase and PAH

	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
ASTH	22.03	2.58	60.73	5.55	23.22	1.67	62.06	2.05
CBE	22.28	2.10	65.21	3.81	23.31	1.70	64.38	5.67
ILD	22.75	2.75	62.71	6.04	22.98	2.01	63.91	4.86
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4
Effect of rutile and antibiotics on digoxin and bile acids

	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile acids % change (Increase with Rutile)		Bile acids % change (Decrease with Doxy)	
Normal	0.11	0.00	0.541	0.003	4.29	0.18	18.15	0.58
ASTH	0.49	0.07	0.199	0.022	23.38	2.13	64.52	6.49
CBE	0.55	0.04	0.219	0.038	23.19	1.72	64.25	6.19
ILD	0.50	0.07	0.183	0.029	22.77	1.97	64.79	5.78
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5
Effect of rutile and antibiotics on pyruvate and hexokinase

	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy)	
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
ASTH	21.26	2.04	55.44	7.92	22.20	2.41	64.44	5.78
CBE	21.53	2.15	58.30	8.80	22.90	2.07	67.17	4.33
ILD	20.89	2.28	58.84	9.44	22.54	2.57	65.57	5.41
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6
Effect of rutile and antibiotics on hydrogen peroxide and delta amino levulinic acid

	H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy)		ALA % (Increase with Rutile)		ALA % (Decrease with Doxy)	
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
ASTH	22.90	1.51	63.27	4.96	23.43	1.57	66.30	3.57
CBE	23.43	1.74	64.28	7.33	22.76	2.20	67.63	3.52
ILD	23.30	1.47	60.35	7.93	22.63	1.63	67.24	3.42
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7
Effect of rutile and antibiotics on ATP synthase and cytochrome F 420

	ATP synthase % (Increase with Rutile)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy)	
Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24	0.66
ASTH	22.94	1.94	66.18	4.15	22.39	1.75	64.24	8.55
CBE	23.32	1.74	65.67	4.16	22.78	2.23	62.58	8.62
ILD	23.33	1.35	66.83	3.27	21.95	1.56	53.17	7.20
F value	449.503		673.081		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

DISCUSSION

There was increase in cytochrome F420 indicating archaeal growth in interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. The archaea can synthesise and use cholesterol as a carbon and energy source.[14,15] The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.[16] There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.[7] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[15] The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.[17] The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.18 There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.[19] Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic non coding DNA using HERV integrase as has been described for borna and ebola viruses.[20] The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.[21] The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.[20,21] This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters.[22] The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in HLA gene expression. This modulation of HLA gene expression by viroidal complementary DNA can result in

autoimmune diseases. The RNA viroids can regulate mrna function by RNA interference.[19] The phenomena of RNA interference can modulate T cell and B cell function and euchromatin/heterochromatin expression. RNA viroidal mRNA interference plays a role in the pathogenesis of autoimmune diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and Borrelia.[23] The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[24] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.[25] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation. The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[26,27] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth.[28] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway

bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses have been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[29,30] The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality.[31] Changes in the length of noncoding region especially human endogenous retroviruses can lead onto autoimmune diseases.[32] The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue This results in a new neuronal, metabolic, immune and tissue phenotype or microchimeras leading to human diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. The microchimeras formed can lead to autoantigens and autoimmune diseases.

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation.[2,33] The archaeal cholesterol aromatase generated PAH can produce immune activation. The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. Immune activation has been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[29,30] PAH has also been related to the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.

The archaea and viroids can regulate the nervous system including the NMDA synaptic transmission.[2] NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. The archaeal cholesterol aromatase can generate serotonin.[17] Glutamatergic and serotoninergic transmission can lead to immune activation. Serotonin can produce bronchospasm leading onto bronchial asthma. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.[2] Right hemispheric dominance can lead to autoimmune diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[2]

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[34] The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. The lymphocytes depend on glycolysis for their energy needs. The increased glycolysis induced by the Warburg phenotype leads to immune activation. Lactic acid generated by increased glycolysis leads to immune stimulation. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity, bacterial porphyrin induced redox stress and mitochondrial dysfunction generates free radicals important in the pathogenesis of interstitial lung disease, chronic bronchitis emphysema and bronchial asthma. The accumulated pyruvate enters the gaba shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.[34] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. Hyperdigoxinemia is important in the pathogenesis of autoimmune diseases like interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.[2] Digoxin can increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation.[2] The archaeal cholesterol atabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell membrane microdomains related receptors producing immune activation. The archaeal bile acids can bind GPCR and modulate D2 regulating the conversion of T4 to T3. T3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF ½ inducing NQO1, GST, HOI reducing redox stress. Bile acids can bind PXR inducing the bile acid shunt pathway of cholesterol detoxification. Bile acids can bind macrophage GPCR and VDR producing immunosuppression and inhibiting NFKB. This helps to modulate the archaea and viroid induced chronic immune activation. Bile acids are thus protective compounds and put a break on the archaea and viroid induced changes.[35] Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto interstitial lung disease, chronic bronchitis emphysema and bronchial asthma.

REFERENCES

[1] Valiathan M.S., Somers, K., Kartha, C.C. (1993). Endomyocardial Fibrosis. Delhi: Oxford University Press.

[2] Kurup R., Kurup, P.A. (2009). Hypothalamic digoxin,

cerebral dominance and brain function in health and diseases. New York: Nova Science Publishers.

[3] Hanold D., Randies, J.W. (1991). Coconut cadang-cadang disease and its viroid agent, Plant Disease, 75, 330-335.

[4] Edwin B.T., Mohankumaran, C. (2007). Kerala wilt disease phytoplasma: Phylogenetic analysis and identification of a vector, Proutista moesta, Physiological and Molecular Plant Pathology, 71(1-3), 41-47.

[5] Eckburg P.B., Lepp, P.W., Relman, D.A. (2003). Archaea and their potential role in human disease, Infect Immun, 71, 591-596.

[6] Adam Z. (2007). Actinides and Life's Origins, Astrobiology, 7, 6-10.

[7] Schoner W. (2002). Endogenous cardiac glycosides, a new class of steroid hormones, Eur J Biochem, 269, 2440-2448.

[8] Davies P.C.W., Benner, S.A., Cleland, C.E., Lineweaver, C.H., McKay, C.P., Wolfe-Simon, F. (2009). Signatures of a Shadow Biosphere, Astrobiology, 10, 241-249.

[9] Richmond W. (1973). Preparation and properties of a cholesterol oxidase from nocardia species and its application to the enzymatic assay of total cholesterol in serum, Clin Chem, 19, 1350-1356.

[10] Snell E.D., Snell, C.T. (1961). Colorimetric Methods of Analysis. Vol 3A. New York: Van NoStrand.

[11] Glick D. (1971). Methods of Biochemical Analysis. Vol 5. New York: Interscience Publishers.

[12] Colowick, Kaplan, N.O. (1955). Methods in Enzymology. Vol 2. New York: Academic Press.

[13] Maarten A.H., Marie-Jose, M., Cornelia, G., van Helden–Meewsen, Fritz, E., Marten, P.H. (1995). Detection of muramic acid in human spleen, Infection and Immunity, 63(5), 1652 – 1657.

[14] Smit A., Mushegian, A. (2000). Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway, Genome Res, 10(10), 1468-84.

[15] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M.H., Hara, H., Anderton, M.C. (2007). A gene cluster encoding cholesterol catabolism in a soil actinomycete provides insight into Mycobacterium tuberculosis survival in macrophages, Proc Natl Acad Sci USA, 104(6), 1947-52.

[16] Francis A.J. (1998). Biotransformation of uranium and other actinides in radioactive wastes, Journal of Alloys and Compounds, 271(273), 78-84.

[17] Probian C., Wülfing, A., Harder, J. (2003). Anaerobic mineralization of quaternary carbon atoms: Isolation of denitrifying bacteria on pivalic acid (2,2-Dimethylpropionic acid), Applied and Environmental Microbiology, 69(3), 1866-1870.

[18] Vainshtein M., Suzina, N., Kudryashova, E., Ariskina, E. (2002). New Magnet-Sensitive Structures in Bacterial and Archaeal Cells, Biol Cell, 94(1), 29-35.

[19] Tsagris E.M., de Alba, A.E., Gozmanova, M., Kalantidis, K. (2008). Viroids, Cell Microbiol, 10, 2168.

[20] Horie M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., Oshida, T. (2010). Endogenous non-retroviral RNA virus elements in mammalian genomes, Nature, 463, 84-87.

[21] Hecht M., Nitz, N., Araujo, P., Sousa, A., Rosa, A., Gomes, D. (2010). Genes from Chagas parasite can transfer to humans and be passed on to children. Inheritance of DNA Transferred from American Trypanosomes to Human Hosts, PLoS ONE, 5, 2-10.

[22] Flam F. (1994). Hints of a language in junk DNA, Science, 266, 1320.

[23] Horbach S., Sahm, H., Welle, R. (1993). Isoprenoid biosynthesis in bacteria: two different pathways? FEMS Microbiol Lett, 111, 135–140.

[24] Gupta R.S. (1998). Protein phylogenetics and signature sequences: a reappraisal of evolutionary relationship among archaebacteria, eubacteria, and eukaryotes, Microbiol Mol Biol Rev, 62, 1435–1491.

[25] Hanage W., Fraser, C., Spratt, B. (2005). Fuzzy species among recombinogenic bacteria, BMC Biology, 3, 6-10.

[26] Webb J.S., Givskov, M., Kjelleberg, S. (2003). Bacterial biofilms: prokaryotic adventures in multicellularity, Curr Opin Microbiol, 6(6), 578–85.

[27] Whitchurch C.B., Tolker-Nielsen, T., Ragas, P.C., Mattick, J.S. (2002). Extracellular DNA Required for Bacterial Biofilm Formation. Science, 295(5559), 1487.

[28] Chen Y., Cai, T., Wang, H., Li, Z., Loreaux, E., Lingrel, J.B. (2009). Regulation of intracellular cholesterol distribution by Na/K-ATPase, J Biol Chem, 284(22), 14881-90.

[29] Fauci A.S. (1998). Harrison's Principles of Internal Medicine. New York: McGraw-Hill.

[30] Crystal R.G. (1996). The Lung: Scientific Foundations. Philadelphia: Lippincott-Raven.

[31] Poole A.M. (2006). Did group II intron proliferation in an endosymbiont-bearing archaeon create eukaryotes? Biol Direct, 1, 36-40.

[32] Villarreal L.P. (2006). How viruses shape the tree of life, Future Virology, 1(5), 587-595.

[33] Eberl M., Hintz, M., Reichenberg, A., Kollas, A., Wiesner, J., Jomaa, H. (2010). Microbial isoprenoid biosynthesis and human γδ T cell activation, FEBS Letters, 544(1), 4-10.

[34] Wallace D.C. (2005)¬. Mitochondria and Cancer: Warburg Addressed, Cold Spring Harbor Symposia on Quantitative Biology, 70, 363-374.

[35] Lefebvre P., Cariou, B., Lien, F., Kuipers, F., Staels, B. (2009). Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation, Physiol Rev, 89(1), 147 - 191.