Endosymbiotic Actinidic Archaea and Viroids Regulate Cellular Organelle Function, Cell Growth, Cell Differentiation and Cell Death

Introduction

A hypothesis regarding the role of endosymbiotic actinidic archaea and viroids in the regulation of cell function, cell differentiation, cell proliferation and cell death is presented in this paper. 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[1,2]. Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases[3-7]. Actinidic archaea and viroids have been related to the pathogenesis of non-hodgkin's B cell lymphoma, multiple myeloma and CNS glioma – glioblastoma multiforme[2]. The incidence of neoplasms is high in the presence of low level radioactivity of the mineral sands of Kerala[1]. Actinidic archaea and viroids have also been related to the pathogenesis of neuronal degenerations like parkinson's disease, alzheimer's disease, huntington's disease and motor neuron disease.[2] 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 regulating the cell cycle is described in the above mentioned disease states[6]. The endosymbiotic actinidic archaea and viroids can regulate the cell cycle and cellular organelle function.

Materials and 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: – Group A: Non-hodgkin's B cell lymphoma, multiple myeloma and CNS glioma – glioblastoma multiforme. Group B: – Alzheimer's disease, Parkinson's disease,

Huntington's disease and motor neuron disease. 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^{o}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 reductase, digoxin and bile acids[10-13]. 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 reductase, 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 3.1 *Effect of rutile and antibiotics on muramic acid and glutamate.*

	Muramic acid % (Increase without Doxy)		Muramic acid % (Decrease with Doxy)		Glutamate % (Increase without Doxy)		Glutamate % (Decrease with Doxy)	
Group	**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
Myel	22.87	1.84	66.31	3.68	23.01	1.67	65.35	3.56
NHL	23.81	1.90	66.95	3.67	23.12	1.71	65.12	5.58
Glio	22.63	1.63	67.24	3.42	22.51	1.85	63.56	5.29
HD	22.30	2.19	66.19	4.20	23.79	1.58	65.56	4.03
AD	23.09	1.81	65.86	4.27	23.66	1.67	65.97	3.36
PD	22.48	2.13	63.12	4.84	23.21	1.74	67.76	3.15
MND	21.94	2.03	64.29	5.35	23.89	1.69	65.09	3.89
Aging	22.93	2.08	63.49	5.01	22.71	1.82	66.13	3.83
F value	348.867		364.999		403.394		680.284	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3.2 *Effect of rutile and antibiotics on free DNA and RNA.*

	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy)	
Group	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
Myel	22.73	2.46	65.87	4.35	23.72	1.73	66.25	3.69
NHL	22.42	1.99	61.14	3.47	23.78	1.20	66.90	4.10
Glio	22.92	1.99	66.55	4.55	23.47	1.60	66.27	3.88
HD	22.48	2.13	63.12	4.84	23.86	1.86	65.93	3.95
AD	23.52	1.65	64.15	4.60	23.29	1.92	65.39	3.95
PD	22.30	2.19	66.19	4.20	23.16	1.60	64.21	3.43
MND	23.11	2.00	61.52	4.97	23.04	1.66	66.13	3.49
Aging	19.73	2.27	65.49	7.28	19.73	2.27	62.70	3.24
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3.3 *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)	
Group	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
Myel	23.54	1.79	61.75	5.76	23.60	2.00	62.37	5.58
NHL	22.28	1.76	61.88	6.21	22.84	1.42	66.07	3.78
Glio	23.18	2.09	63.87	5.36	22.87	1.59	62.02	6.89
HD	22.86	1.78	61.03	6.13	23.37	1.42	61.01	5.91
AD	23.43	1.68	61.68	8.32	23.26	1.53	60.91	7.59
PD	22.12	2.27	60.98	8.29	23.63	1.75	62.23	5.43
MND	21.79	1.68	64.51	6.96	23.17	2.02	61.03	5.40
Aging	22.94	2.59	59.19	7.18	22.66	1.96	65.88	5.01
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3.4 *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)	
Group	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
Myel	0.50	0.03	0.208	0.039	22.05	1.69	62.73	7.31
NHL	0.54	0.04	0.210	0.042	22.98	2.19	64.96	5.64
Glio	0.50	0.05	0.195	0.026	23.31	2.05	61.67	4.54
HD	0.52	0.09	0.177	0.038	23.08	1.56	62.00	5.39
AD	0.55	0.03	0.192	0.040	22.12	2.19	62.86	6.28
PD	0.54	0.03	0.193	0.042	23.77	1.40	65.39	4.88
MND	0.53	0.06	0.229	0.051	23.53	1.78	61.61	6.77
Aging	0.56	0.10	0.238	0.049	24.58	1.08	64.20	5.16
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3.5 *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)	
Group	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
Myel	20.01	2.11	61.13	5.37	22.29	1.98	64.44	6.24
NHL	21.19	1.61	58.57	7.47	22.53	2.41	64.29	5.44
Glio	20.79	1.65	53.57	5.89	21.82	1.86	64.26	6.05
HD	21.13	1.27	61.54	10.03	22.89	1.88	63.39	4.97
AD	22.63	0.88	56.40	8.59	22.96	2.12	65.11	5.91
PD	21.64	0.67	61.36	8.49	22.95	1.82	64.15	4.62
MND	21.58	0.81	59.11	10.05	23.15	1.78	64.41	4.90
Aging	21.31	2.51	60.42	7.65	23.36	1.78	66.62	4.83
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3.6 *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)	
Group	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
Myel	23.35	1.95	58.75	3.75	24.10	1.61	65.78	4.43
NHL	23.35	1.76	59.17	3.33	23.34	1.75	66.80	3.43
Glio	22.71	1.73	57.49	8.26	22.95	1.61	65.76	4.01
HD	22.27	1.71	60.02	8.51	23.21	1.74	67.76	3.15
AD	22.65	2.48	60.19	6.98	23.67	1.68	66.50	3.58
PD	24.17	1.33	56.09	6.56	23.79	1.58	65.56	4.03
MND	23.58	1.94	57.85	6.63	23.06	1.72	64.82	3.31
Aging	22.27	1.87	61.77	6.79	19.73	2.27	64.78	6.62
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3.7 *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)	
Group	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24	0.66
Myel	23.33	1.86	66.46	3.65	23.01	1.89	61.17	9.61
NHL	24.01	1.17	66.66	3.84	22.79	2.13	55.90	7.29
Glio	22.95	1.90	66.39	3.83	22.03	1.64	62.21	5.53
HD	23.16	1.60	64.21	3.43	22.10	2.83	59.72	6.90
AD	23.58	2.08	66.21	3.69	23.12	2.00	56.90	6.94
PD	23.86	1.86	65.93	3.95	22.32	2.17	57.31	9.22
MND	23.75	1.81	66.49	4.11	22.76	2.20	61.60	8.74
Aging	23.19	1.74	65.68	4.06	22.09	1.38	61.42	7.26
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 non-hodgkin's lymphoma – diffuse large B cell type, multiple myeloma and CNS glioma-glioblastoma multiforme. 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]

The archaeal digoxin is the master conductor regulating and coordinating cellular organelle function. Digoxin can produce sodium-potassium ATPase inhibition and inward movement of plasma membrane cholesterol. This produces defective SREBP sensing, increased HMG CoA reductase activity and cholesterol synthesis. The digoxin induced inward movement of plasma membrane cholesterol can alter membrane cholesterol/sphingomyelin ratio producing modified lipid microdomains. The digoxin induced lipid microdomain modulation can regulate the GPCR couple, neurotransmitter – glutamate, dopamine, and serotonin, GPCR coupled endocrine receptors – adrenaline, noradrenaline, glucagon and neuropeptide receptors and protein tyrosine kinase linked insulin receptor. The digoxin mediated inhibition of nuclear membrane sodium-potassium ATPase can modulate nuclear membrane lipid microdomains and steroidal/thyroxine DNA receptor function. Thus endogenous digoxin can modulate all the neurotransmitter and endocrine receptors by regulating lipid microdomains. Digoxin induced sodium potassium ATPase inhibition can increase intracellular calcium and reduce intracellular magnesium. Digoxin by increasing intracellular calcium can produce mitochondrial PT pore dysfunction. There is intracellular magnesium deficiency producing ATP synthase defect. Digoxin can thus modulate mitochondrial function. Decreased intracellular magnesium can lead to altered glycoconjugate synthesis and a protein processing dysfunction and lysosomal dysfunction. Digoxin induced redox stress can produce histone deacetylase inhibition and modulate gene expression.

Digoxin can modulate mRNA splicing and RNA function. Digoxin can thus modulate mitochondrial, cell membrane, golgi body, lysosomal and nuclear functions. It can integrate the function of cell organelle.[2] Archaeal bile acids can modulate mitochondrial function. Bile acids can produce uncoupling of oxidative phosphorylation and produce mitochondrial hibernation. Archaeal pyruvate is a HDAC inhibitor and modulates gene expression. Archaeal ammonia can activate membrane sodium potassium ATPase and produce mitochondrial PT pore dysfunction. Archaeal butyrate functions as a HDAC inhibitor modulating gene expression. Butyrate can also modulate protein conformation and folding. Butyrate can thus regulate protein structure and function. Butyrate is used in the treatment of the unfolded protein response. Archaeal PAH can combine with the cell membrane, proteins and nucleic acids modulating their structure and function. Thus the archaeal cholesterol catabolites can regulate function of multiple cellular organelle and produce integration of cellular organelle function.[2]

The actinidic archaea and viroids can modulate DNA and RNA function and regulate the cell cycle. 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 noncoding 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 modulating gene expression. The RNA viroids can regulate mRNA function by RNA interference[19]. The phenomena of RNA interference can modulate T cell and B cell function, cell differentiation, cell growth and euchromatin/heterochromatin expression. RNA viroidal mRNA interference can modulate the cell cycle producing malignant transformation. The phenomenon of RNA interference and the RNA viroidal complementary DNA related jumping genes can lead onto proof reading errors and generation of trinucleotide repeats contributing to the pathogenesis of huntington's disease. The phenomena of viroidal RNA induced RNA interference can modulate the cell death pathways producing neuronal and cell degeneration.

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 multicellular 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.

The actinidic archaea and viroids can induce cell proliferation and cell dedifferentitation leading on to neoplastic transformation. Bacteria and viruses have been related to the pathogenesis of malignancy. Toll receptor activation has been related to malignant transformation. Chlamydia, mycoplasma and acid fast bacteria as well as ebstein barr virus and retroviruses have been related to the pathogenesis of lymphomas. Staphylococcus has been related to carcinoma of the breast. Herpes viruses have been related to multiple myeloma[29,30,31,32]. The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality[33]. Changes in the length of noncoding region especially human endogenous retroviruses can lead onto lymphomas, teratocarcinomas and other malignancies[34]. 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 leading to malignant transformation. The microchimeras formed can lead to polyploidy and neoplastic changes. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype[35]. 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 increased glycolysis results in the upregulation of mitochondrial PT pore hexokinase resulting in cell proliferation and malignant transformation. 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 and lipid synthesis[35]. The increased lipid synthesis is

required for membrane formation needed for cell proliferation. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity and mitochondrial dysfunction generates free radicals important in the pathogenesis of malignancies. Free radicals can activate oncogenes producing malignant transformation. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate also leads to increased archaeal growth and digoxin synthesis leading to metabolic channeling to the mevalonate pathway. Hyperdigoxinemia is important in the pathogenesis of tumourogenesis. Digoxin can increase lymphocytic intracellular calcium which leads on to activation of oncogenes and cell proliferation[2]. The archaeal cholesterol catabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of cell membrane microdomains related to oncogenic cell growth factors protein tyrosine kinase receptors and AKT PI3K producing cell proliferation and malignant transformation. Cholesterol depleted states can lead onto polyploidy and neoplastic changes. The actinidic archaea and viroids can modulate the immune system leading to malignant transformation. NFKB is involved in malignant transformation. 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 signaling can activate NFKB producing chronic immune activation[2,36]. The archaea and viroid induced chronic immune activation and generation of superantigens. NFKB can promote cell growth and proliferation leading onto malignant transformation. 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 on to cell proliferation and malignant transformation. Mood disorders and schizophrenia can predispose to malignancies. 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 malignant transformation as reported previously from this laboratory. The archaeal cholesterol catabolism also generates PAH which can modulate gap junction intercellular communication resulting in cell proliferation and malignant transformation. Archaeal PAH can thus induce neoplastic change[37]. Archaeal bile acids tend to have an effect opposite to that of digoxin reducing free radical stress and possibly inhibiting malignant transformation. 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. The archaeal bile acids can bind VDR, the vitamin D receptor resulting in inhibition of malignant transformation[38,39]. Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto malignant transformation.

The actinidic archaea and viroids can modulate cell death and neuronal degeneration. Bacteria and viruses have been related to the pathogenesis of motor neuron disease, alzheimer's disease and parkinson's disease. Chlamydia, mycoplasma, cyanobacteria, actinomycetes and borrelia have been reported to be involved in the pathogenesis of alzheimer's disease. Helicobactor pylori, nocardia, streptococcus and corona viruses have been implicated in parkinson's disease. Mycoplasma, borrelia, retroviruses and enteroviruses have been related to the pathogenesis of MND.[40-46] The change in the length and grammar of the noncoding region.[33] 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 leading to human diseases like neuronal degeneration. The microchimeras formed can lead to polyploidy which has been implicated in degenerations like alzheimer's disease. Microchimeras can lead onto autoimmune disease. The actinidic archaea and viroids can regulate the NMDA transmission leading onto cell death.[2] As discussed before NMDA receptors can be activated by digoxin induced calcium oscillations, PAH increasing NMDA activity as well as viroid induced RNA interference.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate contributing to NMDA excitotoxicity. The archaea can regulate dopaminergic transmission with archaeal cholesterol aromatase/ring oxidase generated dopamine.[16] The increased dopamine synthesis can generate increased free radicals consequent to its catabolism. Cholesterol oxidase can generate free radical hydrogen peroxide. Free radicals can produce neuronal degeneration. 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] Previous studies by the authors have related right hemispheric chemical dominance to neuronal degeneration. 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 signaling can activate NFKB producing chronic immune activation.[2,36] The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. Immune activation and autoantibodies have been related to neuronal degeneration. Immune activation and free radicals induce neutral

sphingomyelinase generating ceramide. Ceramide acts upon the mitochondrial PT pore producing cell death. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[35] 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. Mitochondrial dysfunction has been related to neuronal degeneration. The increased glycolysis results in increased generation of the enzyme glyceraldehyde 3 phosphate dehydrogenase (GAPD). GAPD can undergo polyadenylation via free radical activated PARP enzyme. The polyadenylated GAPD can undergo nuclear translocation producing nuclear cell death. 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.[35] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can produce NMDA excitotoxicity and cell death. Ammonia can activate sodium potassium ATPase producing increased neuronal requirement of ATP leading onto mitochondrial transmembrane potential changes and cell death. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. Digoxin can produce sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial PT pore dysfunction and cell death.[2] The archaeal cholesterol catabolism generated PAH can produce NMDA excitoxicity and cell death. The archaeal and mevalonate pathway bacteria cholesterol catabolism can deprive cholesterol from neuronal cell membrane and organelle membranes like mitochondrial, ER and lysosomal membranes producing cellular and organelle dysfunction and death. Cholesterol

metabolic defect has been described in huntington's disease. Thus, the shadow biosphere of actinide dependent archaea, viroids and mevalonate pathway bacteria can lead onto neuronal degenerations like alzheimer's disease, huntington's disease, parkinson's disease and motor neuron disease.

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