Title : Becoming Archaea: Septic Shock, Warburg effect and loss of endosymbiotic relation-Billion year war of two genomes.

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The author have no financial interests to disclose.

This study was not supported by any grants.

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ABSTRACT :

Septic shock is a major problem in medicine and carries high mortality rate. Irrespective of the advances in this field the underlying mechanism behind septic shock still remains a mystery. To understand septic shock we need to understand the evolution of eukaryotic cell and the billion year war between archaeal/nuclear genome and the bacterial/mitochondrial genome. The ancient infection of archaeal host by the bacteria (α-proteobacteria) resulted in the formation of eukaryotes and mitochondrial endosymbiont occurred >1.5 billion years ago and this extraordinary event is occurring from then on all the time till now resulted in formation of complex life forms. In this article I propose *'Warburg common pathogenesis evolutionary model'*, which has the potential to explain septic shock and most of the pathophysiological processes. I hypothesize that the bacterial/mitochondrial invasion of the eukaryote cell is supported by the mitochondrial system of the host eukaryotic cell and resisted by the innate immune system which is the archaeal part of the host eukaryotic cell, as archaea is the real host before it became eukaryote.Three major outcomes may result because of the bacterial /mitochondrial invasion related event,

1) PAMP/DAMP via PRR eg.TLR4 over activates innate immune system which in turn inhibits the mitochondrial respiration and decreases the mitochondrial genome. Nuclear genome overpowers mitochondrial genome which results in the loss of the endosymbiotic relation between them, produces Warburg effect and the bacterial /mitochondrial invasion is successfully defeated. By Warburg effect, the eukaryotic host cell now returned to its original billion year old primitive form i.e. it became archaea like. This dedifferentiated state switching can be seen as the cells local survival strategy in response to injuries as the cells are now archaea like which has the ability to live in harsh environments. But returning to their primitive forms leads to disorder and ends in global collapse of the organ systems and organism which requires order in terms of differentiation which is maintained by the mitochondrial system in the eukaryotic cell and across the cells by intercellular mitochondrial transfer. Death of the organism may be due to the immortality pathway chosen by the cells locally. 2) Successful bacterial /mitochondrial invasion of the eukaryotic host will increase the mitochondrial genome and overpower the nuclear genome which may trigger apoptosis by degrading the nuclear genome and expelling it. 3) Partially successful invasion may result in the formation of cellular memory by increase in both OXPHOS and glycolysis.

I propose that the treatment in septic shock should aim at activation of mitochondrial respiration thereby decreasing the aerobic glycolysis and changing the cell to its normal adult dynamic differentiation phenotype i.e all the drugs should be used as differentiation

therapy. Adrenergic blockers and ascorbic acid may be the main treatment options, which are already used by some research groups. The author stresses the point that this model is general and applies to most of the pathophysiological process of all eukaryotic organisms from single celled to plants & animals.

Keywords: Septic shock, Warburg effect, dedifferentiation, differentiation therapy, ascorbic acid, adrenergic blockers, glycolysis, Endosymbiosis, Archaea, Proteobacteria.

Abbrevations :, Oxidative phosphorylation(OXPHOS),Pathogen associated molecular pattern(PAMP),Danger associated molecular pattern(DAMP),Pattern recognition receptor(PRR),Toll like receptor (TLR).

INTRODUCTION:

Sepsis is the harmful systemic response of the host to the infection (1). According to Lewis Thomas the host's response to pathogen is more detrimental than the pathogen itself (2). Septic shock and severe sepsis associated multiorgan dysfunction carries high mortality rate ~ 40 – 70% (3, 4). Septic shock is refractory to the vasopressors in most of the cases, this includes norepinephrine,the primary drug used in reviving blood pressure in septic shock. Vascular hyporeactivity to various vasopressors in septic shock has been studied extensively, many reviews are available (5, 6). Irrespective of advances in this field, exact underlying mechanism behind the septic shock is still a mystery. Post mortem studies couldn't find the underlying cause in most of the cases, surprisingly most of the organs looked normal and showed only minimal cell death (7,8).

Lot of treatment options which were successful in animal models failed to show benefit in human studies,ranging from Nitric oxide Synthase(NOS) inhibitors, cyclooxygenase (COX) Inhibitors, endotoxin neutralizing proteins, TNF alpha antagonists etc.., (3). Some of the recent promising directions include, counterintuitive use of antihypertensives in septic shock, alpha2 adrenergic receptor agonists - clonidine (9-11), beta blockers reviewed in (12, 13) - aimed to reduce the sympathetic hyperactivation and hypermetabolism associated with sepsis. Alpha2 AR antagonist also has been shown to improve survival in sepsis animal model (14). Vitamin C has been used in sepsis reviewed in (15), glycolysis inhibitor shikonin (16), cytochrome C (17),caffeine (18), alternative oxidase(AOX) expression also showed protective effect in sepsis animal model(19).Interestingly mitochondrial transfer improved sepsis in animal model has been shown recently (20).

I propose "Warburg common pathogenesis evolutionary model", built by extending the Warburg effect, an extensively researched area in cancer biology, proposed by Otto

Warburg in 1920's (21, 22) with ideas borrowed from the evolution of the eukaryotes and endosymbiosis.

Surprisingly this model which will be discussed in a later section, not only has the potential to explain septic shock but most of the pathophysiological processes of eukaryotic organisms including humans. Most of the supporting evidences were already done in the respective subfields, and this article's novelty lies in the fact that by putting the Warburg common pathogenesis evolutionary model, it connects most of the medical problems including septic shock and shows a common pathogenesis could be the underlying mechanism in most of the diseases and the same model may explain most of the pathophysiological processes of the eukaryotic organisms. A clear picture emerges from the fragmented details of different aspects of sepsis.

Brief Overview:

By giving the brief overview iam trying to present an integrated picture on the sepsis problem, this combined with evolutionary viewpoint gives a clear solution theoretically, which has the potential to solve not only septic shock but also most of the pathologies. The Hypothesis is very fundamental and experimentally verifying it will help in the understanding of physiological and pathological processes of the humans and may extend to other divisions of life.

Sepsis, Immunity, Warburg effect and Immunometabolism:

Innate immune system recognizes the presence of the pathogen via PAMP/DAMP by PRR – TLR, NOD like receptor (NLR), RIG like receptor (RLR). Most of the pathways triggered by the PRRs lead to the activation of Nuclear factor kappa B (NFkB), which by its action on the nucleus produces various effects that acts against the pathogen (23-28). In this article, I will focus on TLR but the model which will be explained later applies generally to all aspects of immune system.

Sepsis has been shown to have 2 phases of immune responses –initial immune storm and late immunoparalysis (29, 30). Immunometabolism and Warburg effect is a hot topic in the sepsis research area(31-35). In 1926 Warburg showed tumors relied on aerobic glycolysis metabolism (21). He extended the thoughts in his 1956 paper and showed that the cancer cells originate in two phases, 1.Irreversible inhibition of cell respiration - OXPHOS by agents like H2S, arsenious acid which he called respiratory poisons and this necessitates the cell to change to aerobic glycolysis metabolism for survival and proliferation, 2. This in turn causes a normal differentiated cell to change to a dedifferentiated cancer cell. He also suggested that there may be some cancer like states in between these 2 terminal states,

which he called sleeping cancer cell states (22).These 2 changes –structural (cellular phenotype to dedifferentiated states) and functional (metabolic phenotype to glycolysis) are inseparable. Warburg effect is an extensively researched area in cancer biology; many excellent reviews are available (36). Essentially Warburg told everything what is required for understanding septic shock 90 years back.

Immune cells on activation (e.g. sepsis), shifts from OXPHOS to glycolysis and its relation to Warburg effect has been shown already (31,32,34,37). Dendritic cells shift to glycolysis on activation (34,37). Macrophages on activation shift to glycolysis and exhibit M1 Macrophage phenotype and these changes are associated with increased mTOR activation,HIF1α stabilization, iNOS activation, activation of glycolytic enzymes and decreased AMP activated protein kinase (AMPK) (32),i.e these cells shift to proinflammatory phenotype which may happen in the initial immune phase. During immunoparalysis phase the cells may return to their anti-inflammatory OXPHOS phenotype e.g. M2 macrophage phenotype shift (31). A similar phenomena is seen in lymphocytes also, whereas T effector cells exhibit glycolysis, T regulatory and T memory cells exhibit OXPHOS (38- 40).The fate of Tcells to Teff or T reg or T memory cells itself depends on the metabolism(39,40). Activated B cells depend on glycolysis/Warburg effect for antibodies production has been shown already and inhibiting the glycolysis reduced the antibodies production (41). Neutrophils normal resting state itself is glycolytic (42) and this is exacerbated on activation. Interestingly it has been shown recently that the Neutrophils in resting state showed SOX2 (SRY related HMG box 2) expression and it acted as a cytoplasmic sensor to detect dsDNA (43). This implies that neutrophils even in normal resting state are in mild Warburg effect and this is one of the examples that some cells in the body are already in Warburg effect. Also it has been shown that Neutrophil extracellular Traps (NETs) depend on glycolysis and glycolytic inhibitor 2 deoxy D-glucose(2 DG) inhibited NETosis (44). One can see from the above details that the immune storm or inflammatory phase may be governed by the glycolysis/Warburg effect and the immunoparalysis or anti-inflammatory phase may be governed by the OXPHOS.

Mitochondria & innate immunity: Zhang et al showed that mitochondrial DNA (mtDNA) is a DAMP and it elicits innate immune response through TLR9 and speculated that this process may due to the relation that mitochondria has bacterial origin, i.e. Mitochondrial DNA is a DAMP because of its bacterial origin (45).They also showed using inhibitory oligonucleotide (TTAGGG) which binds to CpG motifs to inhibit the activation of TLR9 , this points importance in relation to aging will be discussed in a later section. It has been already shown that the mitochondrial production of reactive species during infection

due to inhibition of mitochondrial respiration & mitophagy activates NLRP3 inflammasome ,which results in caspase 1 activation and interleukin 1 beta (IL1-β) release (46,47).Central role of mitochondria in innate immunity in relation to activation of TLR pathway, NLRP3 inflammosome and glycolysis has been reviewed by many (47-49).

Mitochondrial dysfunction in sepsis : Nitric oxide (NO) role in septic shock is an extensively researched area, reviewed in (50, 51). Biphasic vascular response has been shown in sepsis, initial hypotension phase is considered to be due to increased endothelial nitric oxide synthase (eNOS) activity and late hypotension phase is considered to be due to inducible nitric oxide synthase (iNOS) activity (52, 53).Also it has been shown eNOS regulates mitochondrial β fatty acid oxidation(FAO) (54) and mitochondrial biogenesis via beta adrenergic receptor(β AR) (55). Mitochondrial dysfunction in sepsis is known for a long time, many reviews are available (7, 8, 56). Usually eNOS produces low level increase in NO and iNOS produces high level increase in NO . Inhibition of mitochondrial respiration by nitric oxide is reversible or irreversible depends on the level of Nitric oxide.(57,58). Like NO, carbon monoxide (CO) and hydrogen sulphide (H2S) also inhibit mitochondrial respiration by their action on cytochrome C oxidase (58). It has been shown that CO, H2S are used to treat sepsis in animal models (8), implies along with other actions CO and H2S might have competitive inhibition with NO and this may activate the mitochondrial respiration. I will generalize this in a later section.

Briefly, when the the mitochondrial respiration is inhibited for example by NO, the electron flux will be stopped, the energy need will be met by the glycolysis and the glycolytic ATP move to the mitochondrial matrix, which makes the ATP synthase to work in reverse way i.e ATP hydrolysis instead of synthesis and pumps the proton from the mitochondrial matrix to the outer aspect of the inner membrane, all this will result in mitochondrial membrane hyperpolarization (57).It has been already shown mitochondrial membrane depolarization lead to cytochrome C release and apoptosis (59) and mitochondrial hyperpolarization is related to cancer state (60). Mitochondrial membrane hyperpolarization may inhibit the release of cytochrome C. Mitochondrial membrane hyperpolarization has been shown in sepsis (61, 19).Increased electron leak during mitochondrial respiration inhibition will lead to increased reactive species-reactive oxygen species (ROS) & reactive nitrogen species (RNS) (7).This along with Hypoxia inducible factor 1 alpha (HIF 1alpha) stabilization due to mitochondrial inhibition by NO and mTORC1 activation leads to antiapoptosis and survival(19,32,57). NFkB activation may inhibit caspase 8 activation (62) and as shown earlier mitochondrial membrane hyperpolarization may lead to inhibition of cytochrome C release in sepsis, thus both intrinsic and extrinsic pathway of apoptosis may be inhibited in sepsis. It is known that reactive nitrogen species(RNS) peroxynitrite(ONOO-)

activate PARP which leads to decrease in NAD+ (63). Also the NADH will not be converted to NAD+ due to the inhibition of the mitochondrial respiration; this also contributes to the decrease in NAD+ level. Decreased NAD+ inturn lead to activation of glycolysis/Warburg effect and loss of nuclear-mitochondrial communication has been already proposed in the aging process (64).

Decreased mtDNA in the cells in sepsis has been already shown by many (65-67). Increased plasma mtDNA has been shown to be associated with mortality (68). Also as mentioned earlier Zhang et al showed that mtDNA acts as a DAMP.(Zhang 2010). Calvano et al by gene network analysis of the data from sepsis induced in humans showed decreased OXPHOS machinery genes, decreased pyruvate dehydrogenase(PDH), increased pyruvate dehydrogenase kinase(PDK), decreased porin or voltage dependant anion channel (VDAC) and Adenine nucleotide translocator(ANT) genes (69).

Activation of NFkB leads to activation of genes like iNOS, glycolytic enzymes in the nucleus which leads to irreversible inhibition of mitochondrial respiration, decreases mtDNA, alters the tricarboxylic acid(TCA) cycle –it may be broken or works as reverse TCA and transformed to glyoxalate cycle , increase citrate and succinate, activates hypoxia inducible factor 1 alpha(HIF1- α) - all these changes leads to Warburg effect (19 ,32,70). NFkB also shown to negatively regulate the mitochondria directly (71).Biphasic mitochondrial response similar to biphasic vascular response with initial increase in mitochondrial activity and late decrease in mitochondrial activity in sepsis has been proposed already (7).

Mitochondrial inhibition lead mtROS increase activates NLRP3 inflammasome (46). It has been shown in animal sepsis models that mitochondrial fusion was decreased and mitochondrial fission was increased (72). Mannam et al showed in sepsis animal models that increased MAP Kinase kinase 3 (MKK3) lead to decreased mitochondrial biogenesis and mitophagy and these effects are inhibited by inhibiting MKK3 (73).Also It has been shown that lipopolysacchride(LPS) preconditioning lead to mitochondrial biogenesis and protective effect (74). Mitochondrial biogenesis is shown to be associated with the survival in sepsis (75). As mentioned earlier eNOS plays a key role in mitochondrial biogenesis (55).

Inhibition of mitochondrial respiration in sepsis may be the underlying cause for multi organ dysfunction in sepsis has been proposed by many, for reviews (7,8, 56,76). Interestingly as mentioned earlier treatments focussed on activating the mitochondrial respiration in animal models of sepsis has been already tried - cytochrome C given exogenously to overcome the mitochondrial inhibition in sepsis animal model showed increased cytochrome C oxidase activity and improved the survival (17),caffeine treatment in the sepsis model also showed similar findings (18).It has been already suggested that the mitochondrial respiration inhibition in sepsis can be seen as an adaptive response(8).

Alternative oxidase expression also showed protective effect in sepsis animal model (19). Recently Islam et al showed that mitochondrial transfer from bone marrow derived stromal cells (BMSC) via connexin 43 showed protective effect in sepsis acute lung injury animal model (20).The significance of this will be discussed in a later section.

Evolution of the eukaryotic cell and endosymbiosis.

Endosymbiotic theory says that the association of α-proteobacteria with the archaeal host cell resulted in the evolution of eukaryotic cell and the α-proteobacteria became mitochondrial endosymbiont after gene transfer from α-proteobacteria to archaeal genome (77). It is already proposed by many that endosymbiosis resulted in the origin of apoptosis and eukaryotic aerobic metabolism (77-79). The ancient infection of archaeal host by the bacteria (α-proteobacteria) which resulted in the formation of eukaryotes and mitochondrial endosymbiont might have occurred >1.5 billion years ago (80) and occurring continuously from then on till now resulting in the formation of complex life forms. Nuclear genome is mainly archaeal (81). In short there are 2 genomes in our eukaryotic cell –archaeal/nuclear genome and bacterial/mitochondrial genome and they have a endosymbiotic pact and continuous negotiations by gene transfer occur, generally from mitochondria to nucleus.It has been already showed that mitochondria continuously colonize the nuclear genome and the horizontal gene transfer from mitochondrial genome to the nuclear genome results in the formation of nuclear mitochondrial sequences(NUMTs) (82 -84).

Increased catecholamines in sepsis, quorum sensing and host-pathogen interaction:

It is well known that the catecholamines in the plasma are increased in sepsis (85, 86). In spite of increased catecholamine level is sepsis, it seems odd to give exogenous catecholamines like norepinephrine for the treatment in septic shock. Many had already pointed out catecholamine treatment carries risk in treating shock, catecholamine treatment in septic shock may do harm rather than saving the patient (85, 87,88). In fact adrenergic blockers – α & β adrenergic blockers were already used long time back in shock states in animals and in patients(85,89,90).It is interesting to see the use of prazosin for treating scorpion sting in this context (91).

It is known that Quorum sensing is used by bacteria via bacterial adrenergic receptors for the bacterial growth, cell to cell communication, virulence and biofilm formation and this has been shown to be blocked by adrenergic receptor blockers, reviewed in (92,93).Thomas Rudel et al already proposed based on the similarity between bacterial porin and mitochondrial porin that the pathogen invasion is similar to mitochondrial endosymbiosis (94). Frade & Michaelidis extended this idea and proposed that bacterial invaders use porins to enter the host and cause host cell death and this process is similar to the

apoptosis/programmed cell death (79).

Lyte pointed out that catecholamines lead to bacterial growth via quorum sensing and it can be blocked by adrenergic blockers.He also pointed out that as the plasma catecholamine levels are already elevated in sepsis, catecholamine treatment may produce detrimental results and mentioned that alpha and adrenergic blockers are used to treat septic shock long back(88).It has been already proposed by Kravchenko and Kaufmann that bacteria may use the quorum sensing to suppress the innate immune system by inhibiting NFkB and this helps in the bacterial colonization of the host(95).

Hypothesis: Warburg common pathogenesis evolutionary model.(Figure1)

The model that is going to be discussed below is a highly simplified model, for the sake of clarity lot of other contributing variables are not included e.g. cholinergic system. One of the key questions to be asked is why PAMP/DAMP is recognized via PRR by the innate immune system and produces response to prevent/destroy the pathogen. What is the self/identity of the cell? The answer lies in the evolution of eukaryotes. The ancient infection of archaeal host cell by the proteobacterial cell >1.5 billion years ago is continuously occurring from then on till now. As mentioned earlier mitochondrial colonization of nuclear genome occurs even now (82). Recently intercellular mitochondrial transfer is shown to occur through tunnelling nanotubes, gap junctions etc.. reviewed in (96).

1. **Real identity/self of the eukaryotic cell is Archaeal:** It is known that innate immune system recognizes - non-self (pathogen), normal and abnormal self and produces different responses (97). Eukaryotic cell recognizes LPS using TLR4 or mtDNA using TLR9 for the non-self bacteria/mitochondria. Eventhough TLR4 recognization of LPS and LPS is a part of bacterial cell wall is well known, significance is not understood so far. It is also well known that LPS is not a part of archaeal cell (98). Does it not implies that the self could be archaeal? which may be the reason why LPS is used to sense the bacterial invasion by the archaeal innate immune system. I propose, the self/identity of the eukaryotic cell could be the real host cell (Archaea) before it became eukaryote after alpha proteobacterial ancient infection.
2. **Innate immune system is governed by the archaeal part of the eukaryotic cell:** I hypothesize that the bacterial/mitochondrial invasion of the eukaryote cell is supported by the mitochondrial system of the host eukaryotic cell and resisted by the innate immune system which is the archaeal part of the host eukaryotic cell, as archaea is the real host before it became eukaryote because of alpha proteobacterial endosymbiosis which resulted in

mitochondria.

3. **Normal adult differentiated state or ordered state is regulated by mitochondria:** Win-Win state for both archaeal/nuclear and bacterial /mitochondrial genomes:

As mentioned earlier bacterial invasion of the archaeal host and healthy endosymbiotic relation between 2 genomes occurred after negotiations like gene transfer from bacterial genome to archaeal genome which resulted in the formation of mitochondrial endosymbiont. This is a win-win situation for both bacterial and archaeal genome. Allen's CORR hypothesis says that the reduced bacterial genome is retained in the mitochondria mainly to regulate the redox balance and production/ regulation of OXPHOS machinery and vice versa (99). This state which has healthy mitochondrial-nuclear endosymbiotic relation may be equivalent to our normal adult differentiated cell phenotype. Mitochondrial system may regulate the differentiated state of the cells/organ systems intracellularly and across the cells via intercellular mitochondrial transfer using tunnelling nanotubes/ gap junctions and quorum sensing. Similar to the regulation of the bacterial biofilm by quorum sensing , mitochondria may also regulate cells/organ systems via catecholmines and other chemicals like hormones. Catecholamines in turn help in mitochondrial biogenesis / bacterial growth. As mentioned earlier Lyte had already pointed out the catechomines via quorum sensing may help bacterial growth(88). As mentioned earlier, beta2 adrenergic stimulation via eNOS leads to mitochondrial biogenesis (55). I speculate that eNOS may have bacterial origin and iNOS may have archaeal origin.In short, mitochondrial/bacterial genome regulates order in the cells/organ system/organism by maintaining the differentiated state.

4. **Three major outcomes:**

I propose, atleast three possible major outcomes occur from the bacterial/mitochondrial invasion of the eukaryotic cell and deviate it from the normal differentiated state and healthy endosymbiotic relation.

A) Ist outcome: Bacterial/mitochondrial genome Wins (becoming bacteria): Successful invasion of the bacteria in the eukaryotic host will strengthen the mitochondrial/bacterial genome which overpowers the archaeal/nuclear genome and degrades it, utilizes the host cells resources and destroys it - this is a win situation for bacteria. This may be the basis of the apoptosis in the eukaryotic cells. The relation between the origin of apoptosis and the mitochondrial endosymbiosis has been speculated long

back (78, 79).As mentioned earlier Frade & Michaelidis brilliantly pointed out the relation between endosymbiosis, apoptosis, host-pathogen interaction and showed the similarity between the ancient bacterial invasion using bacterial porins which caused host cell death and apoptosis (79).

I would like to call this as Irreversible differentiated state /Apoptotic state/ anti-warburg effect/ anti-inflammatory state. The term irreversible is used here in the sense that it will be difficult to return back to normal differentiated state. Yadav et al showed recently that mt DNA and OXPHOS are increased during apoptosis (100) supports this view. Also it is well known that apoptosis produces anti-inflammatory / immunosuppressive effects and this can be seen in this context (101, 102). The 1st outcome if it occurs in small scale will not produce any major change in the organ systems. But if 1st outcome state occurs in major scale is detrimental in 2 ways – a)acute effect, it will deplete the host cells resources and b) chronic effect, the 1st outcome may tend towards 3rd outcome finally. For visual clarity 1st outcome state is not connected to the 3rd outcome in the figure1.

B) 2nd outcome: Cellular Memory/Immune memory - acquired/trained immunity/vaccination effects:

As mentioned earlier, it is well known that activation of immune cells during sepsis produces immune memory e.g. T cell memory. Whereas effector T cells exhibit glycolysis, memory T cells exhibit OXPHOS has been shown already .It is already showed that memory cells not only has increased mitochondrial content, OXPHOS and mitochondrial β fatty acid oxidation but it also has increased glycolysis (39).As mentioned earlier, metabolism of the T cells determine its fate to become effector T cells or regulatory T cells or memory T cells. It has been proposed recently that Sepsis induced acute kidney injury (AKI) has produced biological memory in kidney cells as it produced increased response to TLR ligands like LPS (103) and Warburg effect in relation to AKI is reviewed in (104).

I propose that partially successful bacterial or mitochondrial invasion leads to mitochondrial biogenesis and this change may be registered in the metabolic phenotype by increase in both OXPHOS/mitochondrial Fatty acid oxidation and glycolysis (as the invasion is only partially successful and is resisted by the archaeal/innate immune system) and the cellular phenotype may show both differentiated and

dedifferentiated features. This may create a stable structure and may produce amplified response when the bacterial/mitochondrial invasion related event occurs again. This may be the reason why the sublethal dose of LPS produces mitochondrial biogenesis and this may also be the mechanism behind – acquired immunity, trained immunity and vaccination effects. In short, this may be the underlying mechanism in all forms of cellular memory – neuronal memory, cardiac memory, Immune memory- Acquired Immunity/Trained Immunity/ Vaccination effects etc. Memory is a property that occurs not only in neurons , cardiomycytes and immune cells - but in all eukaryotic cells in response to bacterial /mitochondrial related invasion event.

C) 3rd outcome: Warburg effect & becoming Archaea: (Archaeal /nuclear genome wins, both present and ancient bacterial/mitochondrial invasion successfully defeated).

Both present and ancient bacterial/mitochondrial invasion is successfully defeated by the archaeal/nuclear genome by their innate immune system and the eukaryotic cell now becomes archaea like – it's a win situation for archaeal genome. Due to the loss of endosymbiotic relation , both the cellular phenotype and metabolic phenotype of the eukaryotic cell now switches to its billion year old primitive form before the ancient infection by α –proteobacteria occurred, i.e the eukaryotic cell becomes archaea like. This becoming arachea like state may have many substates which i would like to call it as - Irreversible dedifferentiated state/Warburg effect/cancer state/stem cell or induced pluripotent stem cell (iPSC) state /Inflammatory state. Most of the pathologies end point may be this state and lethal infection/lethal dose of LPS may produce this state. These substates eventhough mostly similar may have some minor differences depends on the severity of the endosymbiotic relation loss.

Reduced mitochondrial variants state: Bacterial/mitochondrial invasion occurred and the archaeal/nuclear genome successfully enslaved it and reduced to mitochondrial variants like mitosomes, hydrogenosomes. The process is similar the reductive evolution of anerobic eukaryotes (77). By Allen's CORR hypothesis (99), if the OXPHOS machinery is not working as it occurs in most of the pathologies like septic shock because of irreversible inhibition, there is no need to retain the mitochondrial genome

which may results in the loss of mtDNA. Even without mitochondrial genome mitochondria may be maintained for other purposes. It is already known that the reduced mitochondrial variants –mitosomes ,hydrogenosomes main function is not OXPHOS but maintaining the mitochondrial membrane potential by the proton gradient due to ATP hydrolysis and synthesis of iron sulfur clusters (105). Martin and Muller proposed 'Hydrogen hypothesis' to understand these mitochondrial variants, they proposed archaea may be the hydrogen acceptor and the bacteria may be the hydrogen donor (106).

The mitochondrial genome may be degraded and expelled: This may be the reason behind NETosis? It has been already showed that the DNA that is released from neutrophil & eosinophils extracellular traps during its activation by pathogens is mtDNA (107,108). As mentioned earlier, NETosis is governed by glycolysis and glycolysis inhibitors like 2-deoxy-glucose (2-DG) inhibit NETosis (44).

Increased introns & Numts in Nuclear/archaeal genome: In most of the pathologies e.g. septic shock, there may be increased acquisition of mitochondrial genome by the nuclear genome and this may increase the introns and nuclear mitochondrial sequences (Numts) in the nuclear genome.

5) Induction of pluripotency / stemness in sepsis:

This state may be one of the substates mentioned in the third outcome. LPS induced macrophage activation has been shown to express kruppel like factor 4 (KLF4) and KLF4 upregulated iNOS by its interaction with NFkB (109). A similar finding has been also shown in microglia (110). As mentioned earlier,an unusual role of SOX2 has been shown recently,it acted as a cytoplasmic sensor to detect dsDNA (43). Anne Schuster et al already proposed that LPS may play a role in maintaining stem cell property during inflammation and showed LPS produced dedifferention state (111). Sandbo et al showed that LPS reduced the expression of alpha-SMA in vascular smooth muscle cells(VSMC),implies VSMC dedifferentiation(112).The relation between pluripotent stem cell and the warburg effect is known already, these cells depend on glycolysis like cancer cells (113).

One can see from the above details that induction of pluripotency / stemness occur during sepsis, all the key transcription factors that produce iPSC e.g. all four Yamanaka factors, may be expressed in the cell during septic shock. These transcription factors eg.SOX2 may not only produces

pluripotency but keep a strict vigilance on the bacterial/mitochondrial invasion. In short, one can say that sepsis produces induced pluripotency or stem cell state. This process may occur in most of the pathologies.

6) **Death of the organism/failure of the organ systems:**

I propose that the death of the organism / failure of the organ systems may due to the successful local strategy of the eukaryotic cell in response to injuries related to bacterial/mitochondrial invasion which results in loss of endosymbiotic relation and lead to irreversible dedifferentiation states/Warburg effect. Eukaryotic cells by switching to irreversible dedifferentiation states, goes back to its original primitive form by becoming Archaea like and has the survival advantage to live in harsh environments as archaea is well known for its ability to live in harsh conditions. At the same time this produces disorder due to the collapse of the order of the organ systems/ organism. As mentioned earlier order of the cells/organ systems may be maintained by the mitochondrial genome in terms of differentiation.

7) Mitochondrial respiration uncouplers-good or bad ?

Even though high level of NO via iNOS activation may lead Warburg effect in most of the pathologies like septic shock, irreversible inhibition of mitochondrial respiration by any respiratory poison will do the same. This may be due to the pathological uncoupling of mitochondrial respiration.I propose that when one respiratory poison is irreversibly inhibiting the mitochondrial respiration for eg. High NO, other respiratory poisons like hydrogen sulphide (H2S),carbon monoxide (CO), cyanide, arsenic may relieve the inhibition by competitive inhibition. For example one can use arsenic trioxide or low dose cyanide to treat sepsis. As mentioned earlier that CO, H2S are used to treat sepsis in animal models (8). Also the current treatment options of using sodium nitrite and sodium thiosulfate for cyanide poisoning treatment may work in this way.

As mentioned earlier low level NO via eNOS by adrenergic receptor activation lead to mitochondrial biogenesis and eNOS also regulates uncoupling protein 1 (UCP1) (55).This implies that adrenergic system via eNOS and by increased UCP1 produces mitochondrial biogenesis. This may be due to physiological uncoupling of mitochondrial respiration, it may be mild and reversible compared to the pathological uncoupling mentioned above and

this physiological uncoupling may be regulated by mitochondrial/bacterial system of the cell.

8) **Aging:**

Most of the pathophysiological processes can be seen in the context of the above hypothesis. For example decreased NAD+ leads to loss of communication between nucleus and mitochondrial may be the underlying process in aging has been proposed already (64). Also it is interesting to see the oligonucleotide sequence used to inhibit the CpG motif /mtDNA interaction with TLR9 , the sequence used is TTAGGG (45). This is telomere sequence and it raises many questions.

I propose that the telomere sequence in the chromosomes is regulated by mitochondria and the same telomere sequence may be used by mitochondrial system of the cell to help successful bacterial/mitochondrial invasion by inhibiting the innate immune system activation by its inhibitory action on TLR9 .As mentioned earlier most of the pathologies eg. septic shock lead to loss of endosymbiotic relation and decreased mitochondrial genome, this produces Warburg effect (please see the 3rd outcome in hypothesis section).In these conditions the telomere sequence regulation by mitochondrial system will be affected/decreased and may produce accelerated aging.

9) **Biphasic Immune response in septic shock** :

As mentioned earlier there are 2 phases of immune response shown in septic shock , initial increased immune response and late immunoparalysis. Also it has been shown already that the immune cells have 2 different phenotypes that is related to these 2 phases, on activation they exhibits glycolysis /inflammatory phenotype and later they may exhibit OXPHOS/anti-inflammatory phenotype (32,39). Also as mentioned earlier metabolism determines the fate of the Tcells, by returning to OXPHOS the Tcells produce T regulatory or T memory rather than T effector cells (39,40).

The immune response results should be seen in the light of survival, A) if the innate immune system is over activated the response will be the 3rd outcome mentioned earlier and the patients less likely to survive. B) But if the patient survives which implies that the bacterial /mitochondrial invasion has overcome the resistance offered by the innate immune system and leads to

mitochondrial biogenesis and increased OXPHOS. Depending on the success of the mitochondrial/bacterial invasion event the response may vary, if the invasion is successful, the cells tend to move towards the 1st outcome to irreversible differentiation state /apoptotic state/anti-inflammatory state which inturn makes the cells and system prone for further infections. If the mitochondrial/bacterial invasion is partially successful, the mitochondrial/bacterial invasion event is registered in the cells phenotype and metabolic phenotype, resulting in the memory formation as mentioned earlier in 2nd outcome which gives a stable structure and amplified response when the invasion event occurs next time.

10) Evolutionary importance of the Warburg effect:

Eventhough Warburg effect is known for a long time, it is not clear so far as why it has to occur and what survival advantage it carries. I hypothesize that Warburg effect is due to the return of the eukaryotic cells to their original primitive form before the ancient bacterial infection of the archaeal host cell occurred i.e they become Archaea. All the changes in the septic shock or most of the pathologies can be seen in this context. Warburg effect produced in these conditions produce a shift in metabolic phenotype from OXPHOS to Glycolysis i.e the cells shift from mitochondrial metabolism to archaeal metabolism and a shift in cellular phenotype from differentiated state to dedifferentiated states, i.e, the cells phenotype regulation by mitochondrial genome inside the cell and across the cells by intercellular mitochondrial transfer is lost and now the cell phenotype is governed by archaeal/Nuclear genome .Warburg effect or by becoming archaea gives survival advantage, as now it has the ability to live in harsh enviroments like archaea. Many changes that occur in most of the pathologies can be seen in this light, for example I speculate that eNOS which is constitutively active in our cells may have bacterial origin and iNOS which activated during most of the pathologies may have archaeal origin.

Some of the cells in our body which live in the harsh environments of the body may already be in Warburg effect which gives the survival advantage to live in these harsh environments eg. epithelial and smooth muscle cells in the bronchi which live in high oxygen environment and often exposed to pathogens present in the air and epithelial/smooth muscle cells in the intestine which live in high pathogen environment, renal cells which live in hyperosmolar environment, chondrocytes in the hypoxic and hyperosmolar

environment etc.. It has been shown already that the metabolism is predominantly glycolytic in intestine (114),renal cells (115,116),chondrocytes (117).

Specific expression of archaeal phenotype or bacterial phenotype or the normal hybrid healthy archaeal and bacterial phenotype at different spatial and temporal points due to various internal and external environmental constraints may be the underlying design principle of multicellular eukaryotic organisms.

Archaea and Warburg effect:

Kaminski et al proposed that activation of ADP dependent glucose kinase(ADPGK) in T Cell activation leads to Warburg effect and pointed out that the ADPGK is archaeal (118).It has been showed that changes in cholesterol metabolism in some pathologies like multiple sclerosis is related to activation by archaea and this triggers Warburg effect (119).

A similar idea to the present model has been proposed by Mazzocca et al for cancer recently, which this article's author was unaware till recently. They used an evolutionary approach for cancer and showed that reemergence of prokaryotic subsystems (archaea and bacteria) may be the underlying mechanism for cancer and this leads to Warburg effect (120).However unlike the model presented here, it is not detailed and generalized to most of the pathophysiological process. Also they did not delineated the roles played by bacterial/mitochondrial part and archaeal/nuclear part. As per the present model in relation to cancer, it says that the eukaryotic cell becomes archaeal like and it degrades the mitochondria/bacterial genome to reduced mitochondrial variants or integrates it to the nuclear genome or expels it (please see figure 1 and text).

11) **Understanding vascular dysfunction in septic shock using this model.**(Figure 2)

As mentioned earlier there are 2 phases of vascular response in septic shock similar to 2 phases of mitochondrial response. Differentiating the septic shock into 2 different phases is crucial from the viewpoint of treatment as some drugs which work in one phase may not work or detrimental in other phase.It has been already showed that methylene blue was beneficial in late phase of

sepsis but it increased mortality when given in the initial phase (121).It has been also shown that alpha1 blocker e.g. prazosin is beneficial in initial phase of sympathetic storm conditons and beta blocker eg. propranolol may be beneficial in the late phase but not in initial phase.It is well known that sympathetic storm occurs in septic shock also(122, 123).

Initial phase of septic shock:

Vascular smooth muscle cells (VSMCs) in normal adult differentiated state may have alpha1 receptor as the predominant adrenergic receptor, as it is already known that alpha1 adrenergic receptors are the predominant adrenergic receptors in adult aorta but not in fetal aorta (124). During the initial phase of septic shock, increased exogenous/endogenous catecholamines lead to adrenergic hyperactivation/quorum sensing through alpha adrenergic receptors(α-AR) predominantly via α1-AR leads to eNOS activation and mitochondrial biogenesis. It is already known that the initial phase of hypotension in septic shock is due to eNOS usually results in increased NO in nanomolar range produce mild reversible inhibition of mitochondrial respiration. As mentioned earlier eNOS activation has been shown to induce mitochondrial biogenesis (55).

Some of the possibilites already explored in understanding the vascular hyporeactivity in sepsis reviewed in (5,6) e.g., NO induced alteration in alpha1 adrenergic receptors by peroxynitrite (125) ,inhibition of RhoA/Rhok (52) etc .. may be some of the reasons for vascular hyporeactivity.

Adrenergic hyperactivation may act through G beta gamma (G βγ) subunit and activates phosphatidylinositol 3 Kinase (PI3K)/Akt , mitogen activated protein kinase (MAPK) pathways, this may involve calcium independent protein kinase C (PKC) isoforms (126-130) and all this finally lead to eNOS hyperactivation (131), then eNOS uncoupling (132,133) and iNOS activation (52,53). The increased NO due to eNOS activation inhibits the mitochondrial respiration reversibly leading to increased reactive species (ROS/RNS) and the reactive species may oxidize the tetrahydrobiopterin (BH4) resulting in eNOS uncoupling (132,133).

Late phase of septic shock: Late phase of hypotension in septic shock has been shown due to iNOS & high level increase in NO may irreversibly inhibit the mitochondrial respiration(57,58). Generally iNOS activation leads to very high NO and irreversible inhibition of mitochondrial respiration. But in some cases like anaphylaxis it may happen through eNOS hyperactivation (134). It

was pointed out by Lowenstein et al that what matters is the high NO level (135).

Irreversible mitochondrial respiration may leads to mtDNA decrease. For the changes in mitochondria please see figure1 and mitochondrial dysfunction section. Briefly, eNOS and liver kinase B1(LKB1) /AMP activated protein kinase(AMPK)/Sirtuin / peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC1α) mediated mitochondrial biogenesis is activated during the initial phase of septic shock and is inhibited in the late phase due to innate immune system overactivation which results in NFkB activation and this in turn leads to changes like activation of glycolytic enzymes,iNOS etc. .All these changes may lead to Warburg effect as mentioned earlier (Please see figures 1 & 2 and text).

The normal adult differentiated vascular smooth muscle cells (VSMCs) may change in the late phase initially to –embryonic/ fetal phenotype and later to synthetic/proliferative phenotype, this state may have 2 phases -acute phase, and rarely may go to chronic phase if the patient survives.

VSMC Embryonic dedifferentiated state (Figure 2):

When the VSMC are in this state, i propose a change in adrenergic receptor expression by VSMC and the cells may have β2 AR as the predominant receptors like it was in fetal state (124).It has been already showed that β ARs are overexpressed in sepsis late phase in animal models (136). Activation of eNOS via β ARs produce mitochondrial biogenesis has been shown already(55).For visible clarity in figure 2, β2 AR is directly linked to show eNOS activation/mitochondrial biogenesis and α 1 AR during hyperactivation may also work in the same way.

Paradoxical vascular responses to Norepinehrine: Exogenous/endogenous catecholamines given when the VSMCs are in embroyonic state in septic shock may produce paradoxical vasorelaxation via β2 AR. It is interesting to see that noradrenaline induced vasorelaxation in neonatal arteries in this context (137) where VSMCs are expected to be in embryonic dedifferentiated state expressing β 2 AR as the predominant ARs. Also it has been shown already that norepinehrine induced vasodilation in the isolated coronary arterioles of heart failure patients in this context, where the VSMCs are expected to be in dedifferentiated state (138). Based on the above details, catecholamines used in the septic shock treatment may produce detrimental effect of decreasing the blood pressure further.

Also it is well known that in normal conditions itself catecholamines produce relaxation effects in intestinal and bronchial smooth muscle, without knowing the significance, it is generally assumed that a simple model like catecholamines action via β-ARs produced relaxation explains it. Here I propose that these bronchial & intestinal smooth muscle cells may already in warburg effect even in normal physiological state and that's how they survive in these harsh enviroments. The normal physiological catecholamine response in intestine/bronchi which produces relaxation is equivalent to the pathological condition in septic shock where catecholamines may produce hyporeaction or vasorelaxation. In other terms vascular smooth muscle becomes like bronchial/intestinal muscle during septic shock.

2. VSMC synthetic / proliferative dedifferentiated state (Figure 2):

This state can be further divided into acute phase and chronic phase. In acute phase, the cells contractile apparatus may be decreased due to the VSMC phenotype change. It is already known that VSMC contractile phenotype to VSMC synthetic / proliferative phenotype resulted in decreased contractile apparatus (139). It has been already shown that lipopolysacchride (LPS) produced decrease in alpha smooth muscle actin (α-SMA) in VSMC, which implies the VSMC dedifferentiated state switching in sepsis and they proposed that it may contribute to the vascular hyporeactivity to catecholamines in sepsis (112), this finding supports the present model. In this state the due to decreased contractile apparatus and β2 AR overexpression the vascular response to exogenous/endogenous catecholamines may produce hyporeaction or paradoxical vasorelaxation.

In chronic phase, the vascular tone may be increased due to increased VSMC proliferation or hypercontractile due to the presence of myofibroblasts. I propose that this chronic phase is equivalent to systemic hypertension (SHT) and pulmonary arterial hypertension (PAH), patient may not be alive till this stage.

We also need differentiate the lethal and sublethal infection effects as they produce different results, please see (Figure 1)

a) **Sublethal infection effect** (indicate partially successful invasion): In this condition, Innate immune system of the host eukaryotic cell is not alarmed much and its resistance to mitochondrial/ bacterial invasion is not much, which leads partially successful invasion and produces mitochondrial biogenesis via

activation of adrenergic receptors, AMPK, Sirtuins, PGC 1 α and eNOS. But the partial invasion is also resisted partially by the archaeal/innate immune system, so the cells may have both increased OXPHOS and increased glycolysis, as mentioned earlier in the cellular memory section, this forms cellular memory of the bacterial/mitochondrial invasion related event by stable cell structure and produces amplified response when the event occurs next time.

b) **Lethal effect of mitochondrial/bacterial infection**(indicate bacterial/mitochondrial invasion is successfully defeated): Innate immune system of the host eukaryotic cell is alarmed much and its resistance to mitochondrial/ bacterial invasion is high, which leads not only to successfully defeat the present bacterial/mitochondrial invasion but also the ancient invasion which resulted in the mitochondrial endosymbiont. This may occur by irreversible inhibition of mitochondrial respiration and degradation of mitochondrial genome which results in Warburg effect (Figure 1). Lethal dose LPS via TLR4 activate NFkB ,PI3K/AKT/mTOR which leads to the activation of iNOS,HIF -1α stabilization and glycolytic enzymes Increased NO due to iNOS irreversibly inhibit the mitochondrial respiration by inhibiting cytochrome C oxidase. As mentioned earlier, this will lead to mitochondrial membrane hyperpolarization due to the proton build up by ATP hydrolysis as the F0F1 ATP synthase is working in reverse mode(57). From the above details one may say that instead of F0F1 ATP synthase working in reverse mode, it may be transformed to V-ATPase and it has to be seen in this context that V-ATPase might have originated from Archaea (140). Irreversible inhibition of mitochondrial respiration leads to decreased mtDNA. It has been already showed that mtDNA is decreased in sepsis (65-67). Other events happening in mitochondria are – inhibition of mitophagy (73), inhibition of mitochondrial fusion and increased mitochondrial fission (72) and decreased cytochrome C release(61).The TCA cycle may be modified in sepsis has been proposed already– it may be broken or work as reverse TCA cycle or as a glyoxalate cycle(70). In short**,** lethal effect of the bacterial/mitochondrial related event triggers the activation of the innate immune system fully which leads to the inhibition of mitochondrial respiration ,decreased mitochondrial DNA ,loss of endosymbiotic relation and produces Warburg effect/Irreversible dedifferentiated states/stem cell or iPSC state, antiapoptotic state/inflammatory state – the eukaryotic cell will became Archaea like.

Few treatment options for septic shock:

Based on this model many treatment options are possible like use of red light or maintaining cold temperature in intensive care units to activate mitochondrial respiration in most of the pathologies like septic shock. Due to space constraint I will specify 3 treatment options only.All the drugs used in the septic shock should be used as differentiation therapy – aiming to revive mitochondrial respiration and thereby maintain the order of the cells/organ systems/organism in terms of differentiation .

Primary drug options mentioned here are already used by some research groups but they have simple assumptions of blocking the adrenergic hyperactivation induced hypermetabolism or activating the antioxidant system without knowing the essence of the problem like the present model.

1. Vasopressors like Norepinephrine should not be used in septic shock. As discussed earlier, catecholamine treatment in septic shock may do harm rather than saving the patient (85,87,88).
2. Adrenergic blockers should be used in the septic shock and most of the pathologies. Alpha blockers especially α 1 blockers e.g. Prazosin should be used in the initial phase of the septic shock and β blocker should be used in the late phase of septic shock eg. Propranolol. Infact all the current antihypertensive drugs may be used to treat septic shock, as mentioned earlier, hypertension can be seen as the chronic phase result of septic shock (Please see figure 2). As mentioned earlier adrenergic blockers were already used in septic shock long time back and now there is a revived interest in using adrenergic blockers in septic shock (89, 90, 9-11,13,141-143).Also as mentioned earlier treatment depends on which phase the patient is in, as some drugs which are helpful in one phase may not work or detrimental in other phase, e.g. methylene blue and β blockers should be given only in late phase.
3. **Antioxidants** : Ascorbic acid may work as a differentiating factor regulating the differentiated state of the cell by activating mitochondrial respiration at cytochrome C oxidase there by making the electron flux to proceed normally.It should be used only by parenteral route and not by oral route. Use of ascorbic acid in sepsis and in many pathologies has been already shown (15,144,145).Ascorbic acid levels were shown to be decreased in sepsis patients and it was used intravenously in a phase 1 trial which showed it is safe and reduces multi organ dysfunction (145).Ascorbic acid has been shown to restore the endothelial dysfunction, insulin sensitivity, restored eNOS,, decreased HIF 1α level (146), inhibited TNF α induced NFkB (147), enhanced eNOS action by increasing BH4 level (148). Ascorbic acid has been shown to inhibit iNOS and restore vascular response to norepinephrine in sepsis animal model (149).

Ascorbic acid has been used intravenously which reversed the vascular hyporeactivity to vasopressors during the inflammation made by endotoxin in healthy humans (150).N acetyl cysteine can also be used to increase glutathione and glutathione may protect the respirtatory inhibition by NO (151). But ascorbate itself may increase glutathione level (152).

Conclusion:

To understand most of the pathologies we need to understand the evolution of eukaryotic cells. I had proposed Warburg common pathogenesis evolutionary model to understand septic shock and it has the potential to explain most of the pathophysiological processes. During septic shock and most pathologies the eukaryotic cell tend to move towards Warburg effect, i.e they became archaea like – the metabolic phenotype shifts from OXPHOS (mitochondrial/bacterial based metabolism) to glycolysis (archaea based metabolism) and the cell phenotype changes from ordered, differentiated phenotype (mitochondria/bacteria regulated phenotype) to disordered, irreversible dedifferentiated phenotypes (archaea regulated phenotype). Many key processes like apoptosis , memory, cell self-identity, death etc.. are redefined using this model. Differentiation therapy is suggested for septic shock treatment. This model is fundamental and general, may have the potential to explain most of the pathophysiological process of all eukaryotic organisms from single celled to humans, plants and animals. If experimentally verified, Warburg common pathogenesis evolutionary model will act like a fundamental theorem for medicine and open many new unknown avenues.

Acknowledgement:

The author would like to dedicate this article to Otto Warburg, Albert Szent Gyorgyi, Charles Janeway Jr, Ruslan Medzhitov and William Martin. I would like to thank my wife and kid who suffered a lot during last 2 years while preparing this article.

Conflict of Interest statement:

This study was not supported by any grants. The author have no financial interests to disclose.

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Figure1: Warburg common pathogenesis evolutionary model.

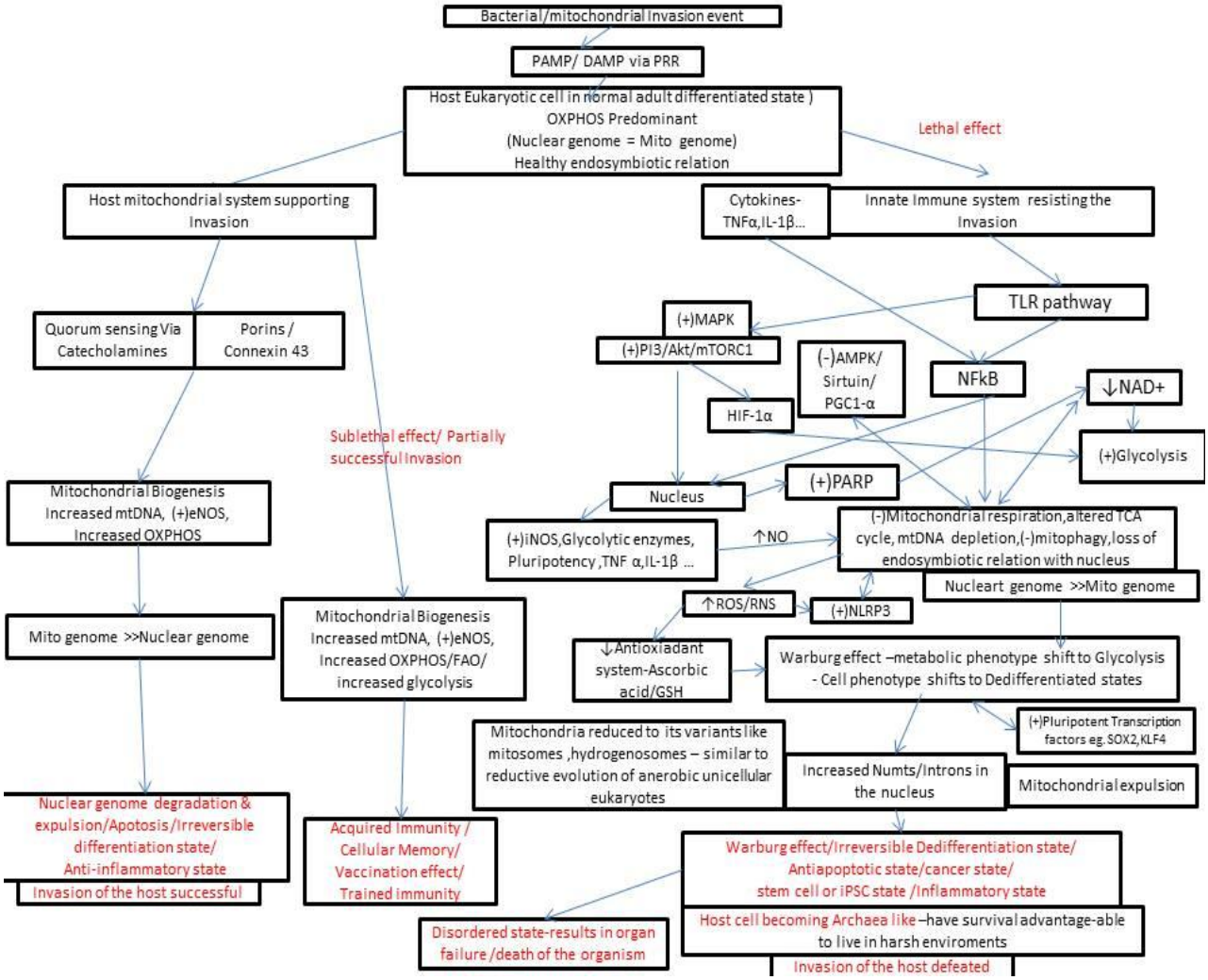

Figure 1 . Warburg common pathogenesis evolutionary model: Bacterial/Mitochondrial invasion event of the eukaryotic host cell (which is in normal adult differentiated state /predominant OXPHOS metabolism/healthy endosymbiotic relation) via PAMP/DAMP and PRR may trigger 3 major outcomes. The invasion event may be supported by the mitochondrial system of the host cell and resisted by the innate immune system of the host cell .A)Ist outcome, Increased catecholamines during the sepsis may act similar to bacterial quorum sensing through alpha1 receptors initially and beta2 receptor during late phase results in mitochondrial biogenesis via eNOS .Bacterial and mitochondrial porins,connexin 43(CX 43) may play a role in supporting the invasion. Increased mitochondrial genome and OXPHOS shifts the cell to irreversible differentiation state. In this state mitochondrial genome overpowers nuclear genome, this degrades nuclear genome and expels it, i.e it produces apoptosis.And this state is anti-inflammatory and as the invasion of the host is successful the system is now prone for further bacterial/mitochondrial invasion. B)Second outcome is due to partially successful bacterial/mitochondrial invasion which results in increased mitochondrial biogenesis and increased OXPHOS but as the invasion is only partially successful glycolysis may also be increased.This state can be seen as a hybrid of 1st and 3rd outcome –cell has increased both

OXPHOS &glycolysis and the cell phenotype may have features of both differentiated and dedifferentiated features.This state may form the basis of cellular memory/Acquired Immunity/Vaccination effect. This state may produce stable structure and future invasions will produce amplified response. C) 3rd outcome, due to high resistance by the innate immune system and via TLR4 pathway NFkB is activated. Proinflammatory Cytokines also produce similar effect. MAPK and PI3K/AKT /mTORC may also be activated.NFkB in the nucleus may induce the genes responsible for iNOS,glycolytic enzymes and pluripotency. NFkB may negatively regulate mitochondrial genome. High level of NO due to iNOS irreversibly inhibits the mitochondrial respiration , decreases mtDNA and leads to the loss of endosymbiotic relation. Also it increases Reactive oxygen/Nitrogen species .mTOR activation stabilize HIF1 alpha and activate glycolytic enzymes. AMPK/Sirtuin /PGC1 alpha -mitochondrial biogenesis pathway is inhibited in sepsis. Activation of PARP and inhibition of mitochondrial respiration results in decreased NAD+ , this inturn activates glycolysis.Increased Reactive species will activate NLRP3 inflammasome, which leads to caspase 1 activation and IL 1beta release.All these will produce Warburg effect – cells metabolic phenotype switches to glycolysis and cellular phenotype switches to irreversible dedifferentiation states.This state gives survival advantage as the cells became Archaea like.For more details please see the text.

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Figure 2: Understanding Vascular dysfunction in septic shock using this model.

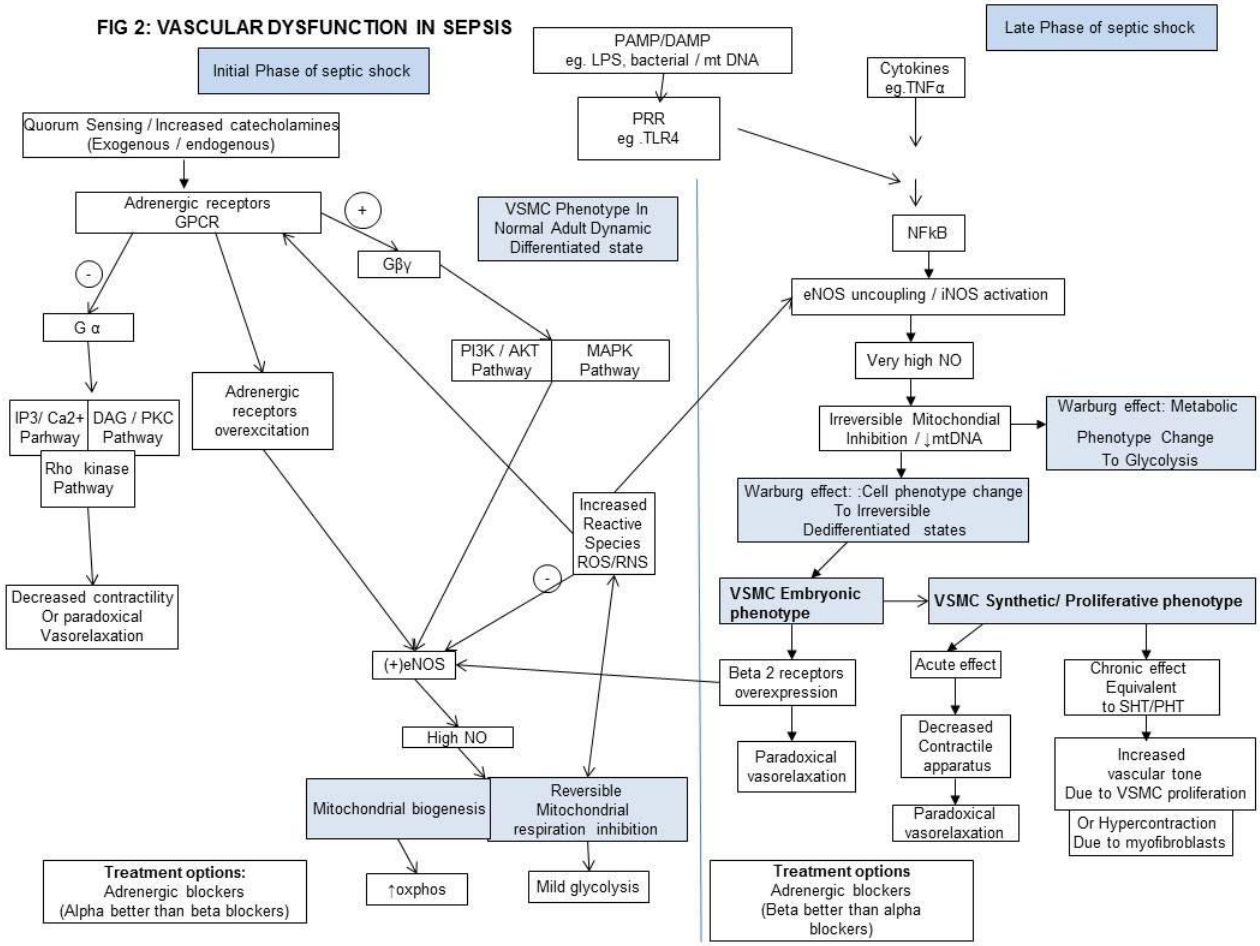

Figure 2: Vascular Dysfunction in Sepsis: Normally alpha adrenergic receptors (ARs)are the predominant ARs in the adult differentiated vascular smooth muscle cells(VSMC). Increased catecholamines in sepsis leads to hyperactivation of adreneric receptors(ARs) which are G protein coupled receptors (GPCRs) resulting in activation of G beta gamma subunit (G βγ)pathway, and inhibition of G alpha subunit (Gα) pathway leading to decreased contractility or paradoxical vasorelaxation by inhibition of - IP3/Calcium, DAG /PKC,Rho kinase pathways. Activation of G βγ pathway through mitogen activated protein kinase(MAPK) and phosphatidylinositol 3 Kinase (PI3K) / Akt pathway lead to hyperactivation of eNOS which results in increased NO and reversible inhibition of mitochondrial respiration and reactive speacies production. Increased eNOS will lead to mitochondrial biogenesis and increased OXPHOS. NO may act on alpha ARs and inhibiting the Gα pathway further.Reactive species may affect eNOS leading to eNOS uncoupling and the same pathways may now activate iNOS. PAMP/DAMP eg. lipopolysacchride (LPS),Bacterial/mtDNA via PRR eg.TLR4 and Cytokines activate NFkB .This inturn activate iNOS and glycolytic enzyme genes in the nucleus. High NO irreversibly inhibits mitochondrial respiration at cytochrome C Oxidase and

decreases the mitochondrial genome(For more details please see figure 1). This triggers the metabolic phenotype change to glycolysis and cell phenotype change to-irreversible dedifferentiation states – initially to VSMC embryonic phenotype and then to VSMC synthetic / proliferative phenotype. In the late phase of sepsis Beta ARs may be overexpressed and they are the predominant ARs in these states resulting in paradoxical vasorelaxation response to catecholamines.For more details please see the text.