Review Article

Fundamental Role of Warburg Effect in Various Pathophysiological Processes

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Abstract

In this review article, the role of Warburg effect in various pathologies is discussed using septic shock as the base model. I had proposed a slightly extended Warburg effect which I would like to call it as "Warburg common pathogenesis model or Warburg differentiation–dedifferentiation effect," which has the potential to explain septic shock and sepsis-associated multiorgan dysfunction and many other major pathologies such as systemic hypertension, pulmonary arterial hypertension, congestive heart failure, diabetes mellitus, asthma, acute respiratory distress syndrome, and acute kidney injury, implying that most of the diseases may have a common pathogenesis as the underlying mechanism. Increased nitric oxide (NO) in sepsis via inducible nitric oxide synthase (iNOS) or any respiratory poison, in general, irreversibly inhibits the mitochondrial respiration and shifts the metabolic phenotype of the cell from oxidative phosphorylation to glycolytic phenotype, and the change in metabolic phenotype is followed by the change in cell phenotype from the normal adult dynamic differentiation state to irreversible dedifferentiation states – embryonic phenotype, synthetic/proliferative phenotype, and cancer phenotype. This dedifferentiated state switching can be seen as the cells' local survival strategy in response to injuries, 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. Treatment in most of the pathologies should aim at reversing Warburg effect by the 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 are used here as differentiation therapy. Adrenergic blockers and ascorbic acid may be the main treatment options, which are already used by some research groups. Even though high NO via iNOS was involved in most of the pathologies including sepsis, any substance that inhibits or uncouples the mitochondrial respiration can initiate this Warburg effect and irreversible dedifferentiation. A mild and reversible Warburg differentiation–dedifferentiation effect may be necessary for normal functioning, and the same effect in exaggerated and irreversible way leading to irreversible dedifferentiation states may be the underlying mechanism in most of the diseases including septic shock.

Keywords: Adrenergic blockers, ascorbic acid, dedifferentiation, differentiation therapy, glycolysis, septic shock, Warburg effect

Received: 29th November, 2017; ***Revised:*** 02nd January, 2018; ***Accepted:*** 07th February, 2018

Introduction

This review article tries to show the fundamental role played by Warburg effect in most of the pathologies. Warburg common pathogenesis model is proposed to show the common underlying mechanism in most of the pathologies and septic shock was used as the base model.

Sepsis is the harmful systemic response of the host to the infection.[1] According to Thomas, the host's response to pathogen is more detrimental than the pathogen itself.[2] Septic shock and severe sepsis-associated multiorgan dysfunction carry high mortality rate of ~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, and hence, many reviews are available.[5,6] Irrespective of advances in this field, exact underlying mechanism behind septic shock is still a mystery. Postmortem studies could not find the underlying cause in most of the cases; surprisingly, most of the organs looked

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Quick Response Code:

Website: www.ijcep.org

DOI: 10.4103/ijcep.ijcep_55_17

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How to cite this article: Natesan V. Fundamental role of Warburg effect in various pathophysiological processes. Int J Clin Exp Physiol 2018;5:3-21.

normal.[7] Lot of treatment options which were successful in animal models were failed to show benefits in human studies, ranging from nitric oxide synthase (NOS) inhibitors, cyclooxygenase (COX) inhibitors, endotoxin-neutralizing proteins, tumor-necrosis-factor (TNF) alpha antagonists, etc.[3] Some of the recent-promising directions include counterintuitive use of antihypertensive in septic shock. Alpha 2 adrenergic receptor (AR) agonists – clonidine,[8-10] beta blockers[11,12] – were used to reduce the sympathetic hyperactivation and hypermetabolism associated with sepsis. Alpha 2 AR antagonist also has been shown to improve survival in sepsis animal model.[13] Vitamin C has also been used in sepsis,[14] glycolysis inhibitor shikonin,[15] cytochrome C,[16] and caffeine.[17]

Warburg common pathogenesis model has been proposed in this review article to explain the role of Warburg effect in most of the pathologies using septic shock as the base model. The model was built by slightly extending the "Warburg effect," an extensively researched area in cancer biology, proposed by Otto Warburg in the 1920s.[18,19] Warburg common pathogenesis model which isdiscussed in the following section not only explains septic shock and multiorgan dysfunction associated with severe sepsis but also explains most of the major medical problems such as systemic hypertension (SHT), pulmonary arterial hypertension (PAH), congestive heart failure (CHF), asthma, acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI). Cancer is not discussed here as Warburg effect is an extensively researched topic in cancer field.[20] Most of the supporting evidence was already done in the respective subfields, and this review article tries to show by putting the Warburg common pathogenesis model that there may be a common underlying mechanism in most of the pathologies. Furthermore, the same model in a mild and reversible way may be necessary for normal functioning.

The Hypothesis: Warburg Common Pathogenesis Model or Warburg Differentiation–Dedifferentiation Effect

In 1926, Warburg showed tumors relied on aerobic glycolysis metabolism.[18] He extended the thoughts in his 1956 paper and showed that the cancer cells originate in two phases: (1) irreversible inhibition of cell respiration – oxidative phosphorylation (OXPHOS) by agents such as hydrogen sulfide and arsenious acid which he called respiratory poisons and this necessitates the cell to change to aerobic glycolysis metabolism for survival and proliferation and (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 two terminal states, which he called sleeping cancer cell states.[19] Warburg effect is an extensively researched area in cancer biology; many excellent reviews are available.[20]

Essentially, Warburg told everything what is required for understanding septic shock 90 years back. A slightly extended Warburg effect proposed in this review article [Figure 1] named as "Warburg common pathogenesis model or Warburg differentiation–dedifferentiation effect" may explain most of the pathologies including septic shock. All the injuries to the cell can be divided into two types: (1) injuries that increase OXPHOS, e.g., inappropriate high-energy food intake seen today in modern civilization, and (2) injuries that increase aerobic/anaerobic glycolysis, e.g., sepsis [Figure 1].

Injuries such as increased nitric oxide (NO) in sepsis inhibit the mitochondrial respiration by inhibiting cytochrome C oxidase enzyme in the electron transport chain, and based on the concentration of NO, the inhibition can be reversible or irreversible.[21-23] This switches the cells metabolic phenotype from OXPHOS to aerobic glycolysis;[21] anaerobic glycolysis also included here as the endpoints may be the same.[20] Irreversible mitochondrial respiration inhibition by highly increased NO via inducible NOS (iNOS) is pathological, whereas reversible inhibition by mildly increased NO via endothelial NOS (eNOS) is physiological. In septic shock and most of the pathologies, these injuries lead to irreversible inhibition of cytochrome C oxidase and thus inhibition of mitochondrial respiration which triggers the metabolic phenotype change from OXPHOS to glycolysis. This metabolic phenotype change will be followed by switching of the cell phenotype from normal adult dynamic-differentiated state to irreversible dedifferentiation states – embryonic phenotype, synthetic/proliferative phenotype, and cancer phenotype. Injuries that increase OXPHOS lead to irreversible-differentiated state, where the cells have two options to proceed further: (1) first path leads to apoptosis, which may be due to increased cytochrome C release, and (2) the second path which may lead to the inhibition of mitochondrial respiration and switching to glycolytic phenotype/irreversible dedifferentiation phenotype for survival.

When 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 adenosine triphosphate (ATP) moves 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.[21] It has been already shown that mitochondrial membrane depolarization leads to cytochrome C release and apoptosis,[24] mitochondrial hyperpolarization is related to cancer state,[25] and the mitochondrial membrane hyperpolarization may inhibit the release of cytochrome C. This along with hypoxia-inducible factor 1 alpha (HIF1 alpha) stabilization due to mitochondrial inhibition by NO may lead to antiapoptosis and survival.[21,26]

But why the cells have to switch to the irreversible dedifferentiation, because this may be the local survival

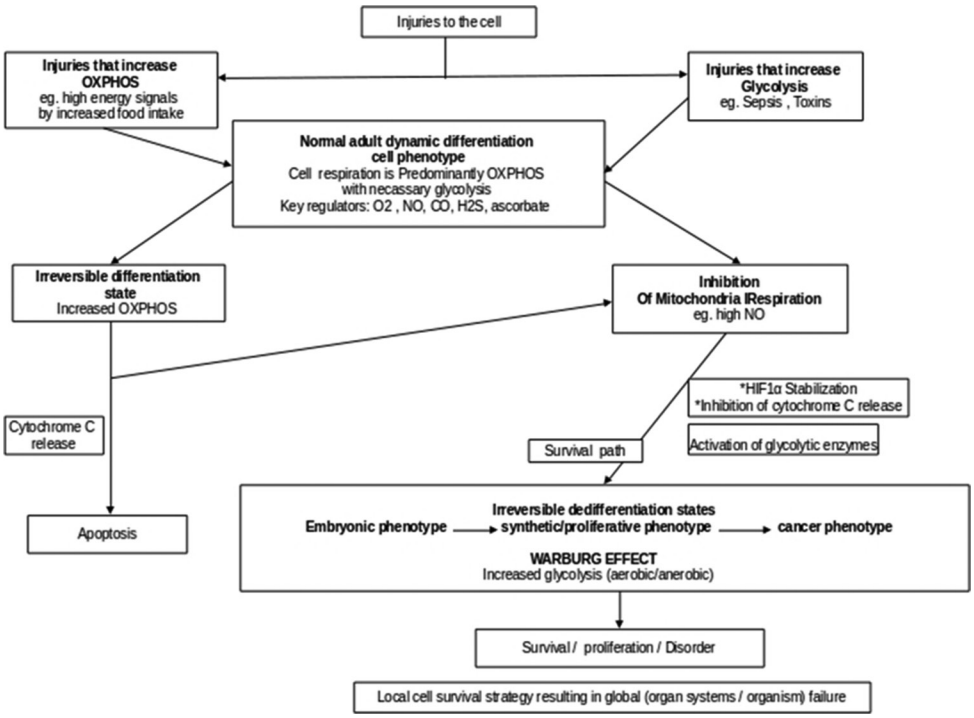

Figure 1: Warburg common pathogenesis model or Warburg differentiation–dedifferentiation effect: Injuries to the cells can be of two types, injuries that increase glycolysis and injuries that increase oxidative phosphorylation. Normally, the cells will be in adult dynamic differentiation state; some of the key factors that regulate this state are oxygen, ascorbate and low levels of nitric oxide, carbon monoxide, and hydrogen sulfide. Injuries that increase glycolysis such as sepsis lead to high nitric oxide, which irreversibly inhibits the mitochondrial respiration and shifts the cells metabolic phenotype from oxidative phosphorylation to glycolytic, and this is followed by change in cell phenotype leading to irreversible dedifferentiation states; these shifts may involve hypoxia-inducible factor 1α stabilization, activation of glycolytic enzymes, and inhibition of cytochrome C release. This shift leads to proliferation of the cells and survival, but it also leads to disorder and global collapse of the organ systems/organism which requires order. The other injury which leads to increase in oxidative phosphorylation have two ways to proceed, one way ends in apoptosis may be due to increased cytochrome C release and the second way leads to survival, which proceeds in same way as discussed for glycolytic injury

strategy of the cells under the circumstances of injury. These primitive irreversible-dedifferentiated states may have survival advantage over the differentiated states. What happens in pathologies such as sepsis is this local survival strategy of the cells to return to their primitive-dedifferentiated states results in global order collapse in organ systems and organism. For the organ systems to function properly needs ordered state in terms of differentiation.

Even though, in normal state, the cell is in adult dynamic differentiation state with predominant OXPHOS, there are exceptions to it, where some cells in some organ systems may already be in mild Warburg dedifferentiation state with increased glycolysis to survive in the harsh environment they live, and it may be necessary for its normal function, e.g., podocytes in renal system.[27]

The same Warburg common pathogenesis model in a mild and reversible way may be necessary for managing day-to-day minor injuries and for managing other normal functions. If a minor injury happens, the cells switch from its normal adult dynamic-differentiated state to reversible Warburg-dedifferentiated state, and after responding to the injury by surviving and proliferation, the cells return to their normal adult dynamic-differentiated state. This kind of approach has been already shown, for example, in renal system.[28] Considering the potential role played by the mild and reversible Warburg common pathogenesis model in normal functioning, it would be more appropriate to call it as "Warburg differentiation–dedifferentiation effect."

What happens in sepsis and in major medical problems such as SHT, PAH, CHF, DM, AKI, asthma, and ARDS is the cells in the specific organ system that may exhibit Warburg effect with the metabolic phenotype shift to glycolytic phenotype and cellular phenotype shift to irreversible-dedifferentiated states. Irreversible term is used here in the sense that it is very difficult to return to normal adult dynamic-differentiated state. In short, Warburg differentiation–dedifferentiation effect in a mild and reversible way is necessary for normal functioning, and exaggerated irreversible way leads to various pathologies.

Warburg Common Pathogenesis Model in Sepsis

In sepsis, lipopolysaccharide (LPS) acting through toll-like receptor 4 (TLR4) activates nuclear factor kappa B (NFkB),[1] leading to activation of iNOS and increased NO.[29] Through TLR4, LPS also leads to the production of cytokines.[1,30] Cytokines in turn again act on NFkB to activate iNOS, thus

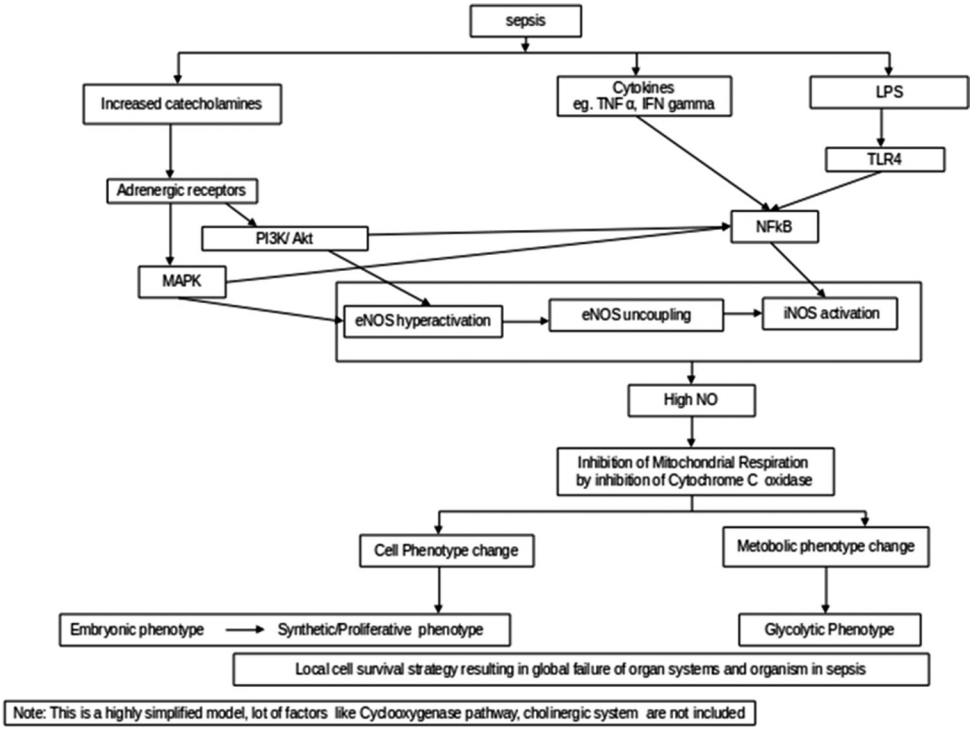

Figure 2: Warburg common pathogenesis model or Warburg differentiation–dedifferentiation effect in sepsis: In sepsis, increased catecholamines through adrenergic hyperactivation may lead to initial endothelial nitric oxide synthase hyperactivation and this leads to endothelial nitric oxide synthase uncoupling and inducible nitric oxide synthase activation. Toxins such as lipopolysaccharide through toll-like receptor 4 and cytokines such as tumor necrosis factor alpha and interferon gamma lead through nuclear factor kappaB to inducible nitric oxide synthase activation. Mitogen activated protein kinases and phosphatidylinositide 3 kinase/Akt pathways may be involved. The increased nitric oxide may irreversibly inhibit the cytochrome C oxidase and thus irreversibly inhibits the mitochondrial respiration; this leads to the metabolic phenotype change from oxidative phosphorylation to glycolysis and cell phenotype change from normal adult dynamic-differentiated state to irreversible-dedifferentiated states – Embryonic phenotype and synthetic/proliferative phenotype. This local cell survival strategy leads to global failure in organ systems and organism

amplifying the NO production.[31,32] These pathways may involve mitogen-activated protein kinase (MAPK) and calcium-independent protein kinase C (PKC) isoforms.[29] It is well known that the catecholamines in the plasma were increased in sepsis.[33,34] Even though other factors such as renin angiotensin aldosterone system (RAAS)[35] and COX pathway[36] are also involved and their activity is increased in sepsis, I focus here only on sympathetic hyperactivation [Figure 2].

In spite of increased catecholamine level is sepsis; it seems odd to give exogenous catecholamines such as norepinephrine for the treatment in septic shock. Many had already pointed out that catecholamine treatment carries risk in treating shock.[33,37] In fact, adrenergic blockers are already used long time back in shock states in animals and in patients.[11,12,33,38,39] We see more about this aspect in vascular dysfunction section.

It is already known that the alpha 1, beta 2 AR activation can lead to eNOS activation and NO production; this pathway involves Akt.[40-42] Norepinephrine has been shown to enhance cytokine-induced in iNOS; this pathway involves alpha and beta ARs and MAPK.[43] From the above evidence, one can see usually ARs activation at basal level may lead to mild eNOS activation and this pathway seems to involve PI3K/Akt and MAPK.

AR hyperactivation during sepsis due to increased catecholamines may cause hyperactivation of eNOS; this has been shown already in relation to the early hypotension seen in the biphasic vascular response in sepsis.[44,45] Adrenergic hyperactivation and cytokines such as TNF alpha, interferon gamma, and toxins in sepsis – LPS, all acting through PI3K/Akt/mTOR and MAPK, may lead to eNOS hyperactivation initially and ends up in eNOS uncoupling and iNOS activation, and the late hypotension seen in the biphasic response in sepsis was already shown to be related to iNOS activation.[44,45]

NO role in septic shock is an extensively researched area.[46,47] Early hypotension and late hypotension have been already shown in sepsis; initial phase is considered to be due to increased eNOS activity and late hypotension is considered to be due to iNOS action.[44,45] Inhibition of iNOS has been tried as a treatment option for shock even though NOS inhibitors were successful in animal studies; TRIUMPH trial conducted using nonspecific NOS inhibitor tilarginine in cardiogenic shock in humans did not show beneficial effect; further, it showed that it may be harmful.[48] Many thought that the reason for failure may be due to the nonspecific inhibition of NOS and selective iNOS inhibition with eNOS restoration may be beneficial.[49,50]

As discussed in the previous section, very high NO concentration in sepsis leads to irreversible inhibition of the mitochondrial respiration which has been known already.[21,22,51,52] This may lead to HIF1 alpha stabilization and activation of glycolytic enzymes.[21,53] It is known already that the aerobic glycolysis leads to the formation of glycolytic ATP, which moves from the cytosol to mitochondrial matrix and makes the ATP synthase to work in reverse mode and hydrolyze the glycolytic ATP and pumps the protons from matrix to inner mitochondrial membrane, leading to mitochondrial hyperpolarization.[21] Mitochondrial depolarization has been shown to lead to cytochrome C release and thus initiates apoptosis.[24] Mitochondrial hyperpolarization has been related to cancer[25] and may be through inhibiting the cytochrome C release, which along with HIF1 alpha stabilization leads to the inhibition of apoptosis.[21]

Fink had already shown the inhibition of mitochondrial respiration in sepsis and suggested that this may be the underlying cause of multiorgan dysfunction in sepsis.[22] Geng *et al*. showed that cytokine-induced NO inhibits mitochondrial respiration in vascular smooth muscle cell (VSMC).[54] Interestingly, treatments focused on activating the cytochrome C oxidase in animal models of sepsis have been already shown; cytochrome C that has been given exogenously to overcome the mitochondrial inhibition in sepsis animal model showed increased cytochrome C oxidase activity and improved the survival.[16] Caffeine treatment in the sepsis model also showed similar findings,[17] and the same team suggested that the mitochondrial respiration inhibition in sepsis can be seen as an adaptive response and suggested as similar to Fink that this mitochondrial dysfunction may be the underlying cause for multiorgan dysfunction in sepsis.[55,56]

Lactic acidosis in septic shock – The key

Lactic acidosis happens in septic shock is well known, and many thought that it could be used as a prognostic indicator.[57] Conventionally, lactic acidosis in septic shock and in other pathologies is thought to be due to hypoxia as a result of anaerobic metabolism. However, many showed that this may not be the case and pointed out that lactic acidosis in septic shock may be due to aerobic glycolysis.[23,58-61] Yang *et al*. showed using shikonin that the inhibition of aerobic glycolysis could be used as a treatment option for septic shock and linked the aerobic glycolysis to Warburg effect, but they focused only on the aerobic glycolysis aspect not on the cell phenotype changes.[15] Many works on using dichloroacetate (DCA) to treat the lactic acidosis in sepsis can be seen in this context.[61,62] It has already been shown that DCA can be used for reversal of Warburg effect in cancer.[63]

Endotoxin has already been shown to increase glycolysis in animal sepsis model, and adrenergic system that plays a role in it was shown by blocking it with alpha + beta-adrenergic blockers[64] and it was also shown to be reduced by ouabain.[65] ARs are already shown to be involved in glycolysis and lactate production and involve sodium-potassium ATPase.[39,58,66,67] Interestingly, Levy *et al*. showed that beta 2 ARs are involved in lactate production in shock and showed that beta blocker, ouabain reduced this,[58] and Luchette *et al*. used combined alpha + beta blocker to reduce the lactate in hemorrhagic shock.[39] In short, many studies in septic shock already showed NO inhibition of mitochondrial respiration, aerobic glycolysis, use of glycolytic blockers, adrenergic blockers, and cytochrome C oxidase activators.[8-12,15-17,21-23,68] The stage is already set. In spite of all these, a full application of Warburg effect including cell phenotype change to solve the septic shock mystery has not been done seems to be surprising.

In septic shock, the high NO via iNOS activation irreversibly inhibits mitochondrial respiration, which changes the metabolic phenotype from OXPHOS to glycolysis, and this may be followed by cell phenotype change from normal adult dynamic differentiation state to irreversible dedifferentiation states similar to cancer phenotype change in Warburg effect [Figure 2]. Irreversible dedifferentiation has at least two states – embryonic state and synthetic or proliferative state. These states are equivalent to the sleeping cancer states as mentioned by the great Warburg.[19]

Cell type change to embryonic-dedifferentiated state may express fetal or neonatal state properties. For example, vascular smooth muscles (VSMs), have beta 2 ARs as their predominant receptors in the fetal pulmonary and aortic VSM. And alpha 1 ARs, which were low in fetal state compared to the adult pulmonary and aortic VSM, tend to increase during the developmental maturation.[69]

Cell type change to synthetic/proliferative-dedifferentiated state is associated with the proliferation of cells with loss of contractile apparatus;, for example, VSMC phenotype changes have been shown long back, and the change from contractile to synthetic/proliferative phenotype leads to loss of contractile apparatus, and it has already been suggested that these changes may be the underlying cause in various vascular pathologies.[70] VSMC proliferation/dedifferentiation has already been related to various pathologies and this change has been related to Warburg effect.[71]

These changes to irreversible dedifferentiation state may be accompanied by changes in the ion channels, with many types of ion channels; it seems to be difficult to identify which ion channels are changed or expressed in these states. However, there is a simple solution for it if we take the guide that the cancer cells have depolarized cell membrane potential.[72] All the changes in the ion channels during irreversible-dedifferentiated states in many pathologies such as septic shock tend to move toward the depolarized cell membrane potential. For example, L-type calcium channels in contractile VSMC have been shown to be lost on switching to synthetic/proliferative phenotype, and increased expression of transient receptor potential channels has been shown.[73,74] Spontaneously hypertensive rat model VSMC synthetic type was already shown to be more depolarized when compared to

the normal wild-type counterpart, and the depolarized state of the cell has been related to proliferation.[75]

During Injury, All the Cells in an Organ System Move toward a Common Cell Type Which Has Better Survival Advantage

In most pathology, each organ system-specific cell types may tend to move toward one dedifferentiated cell phenotype that has the better survival advantage and proliferation. For example, in septic shock, all the cells in the vascular system – vascular endothelial cells, VSMCs (contractile phenotype), and fibroblasts – all tend toward VSMC (synthetic/proliferative phenotype) [Figure 3]. This kind of phenotype change has been shown already in atherosclerosis[76-78] and asthma.[79] Vascular endothelial cells by endothelial to mesenchymal transition change to VSMC (synthetic/proliferative) phenotype. VSMC (contractile) by phenotype change switch over to its synthetic/proliferative type. And fibroblasts switch to myofibroblasts which have the features similar to VSMC (synthetic/proliferative) phenotype but are hypercontractile [Figure 3]. In spirit of aerobic glycolysis/proliferation happening in these states, I call these states as Warburg irreversible dedifferentiation states.[71,80]

Ascorbic Acid and Phenotype Change

However, what triggers this cell phenotype change apart from the glycolysis shift? One possibility is that the decreased ascorbate level in the body has the potential to induce phenotype change [Figure 4]. Cameron *et al*. thought that endothelial dysfunction and the problem in extracellular matrix (ECM) production by ascorbic acid may lead to cancer.[81] It is well known that ascorbate is one of the key substrates used to activate cytochrome C oxidase[54] which has to be seen in this context, and ascorbate deficiency may lead to respiratory dysfunction which has been suggested long back.[81] As seen earlier, increased NO in sepsis inhibits mitochondrial respiration and triggers glycolytic phenotype change. Ascorbic acid level has been shown to be decreased in sepsis.[82] Ascorbate level may be decreased due to increased scavenging that might have occurred in these conditions. Ascorbic acid is essential for ECM production. Serum heparan sulfate level has been shown to be elevated in sepsis.[83] Serum hyaluronan and syndecan were also shown to be decreased in sepsis.[84] Nelson *et al*. showed increased glycosaminoglycans (GAGs) in septic shock.[85] All this evidence shows endothelial glycocalyx degradation and endothelial dysfunction in sepsis. Ascorbic acid role in the synthesis of GAG has been shown long back.[81] It has been already shown that the removal of heparan sulfate from the cell surface may trigger phenotype change in vascular smooth muscle.[70] Increased degrees of movement of a cell may trigger cancer phenotype change.[86] On the whole, decreased ascorbate may lead to failure in the regulation of mitochondrial respiration activation, decreased ECM regulation, and endothelial dysfunction, which may increase the degree of movement of the cells and trigger phenotype change.[81]

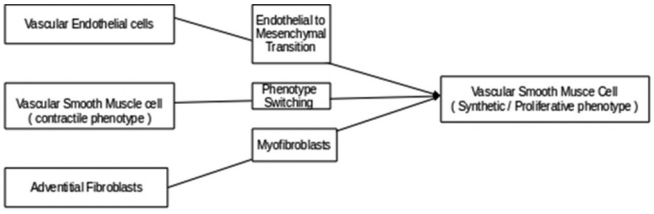

Figure 3: Phenotype change in vascular system during septic shock: In septic shock all the cells in the vascular system –vascular endothelial cells, vascular smooth muscle cells (VSMCs) (contractile phenotype), adventitial fibroblasts – tend to move toward vascular smooth muscle cells (synthetic/proliferative phenotype). The same phenomena may occur in other organ systems also in the septic shock where different cell types of the specific organ system may tend to move toward one dedifferentiated cell phenotype for that specific system that has the better survival advantage and proliferation

Explaining Vascular Dysfunction in Septic Shock using Warburg Common Pathogenesis Model

Normally, catecholmines act on ARs in VSMC, which are G protein-coupled receptors, and this in turn leads to G alpha subunit activation of the following three pathways to cause vasocontraction: (1) inositol triphosphate (IP3)/calcium

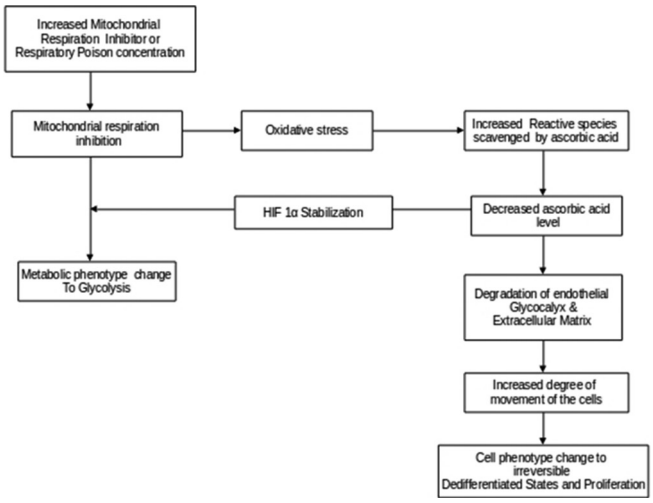

Figure 4: Ascorbic acid and phenotype change: Increased nitric oxide in sepsis or any respiratory poison in general may inhibit mitochondrial respiration and lead to increased reactive species. Ascorbate level may be decreased due to increased scavenging. Decreased ascorbic acid level may lead to stabilization of hypoxia-inducible factor 1 alpha and this in turn may activate glycolytic enzymes and lead to glycolysis. Decreased ascorbic acid level may lead to degradation of endothelial glycocalyx and extracellular matrix. All these changes in endothelium and extracellular matrix may lead to increased degrees of movement of the cells, which may trigger the phenotype change to irreversible dedifferentiation states (Warburg effect). Thus normal ascorbic acid level may be essential for the regulation of normal adult dynamic differentiation state of the cells

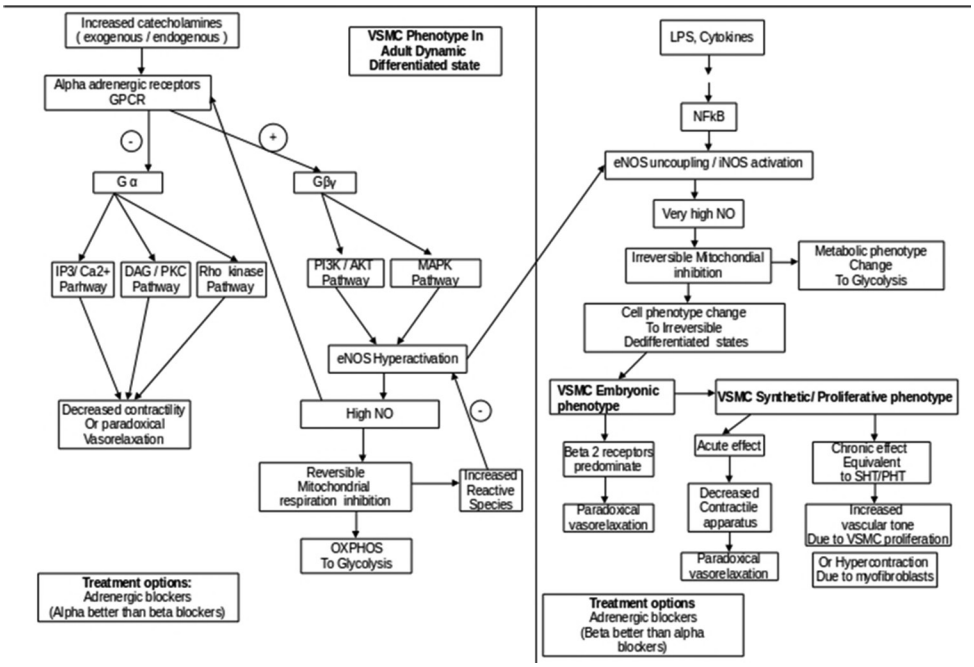

Figure 5: Vascular dysfunction in sepsis: Increased catecholamines in sepsis leads to hyperactivation of adrenergic receptors which are G protein coupled receptors resulting in activation of G beta gamma subunit pathway, and inhibition of G alpha subunit pathway leading to decreased contractility or paradoxical vasorelaxation by inhibition of – inositol triphosphate/calcium, diacylglycerol/protein kinase C, Rho kinase pathways. Activation of G beta gamma subunit pathway through mitogen activated protein kinase and phosphatidylinositide 3 kinase/Akt pathway lead to hyperactivation of endothelial nitric oxide synthase which results in increased nitric oxide and reversible inhibition of mitochondrial respiration and reactive species production, nitric oxide may act on alpha adrenergic receptors and inhibiting the G alpha subunit pathway further. Reactive species may affect endothelial nitric oxide synthase leading to endothelial nitric oxide synthase uncoupling and the same pathways now activate inducible nitric oxide synthase. Normally, alpha adrenergic receptors are the predominant adrenergic receptors in the adult vascular smooth muscle cells. Cytokines and lipopolysaccharide through nuclear factor kappaB also activate inducible nitric oxide synthase resulting in high nitric oxide production and this irreversibly inhibits mitochondrial respiration at cytochrome C oxidase. This triggers the metabolic phenotype change to glycolysis and cell phenotype change to irreversible dedifferentiation states – initially to vascular smooth muscle cell embryonic phenotype and then to vascular smooth muscle cell synthetic/proliferative phenotype. Beta adrenergic receptors may be the predominant adrenergic receptors in these states resulting in paradoxical vasorelaxation response to catecholamines

pathway leads to increase in intracellular calcium level and activate myosin light chain kinase to phosphorylate myosin light chain to produce vasocontraction; (2) diacylglycerol (DAG)–PKC; and (3) RhoA/Rho kinase (RhoA/Rhok) pathway, both these pathways inhibit myosin light chain phosphatase and produce vasocontraction.[5,87] As we had seen earlier, septic shock-induced hypotension is refractory to vasopressor agents including the first-choice drug norepinephrine.[5] As discussed earlier, biphasic hypotension has been shown in sepsis – early hypotension is considered to be due to increased eNOS activity and late hypotension is to considered to be due to iNOS action.[44,45] Some of the possibilities already explored in understanding the vascular hyporeactivity in sepsis include NO-induced alteration in alpha 1 ARs by peroxynitrite,[88] inhibition of RhoA/Rhok,[44] involvement of PKC, MAPK seems to be activated in shock, AR desensitization, COX2 activation, etc., are reviewed by many.[5,6] Many treatment options which were successful in septic shock animal models failed in human studies. Failure of nonspecific NOS inhibitors in septic shock and activated protein C are few examples [Figure 5].[3]

It has been already shown that AR activation through G beta-gamma subunit activates PI3K/Akt and MAPK pathways that may involve calcium-independent PKC isoforms[43,89-92] and finally may hyperactivate eNOS.[40] It is interesting in this aspect to see beta 2 receptors action which normally by Gs alpha subunit leads to protein kinase A (PKA) activity and has been shown by Daaka *et al*. to phosphorylate the beta receptor and switch over to its activity through G beta-gamma subunit pathway to MAPK.[93] Furthermore, adrenergic activation of glycolysis is well known.[58,66,67] Overall, the AR-activated G subunit beta-gamma-mediated pathway through PI3K/Akt and MAPK leads to eNOS activation and glycolysis but mildly under normal activation. During adrenergic hyperactivation, this pathway may lead to hyperactivation of eNOS and increased glycolysis as shown above. The increased NO inhibits the mitochondrial respiration reversibly and leads to increased reactive species, and the reactive species may oxidize the tetrahydrobiopterin (BH4), resulting in eNOS uncoupling.[94,95]

From the above evidence, we can see that the adrenergic pathway hyperactivation along with cytokine and LPS activates iNOS leading to very high NO. Usually, a very high NO occurs through iNOS as in sepsis; however, in some cases

such as anaphylaxis, it may happen through eNOS itself.[96] What matters is the high NO level, it does not matter which way it comes through as rightly pointed out by Lowenstein and Michel[97] High NO in sepsis due to iNOS activation,[5] as shown above, inhibits the mitochondrial respiration irreversibly.[21,22,51,52]

With this background, we can see that the Warburg common pathogenesis model may be the underlying mechanism behind the septic shock. The high NO level in sepsis irreversibly inhibits the mitochondrial respiration in VSMC and shifts the cell to change its metabolic phenotype from OXPHOS to glycolysis, and this in turn may be followed by a change in cell phenotype from the normal adult dynamic-differentiated state to irreversible dedifferentiation states initially to VSMC embryonic state and later to VSMC synthetic/proliferative state [Figure 5]. In addition, all the key cells in the vascular system tend to move toward the VSMC synthetic/proliferative phenotype which may have better survival advantage [Figure 3]. Decreased ascorbate level in sepsis may play a key role in this phenotype change [Figure 5].

There may be at least two stages in this septic shock progression [Figure 5]. (a) The initial state occurs when the cell phenotype is in its normal adult dynamic-differentiated state. Adrenergic hyperactivation through G beta-gamma subunit activated pathways as seen earlier leads to eNOS hyperactivation and finally ends in eNOS uncoupling. As already shown by many increased NO leads to the inhibition of IP3/calcium pathway, DAG calcium-dependent PKC isoform pathway, and RhoA/Rhok pathway, it is interesting to see that all of these are G alpha subunit-mediated pathways. The net result is that exogenous or endogenous catecholamines may cause (1) decreased vasoconstriction due to inhibition of IP3/calcium pathway or (2) paradoxical vasorelaxation due to inhibition of PKC and RhoA/RhoK pathway. (b). As shown earlier adrenergic hyperactivation may act through G beta-gamma subunit and activates PI3K/Akt and MAPK pathways, this may involve calcium-independent PKC isoforms,[43,89-92] and all this finally leads to eNOS hyperactivation,[40] then eNOS uncoupling,[94,95] and iNOS activation.[44,45] iNOS activation also occurs through cytokines and LPS as shown earlier.[43,44] eNOS uncoupling and iNOS activation will lead to very high NO level and this as seen earlier irreversibly inhibits the mitochondrial respiration at cytochrome C oxidase and shifts the cells metabolic phenotype from OXPHOS to glycolysis and followed by change in cell phenotype from its normal adult dynamic-differentiated state to irreversible-dedifferentiated states initially to embryonic state and then to synthetic/proliferative state.

Vascular smooth muscle cell embryonic-dedifferentiated state

When the VSMC is in this state, there may be a change in AR expression by VSMC and the cells may have beta 2 AR as the predominant receptors as it was in fetal state.[69]

Paradoxical vascular responses to norepinephrine and acetylcholine

Exogenous/endogenous catecholamines given when the VSMC are in embryonic state in septic shock may produce paradoxical vasorelaxation. It is interesting to see that noradrenaline induced vasorelaxation in neonatal arteries in this context[98] where VSMCs are expected to be in embryonic-dedifferentiated state expressing beta 2 AR as the predominant ARs. It is interesting to see that the norepinephrine induced vasodilation in the isolated coronary arterioles of heart failure patients in this context, where the VSMCs are expected to be in dedifferentiated state.[99] Further, at this point, the endothelial dysfunction might have happened as all the cells in the vascular system tend to move toward VSMC synthetic/proliferative type. In this state as the paradoxical response of norepinephrine, one can expect that acetylcholine may also produce paradoxical response of vasocontraction, instead of its usual vasodilation, which is indeed the case as shown in LPS model,[100] in atherosclerotic coronary artery,[101] and in PAH.[102] In addition, it has been shown that this paradoxical vasoconstriction by acetylcholine was associated with high mortality.[103]

Vascular smooth muscle cell synthetic/proliferative-dedifferentiated state

This state may 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. As shown earlier, VSMC contractile phenotype to VSMC synthetic/proliferative phenotype shows decreased contractile apparatus.[70] In this state, the vascular response to exogenous/endogenous catecholamines may produce paradoxical vasorelaxation [Figure 5]. In chronic phase, the vascular tone may be increased due to increased VSMC proliferation or hypercontractile due to the presence of myofibroblasts. This chronic phase may be seen as an equivalent to SHT and PAH, which will be explained later.

Treatment options for septic shock

Many of the treatment options mentioned below were already tried in sepsis but failed to understand the full significance of it. In this section, the focus will be only on adrenergic blockers. Other treatment options will be explored later including the key drug ascorbic acid. Treatments were proposed here as differentiation therapy. (1) In the first state, when the cells are in normal adult dynamic-differentiated state: As alpha 1 ARs are the predominant receptors in VSMC in adult state,[69] alpha 1 blockers such as prazosin may be a better choice than beta blockers, and combined alpha + beta blockers may work well. (2) When the cells are in irreversible-dedifferentiated states (embryonic and synthetic/proliferative state): As the cells were gone back to their primitive states, beta 2 ARs are the predominant receptors in VSMCs in this fetal state.[69] Beta blockers may be a better choice than alpha blockers at this stage. Again, combined alpha-beta blockers may work well. As discussed earlier, catecholamine treatment in

septic shock may do harm rather than saving the patient.[33,37] Adrenergic blockade in septic shock has been tried long back, where beta blocker was used.[38] Adrenergic blockers were used in hemorrhagic shock to reduce lactate level, where combined alpha and beta blocker reduced the lactate level.[39] It is interesting to see the use of prazosin in treating scorpion sting in this context.[104] Many recent advances in septic shock include the counterintuitive use of antihypertensive in septic shock.[9] Alpha 2 agonist clonidine has been shown to reduce the sympathetic hyperactivation in septic shock;[8,10] alpha 2 adrenergic blocker yohimbine has been used in sepsis model,[105] beta blocker esmolol has improved the cardiac dysfunction in sepsis model which can also be seen in this context.[106] Use of beta blockers in sepsis[12] is waiting for a systematic review.[107] Beta blockers and alpha blockers were used in different conditions to reduce the cell proliferation.[108-110] COX pathway activation and increased RAAS activity in sepsis also seem to work in the same way as adrenergic hyperactivation.[35,36] However, cholinergic pathway seems to work in a opposite way in sepsis. Cholinergic agonists increased the survival in experimental sepsis[111] and vagal nerve stimulation (VNS) prevented the shock in sepsis model.[112]

Explaining Multiorgan Dysfunction in Sepsis and Equivalent Key Diseases using Warburg Common Pathogenesis Model

Various other pathologies may also be explained using this Warburg common pathogenesis model by explaining the multiorgan dysfunction in sepsis. Most of the supporting evidence was already shown, and in some pathologies, it is already linked to Warburg effect, for example, in PAH.[113]

Systemic hypertension

It is well known that VSMC proliferation occurs in hypertension.[114,115] VSMC phenotypic switching has been known for long time[70] and shown to play a crucial role in various vascular pathologies.[116,117] It is surprising to see that Warburg effect was not used to explain SHT. Warburg common pathogenesis model may explain SHT. All the events which were mentioned for vascular dysfunction in sepsis except the triggering event seem to underlie in the evolution of SHT, and SHT may be equivalent to the chronic phase of irreversible-dedifferentiated state of VSMC seen in Figure 5. The triggering injury for SHT includes many possibilities such as stressful life leading to sympathetic hyperactivation and high-energy food intake. Nifedipine one of the main drugs used in the treatment of SHT has been shown to inhibit dedifferentiation of VSMC by inhibiting Akt.[118] All the antihypertensive drugs mode of function can be seen in this context as differentiation therapy including adrenergic blockers. Retinoic acid has been shown to inhibit VSMC proliferation.[119]

Pulmonary arterial hypertension

Surprisingly unlike SHT, the pathogenesis of PAH has been already linked to Warburg effect, including metabolic phenotype change, pulmonary artery SMC proliferation, HIF1 alpha activation, and hyperpolarized mitochondrial potential in pulmonary artery SMC in PAH.[113,120,121] All-trans-retinoic acid (ATRA) has been shown to be decreased in idiopathic PAH, and ATRA could be a potential therapy for this patients.[122] ATRA is used here as a differentiation therapy.

Atherosclerosis

Vascular proliferation and VSMC phenotype change to synthetic/proliferative type have been already explored in atherosclerosis.[76,117] Statins are one of the standard drugs used in this condition; if the atherosclerosis and septic shock have common underlying pathogeneses, then one can expect statins may also work in septic shock. Indeed, it has been already shown that the statins reduced the vascular hyporeactivity in animal sepsis model.[123,124]

Cardiac dysfunction in sepsis and congestive heart failure

Cardiac dysfunction in sepsis and CHF can be explained by Warburg common pathogenesis model [Figures 1 and 2]. Except the injuries that trigger the cardiac dysfunction in sepsis and CHF may be different, all the other events are same for both. Injuries that trigger the CHF are many, e.g. stressful life, sedentary lifestyle, and high-energy food intake. In both cases, the cardiomyocytes change their metabolic phenotype from OXPHOS to glycolytic state and this may be followed by a change in cell phenotype from the normal adult dynamic-differentiated state to the primitive irreversible-dedifferentiated states – embryonic state and synthetic/proliferative state, which results in decreased contractility and decreased cardiac output. Increased sympathetic activity has been shown in CHF.[125-127] Decreased eNOS and iNOS activation has been shown in heart failure.[128-130] Mitochondrial respiration has been modified in heart failure; OXPHOS is decreased with increase in glycolysis.[131] In addition, AR states were changed in CHF, whereas beta 1 ARs are decreased with increase in beta 2 ARs and increased G protein receptor kinase which lead to beta receptor uncoupling.[127,130,132,133] Myosin light and heavy chains are changed to their fetal isoform in CHF.[130] All these findings support the Warburg common pathogenesis model's role in CHF. Fetal cardiac development has been shown to be associated with glycolysis. Increased mitochondrial OXPHOS occurs during cardiac maturation to adult state and adult heart may switch to it fetal metabolic phenotype, i.e., glycolysis under the conditions of stress.[134] Adult cardiomyocytes during dedifferentiation express increased glucose transporter 1 (GLUT1) and decreased GLUT4 leading to insulin resistance,[135] and Akt plays a role in this insulin resistance.[136] It has been shown that the NO in cardiomyocytes induces HIF 1 alpha to produce vascular endothelial growth factor (VEGF) and angiogenesis involves PI3K/Akt pathway.[26] Levy *et al*. already showed glycolysis in septic animal model and suggested cytochrome C oxidase inhibition in this condition as an adaptive response and this may be the cause for other organ dysfunctions also in sepsis.[55,56] By activating cytochrome C

oxidase by caffeine and cytochrome C in animal sepsis model, the same team showed that this could be used as treatment in sepsis.[16,17]

Ion channel expression change during dedifferentiated state as mentioned before can be expected to happen in cardiomyocytes. It has been shown already that cultured cardiomyocytes on dedifferentiation express a nonselective cation channel.[137] Decreased L-type calcium channels in failing heart myocytes have been shown;[138] one can relate this to the decrease in L-type calcium channels in dedifferentiated VSMC as discussed above.[73,74] Late component of sodium current has been shown to be increased in failing heart; increased intracellular sodium as a result of this makes the sodium/calcium exchanger to work in reverse mode and results in increased intracellular calcium.[139] It has been shown that intracellular sodium was increased and this leads to increased calcium in cardiomyocytes in heart failure.[140,141]

Cardiac glycosides are used in the heart failure treatment shown to improve contractility by inhibiting the sodium potassium ATPase. However, it is difficult to see from the above evidence why the inhibition of the sodium potassium ATPase which leads to increase in intracellular sodium should work in heart failure, as the cells were already loaded with increased intracellular sodium and calcium. It looks as in heart failure; the sodium potassium ATPase may work in reverse mode leading to increased intracellular sodium and thereby increased intracellular calcium like other ion channels as mentioned above in this heart failure-dedifferentiated condition leading to depolarized membrane potential. Cardiac glycosides may work in heart failure by inhibiting this reverse mode sodium potassium ATPase. Ouabain has been shown to inhibit lactate, i.e., glycolysis.[65]

Adrenergic blockade is one of the treatment options in CHF and beta blockers are one of the key drugs used in CHF. Alpha 2 blocker yohimbine[105] and beta blocker esmolol[106] have been used to treat cardiac dysfunction in sepsis animal models.[12] Alpha 1 blocker prazosin, beta blocker propranolol, and MAPK inhibitor were used in reducing NO production by blocking the iNOS in cardiomyocytes, which was induced by norepinephrine with cytokine.[43] All the evidence supports the hypothesis that Warburg common pathogenesis model may underlie in CHF and sepsis-induced cardiac dysfunction. Moreover, most of the drugs already tried in CHF can be seen as differentiation therapy.

Hyperglycemia in sepsis and diabetes mellitus type 1 and 2

Warburg common pathogenesis model may be the underlying mechanism for hyperglycemia in sepsis and DM 1 and 2. Injury triggering the pathogenesis of these problems is many; for example, sepsis may cause hyperglycemia in septic shock, sepsis, or cytokines in DM1 and high-energy food intake and sedentary lifestyle in DM2. Talchai *et al*. showed that dedifferentiation of beta cells may be the cause for DM2 and treatment of diabetes should aim at redifferentition.[142] It has been already shown that sympathetic hyperactivation may play a role in insulin resistance.[136] In all these conditions, two key changes occur: (a) Dedifferentiation of beta cells in the pancreas leading to impaired insulin release, either no insulin release or decreased insulin release which depends on the level of beta cell dedifferentiation, and as seen earlier, dedifferentiation of beta cells has been already shown[142-146] and a recent article showed beta cell dedifferentiation in DM2 in humans.[147] (b) Dedifferentiation in the periphery, for example, in cardiomyocytes, changes in the GLUT expression where fetal type GLUT1 increased and GLUT4 decreased lead to insulin resistance are already shown.[135,136,148,149]

It has been shown already that DM1 and DM2 may have common underlying mechanism and differ only in the triggering factors and the time it happens[150] and this viewpoint was challenged by many.[151] Dedifferentiation of beta cells in the pathogenesis of DM2 may involve MAPK, NO, PI3K, NFkB,[136,142,145,151,152] and insulin resistance in the periphery due to dedifferentiation resulting in altered GLUT expression – increased GLUT1 and decreased GLUT4 – for example, in cardiomyocytes and adipocytes.[35,136,148,149] It has been already shown that retinoic acid is necessary for normal beta cell function,[153] which shows that maintenance of normal-differentiated state of beta cell is necessary for its normal function. Change in GLUT expression with increased GLUT1 and decreased GLUT4 has been shown animal models of sepsis.[154,155] Altered GLUT expression in sepsis models may imply the dedifferentiated state of the periphery, and the same dedifferentiated state can be expected to occur in pancreatic beta cells also in sepsis.

Insulin and insulin-like growth factors (IGFs) activate PI3K/Akt pathway leading to anabolic effects, cell growth, and survival. A high level of insulin can hyperactivate this pathway, leading to Warburg effect and cancer.[156] Insulin and thrombin are known to produce VSMC proliferation.[157] It is well known that IGF produces proliferation of SMC.[158-161] In this context, one can see that insulin and IGF may regulate the body as dedifferentiation factors. Hyperglycemia in sepsis is usually managed by insulin therapy.[4] However, the use of insulin has been shown in some studies to increase the mortality rate in sepsis.[4,162] Using the above evidence, insulin can be seen as dedifferentiating factor and using it for treating hyperglycemia may aggravate the already dedifferentiating process which seems to occur in sepsis. Ascorbic acid may be a better treatment option for all these three conditions – hyperglycemia in sepsis, DM1, and DM2 which are discussed more in the treatment section.

Renal dysfunction in sepsis, acute kidney injury, chronic kidney disease, polycystic kidney disease, and Fanconi's syndrome

Warburg common pathogenesis model may be the underlying mechanism in renal dysfunction in sepsis, AKI, and other renal dysfunctions such as Fanconi's syndrome. In all these conditions, irreversible dedifferentiation of the renal system

cells – glomerular endothelial cells, podocytes, mesangial cells, and tubular epithelial cells – may occur. Most of the related evidence for the hypothesis has been done already in renal dysfunction. Importance of dedifferentiation in renal dysfunction has been already showed by Bonventre and he showed that it may help in the regenerative process.[28] Mesangial cells and juxtaglomerular (JG) cells even in normal adult state appear to have synthetic/proliferative properties.[163-166] In this context, one sees the work done by Rinkevich *et al*. on regenerative capacity of renal system and they showed that regeneration may occur even in adult life.[167] Ozawa *et al*. already showed the importance of glycolysis in relation to podocyte foot process and they also showed that dedifferentiated podocytes are highly glycolytic 89% whereas differentiated podocytes are 50% glycolytic.[27]

May be renal system is already in a mild Warburg effect state with mild reversible dedifferentiation in at least few renal system cells such as podocytes, mesangial cells, and JG cells. Considering the harsh environment the kidney has to live, it seems logical to have this mild Warburg state. This is necessary for normal renal function, for example, even the differentiated podocytes have 50% glycolysis shown by Ozawa *et al*.[27] which supports this hypothesis. In pathological states of the renal system, it may go to the extreme irreversible dedifferentiation states. Urine lactate has been shown to be increased in Fanconi's syndrome.[168] Increased NO due to iNOS activation has been shown in animal model Fanconi's syndrome.[169] It has been already shown that in response to injury to renal system, the surviving cells dedifferentiate and repair the injury.[161] Renin activity has been already shown to be increased in sepsis;[35] this along with many other factors may contribute to the phenotype modulation.[166] In polycystic kidney disease (PKD), the cyst lining cell proliferation can be seen as dedifferentiation.[170] Rowe *et al*. showed that glycolysis has been increased in PKD and showed the treatment option by inhibition of glycolysis which decreased the proliferation in PKD.[171] Podocytes dedifferentiation leads to glomerular dysfunction and ends in chronic kidney disease (CKD); interestingly, retinoids were used as a treatment option to reduce the glomerular dysfunction and it was also used as a differentiation therapy in this condition.[172] Ascorbic acid as a differentiation therapy may work in renal dysfunctions.

Respiratory dysfunction in sepsis, acute respiratory distress syndrome, and asthma

Bronchial smooth muscle cells (BSMCs) live in highly toxic increased oxygen environment. BSMCs may be already in the embryonic-dedifferentiated state, i.e. mild Warburg dedifferentiation state, to overcome the problems of living in this hostile high oxygen environment. The proliferative properties of Clara cells in terminal and respiratory bronchioles[173] and type 2 alveolar cells[174] in the normal respiratory system can also be seen in this context and this supports the hypothesis that a mild Warburg dedifferentiation effect is necessary for normal respiratory function. As mentioned above in the vascular and cardiac dysfunction section, beta 2 ARs are the predominant ARs in the primitive fetal-dedifferentiated state;[69] in this context, one can see why catecholamines bronchodialate BSMC. This normal BSMC state is equivalent to the VSMC state in neonatal arteries, and as shown above, norepinephrine paradoxically produced vasorelaxation in neonatal arteries;[98] after seeing the Warburg dedifferentiation relation, one can see that there is no paradox at all in this response. Warburg common pathogenesis model may explain the respiratory dysfunction in sepsis, ARDS/acute lung injury (ALI), and asthma. BSMC changes their cell phenotype to irreversible-dedifferentiated – synthetic/proliferative state and change in glycolysis to a high level and the same thing may occur in other cells of the respiratory system. Most of the groundwork was already done. Keshari *et al*. in animal model of sepsis to mimic lung injury during sepsis showed regeneration in lungs with type 2 alveolar cells and myofibroblasts proliferation, epithelial to mesenchymal transition (EMT), and collagen production.[175] Activation of iNOS has been shown in ARDS/ALI.[176] Lactic acidosis has been shown already shown in asthma and thought to be due to beta-agonist therapy and increased sympathetic activity in asthma.[177] Lung lactate is usually not present in normal humans, but lung lactate level has been shown to be increased in sepsis/ARDS.[178,179] Fibroproliferation in ARDS has already been shown.[180] Alveolar cell EMT involvement in pulmonary fibrosis has been shown already.[181] Bronchial smooth muscle proliferation,[182-184] and its relation to phenotype change and dedifferentiation, EMT in asthma, has been reviewed brilliantly by Bara *et al*., and they showed its relation to remodeling process in asthma.[79] Methotrexate (MTX), a common antimetabolite anticancer drug, inhibited iNOS in cytokine-treated lung epithelial cells.[185] Even though not commonly used, MTX is one of the drug options for asthma.

Coagulopathy

Increased coagulation state and decreased anticoagulation state have been shown in sepsis.[186,187] Decreased hyaluronan and syndecan which are components of the endothelial glycocalyx were shown to be decreased in sepsis,[84] and heparan sulfate levels elevated in sepsis showed that endothelial glycocalyx may be degraded in sepsis leading to endothelial dysfunction.[83] As discussed earlier [Figure 4], endothelial glycocalyx degradation may trigger phenotype change. NO has been shown to increase VEGF and it was related to angiogenesis.[26] VEGF that has been shown to be increased in sepsis implies angiogenesis that may occur in sepsis and these fragile new vessels may cause capillary leak and bleeding complicates the picture further.[188] Thrombin has been shown to change the fibroblasts to myofibroblast type;[189] we may call this in spirit of Warburg effect as dedifferentiation [Figure 3]. As shown earlier, it is well known that thrombin induces VSMC proliferation.[157,190,191] It has been already shown that heparin is antiproliferative, and it inhibited proliferation of VSMC,[192-194] proliferation of uterine SMC,[195] mesangial cell proliferation.[196] It looks as thrombin may be involved in

regulating dedifferentiation state and heparin may be involved in regulating the differentiated state of the vascular system. Overall, there is a decrease in anticoagulant state and increase in coagulation state occurs in sepsis,[186,187] and this has to be seen in the context of the cell phenotype state. Heparin has been suggested by many in the treatment of sepsis.[197] As said above, it may work not only as an anticoagulant but as a differentiating factor. Ascorbic acid has been shown to increase fibrinolytic activity.[198] Many other pathologies also seem to obey the Warburg differentiation–dedifferentiation effect, but due to space constraint, they are not discussed in this review article.

Mild Reversible Warburg Differentiation–Dedifferentiation Effect Is Necessary for Normal Functioning

Exercise induced vasodilation in the skeletal muscle arteries. High plasma catecholamine level has been shown during exercise.[199] Lactic acidosis[200] during exercise implies glycolysis. This may lead to the embryonic state of the VSMC in the skeletal muscle arteries which as shown above may have beta 2 ARs as their predominant receptors and catecholamines act on it to produce vasodilation.

Every woman in their reproductive period produces a highly regulated tumor called fetus. Even though in pregnancy NO has been shown to be increased in animal models, how this is related to normal pregnancy and complications such as preeclampsia is not clear cut.[201,202] It is well known that pregnancy is associated with increased sympathetic activity,[203] increased coagulation state, and increased insulin level,[204] which implies pregnancy may be cancer-like condition. Warburg effect has been already related to embryo metabolism.[205] A mild and reversible Warburg dedifferentiation effect may be necessary for maintaining normal pregnancy and an exaggerated irreversible Warburg dedifferentiation effect [Figure 1], which may cause pregnancy-related complications such as preeclampsia, eclampsia, and gestational diabetes. Due to space constraint, it is not discussed further, but one can relate these conditions to the mechanisms discussed earlier for SHT and diabetes. It has been already shown that the vascular response was decreased in pregnancy to vasopressors;[206] one can see the similarity between this condition and vascular hyporeactivity to vasopressors in septic shock [Figure 5]. Furthermore, it has been shown in animal model that during pregnancy, alpha 1 AR density decreases in aortic VSM,[69] which can be seen as a change in cell phenotype toward embryonic dedifferentiation state. Moreover, this same process when it reaches the irreversible dedifferentiation synthetic/proliferative state may produce the pregnancy complications.

Warburg differentiation–dedifferentiation effect in many other normal processes is not discussed further due to space constraint.

Pauling, Gyorgyi, Warburg, and Ascorbic Acid

Linus Pauling in the latter half of the life was devoted to ascorbic acid research, who believed that ascorbic acid was a universal drug which can be given for many diseases ranging from common cold to cancer. Pauling showed that decreased ascorbic acid level can lead to problems in ECM production and endothelial dysfunction, and most importantly, its regulation of mitochondrial respiration activation will be lost; all these may lead to Warburg effect and cancer.[81] Like Pauling, Gyorgyi who discovered ascorbic acid devoted his latter half of the life in developing the electronic theory of cancer. He believed that stopping the electron flux in the mitochondrial electron transport chain could trigger the events leading to Warburg effect and ends in the primitive cancer state that has the better survival advantage and related his electronic theory of cancer with Warburg effect. He believed that ascorbic acid is essential for life.[207] Irrespective of Pauling and Gyorgyi's contribution, interest in ascorbic acid use in diseases and cancer in particular went down. Recently, one can see the revival of ascorbic acid and has shown many promising directions ranging from cancer to septic shock,[14,208] and to reach high plasma levels of ascorbic acid, it has to be used intravenously.[209]

In sepsis, ascorbic acid levels were shown to be decreased in sepsis patients and it was used intravenously in a phase 1 trial which showed that it is safe and reduces multiorgan dysfunction.[82] Ascorbic acid has been shown to restore the endothelial dysfunction, restore insulin sensitivity, restored eNOS, inhibit iNOS,[210-212] decrease HIF1 alpha level,[213] inhibit TNF alpha-induced NFkB,[214] and enhance eNOS action by increasing BH4 level.[215] Ascorbic acid has shown to inhibit iNOS and restore vascular response to norepinephrine in sepsis animal model.[216] Ascorbic acid has been used intravenously which reversed the vascular hyporeactivity to vasopressors during the inflammation made by endotoxin in healthy humans.[217] Ascorbic acid has been shown to increase fibrinolytic activity in coronary artery disease patients.[198] Furthermore, it is well known that ascorbate activates cytochrome C oxidase and is used as a substrate for activating this enzyme.[54,81] Ascorbic acid has the potential to be a universal drug which may work in treating many pathologies including all those mentioned in this article ranging from septic shock to cancer. Ascorbic acid works as a differentiating factor regulating the differentiated state of the cell by activating mitochondrial respiration at cytochrome C oxidase, thereby making the electron flux to proceed normally; this action includes the removal of mitochondrial respiration inhibition by the uncoupler/respiratory poison. Further, ascorbic acid by decreasing HIF1 alpha may inhibit the activation of glycolytic enzymes. It helps in maintaining normal endothelial glycocalyx, ECM, and endothelial function; this restricts the freedom of the movement of the cells, and thus, the phenotype change may be prevented. It also works by its commonly known antioxidant function by scavenging the reactive species. In short, ascorbic acid may be a key regulator in maintaining

the normal adult-differentiated state of the cell and thus maintains order in the human system. Maintaining normal ascorbic acid level in plasma may be essential for normal healthy life. Ascorbic acid can be used to treat most of the pathologies as a differentiation therapy including septic shock. Why a molecule of this importance has not been synthesized in the human body was related to evolution and is not discussed in this article.[81]

Treatment Options for Septic Shock as Differentiation Therapy

Treatment should aim at reversing the Warburg effect by activating the mitochondrial respiration either by directly activating the cytochrome C oxidase or by removing the inhibition of mitochondrial respiration caused by the uncoupler/respiratory poison. Any uncoupler that can do the same job as NO by inhibiting the mitochondrial respiration would trigger the Warburg effect leading to irreversible-dedifferentiated states, e.g. cyanide poisoning. When one uncoupler/respiratory poison is causing the disease, the pathology can be treated by (1) activating the mitochondrial respiration directly, for example, by ascorbic acid, caffeine,[17] and cytochrome; C;[16] (2) removing the uncoupler source, for example, by reducing the NO in sepsis using antibiotics, adrenergic blockers, eNOS restoration, and iNOS inhibition; (3) counterintuitively, one can use the other uncouplers/respiratory poisons that can inhibit the mitochondrial respiration and may work by competitive inhibition, thereby activating the mitochondrial respiration, for example, this mechanism seems to underlie in the treatment of cyanide poisoning using sodium nitrite and sodium thiosulfate. As shown above, Warburg common pathogenesis model seems to underlie in most pathologies; if most of the diseases have common pathogenesis, then most of the drugs may also work by a common mechanism by reversing the Warburg effect and thus regulate the maintenance of adult-differentiated phenotype of the cells by the drugs action on mitochondrial respiration. In that case, many safe drugs used in one pathology may be used in some other seemingly unrelated pathologies.

Primary drug options in sepsis

1. Ascorbic acid should be the primary drug option in septic shock and in many other pathologies, and 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[14,81,82]
2. Adrenergic blockers should be used in septic shock as mentioned in the vascular dysfunction section; it has been already used in sepsis and shock states.[8,10-13,38,39,104] Alpha blockers may be a better choice in initial state of sepsis, and beta blocker may be a better choice in later stages of sepsis; combined alpha + beta blocker may work in all stages of sepsis [Figure 5]
3. Antibiotics
4. Vasopressors should not be given.

The primary drug options along with no vasopressor use may be sufficient to treat the septic shock.

Secondary drug options

1. In general, all the antihypertensives may be used for treating septic shock. For example, amlodipine can be used in septic shock. It has been already shown that amlodipine-inhibited TNF alpha, iNOS expression in VSMC treated with LPS[218]
2. Antiglycolytic drugs – DCA,[62] shikonin[15]
3. Anticancer drugs: ATRA, MTX
4. Cholinergic agonists or VNS:[111,112] Acetylcholine may be helpful, but it also carries the risk of causing bronchoconstriction when given in the initial phase of septic shock. How VNS can be used in septic shock has to be sorted out in the future
5. Andrographolide has been already shown to restore the normal vascular response in LPS-treated rat aorta by inhibiting iNOS and it improved the arterial pressure in septic shock animal model[219]
6. Heparin as mentioned above works not only as an anticoagulant but also as a regulator of differentiation
7. Near-infrared light (NIR) or red light: NIR has been shown to activate mitochondrial respiration by its action on cytochrome C oxidase, and it has been used in various pathologies.[220,221] Red light incubators can be used in the future in critical care units
8. Low-dose metformin may be helpful and metformin anticancer role can be seen in this context.[222] Tsoyi *et al*. already had shown that metformin improved survival in animal sepsis model by its inhibitory action on high mobility group box 1[223]
9. Cytochrome C has been already used to activate mitochondrial respiration in sepsis animal model and showed beneficial effects[16]
10. Caffeine,[17] as cytochrome C, activated mitochondrial respiration in sepsis animal model and produced beneficial effects
11. Methylene blue (MB): It is well known that MB increases cytochrome c oxidase activity and mitochondrial respiration.[224] MB has been used in septic shock patients and showed improved mean arterial pressure, but its effect on mortality has not been determined; here, MB was used from the viewpoint of soluble guanylyl cyclase inhibition to reduce the NO level.[225,226] MB should be used only in the late phase of septic shock
12. Statins[121,122]
13. Sildenafil has been used in PAH and erectile dysfunction (ED) and it has been shown to restore eNOS, prevent endothelial dysfunction, and decrease iNOS in the ED animal model.[227] Sildenafil can be given in later stages of septic shock, whereas in the initial state [Figure 5], where eNOS is already hyperactivated, sildenafil may aggravate by further activating eNOS and may complicate the condition

14. N-acetyl cysteine can be used to increase glutathione and glutathione may protect the respiratory inhibition by NO.[228] However, ascorbate itself may rise glutathione level.[229]

Due to space constraint, I restrict the treatment options. Timing of the drugs plays a key role as some drugs which were helpful in one phase of the septic shock may not be helpful in other phase, e.g., propranolol may work better only in the late phase of the septic shock.

As discussed earlier, because of its effect on proliferation, insulin carries the risk of double-edged sword.

Conclusion

Warburg common pathogenesis model or Warburg differentiation–dedifferentiation effect has the potential to explain not only septic shock but also most of the pathologies such as SHT, PAH, atherosclerosis, CHF, ALI/ARDS, asthma, DM 1 and 2, AKI, PKD, CKD, and Fanconi's syndrome. This raises the possibility that most of the diseases may have common pathogenesis and most of the drugs may also have a common action, which may be related to the Warburg differentiation–dedifferentiation effect. A mild Warburg differentiation–dedifferentiation effect may be necessary for normal functioning in some specific parts of the body and is necessary for tissue repair. Most of the pathologies tend toward Warburg effect finally. This can be seen as the successful local survival strategy of the cells in response to injuries by returning back to their primitive irreversible-dedifferentiated states which may have survival advantage. However, this may lead to the disordered state and global failure in organ system/organism, where order in terms of differentiation is necessary for normal functioning. Death of the organism is due to the immortality pathway chosen by the cells locally. All the processes in the body may have relation to this Warburg differentiation–dedifferentiation effect. If the model is experimentally verified, it has the potential to act as a fundamental theorem for medicine. Experimental verification of this model is of paramount importance as it helps not only in treating septic shock but many other medical problems and will open up new unknown territories.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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