Theory of Carbon Signaling. Negentropy vs Entropy - Emergence of Self Propagated Biological Systems

RADOSLAV SABEV BOZOV
Independent researcher Biology department
University of Virginia
P.O. Box 400133 Garrett Hall Charlottesville, VA 22904-4133
rsb5n@virginia.edu http://bg.linkedin.com/pub/radoslav-bozov/12/974/680

Abstract: - How can we model the causative force of reversible covalent modifications? DNA provides information for synthesizing proteins which in term drive metabolic processes. Understanding basic metabolic processes currently do not help explain regulative forces controlling gene expression. Rather it is claimed that the chromatin state determined by DNA and histone modifications regulate gene expression. We now know that chemistry underlines and explains biological phenomena. However, understanding dynamic chemistry in large space such as a cell has been difficult through conventional models capturing structural changes of metabolites in spatially defined motifs where active sites determine change of mass. How do we expand in space? We certainly need to implement defined physical concepts and to elaborate on set of principles in order to construct emergent principles. The results from sequencing technology have posed new questions that require alternative approaches of system analysis. The functions of non-coding RNA's have linked gene expression with the smallest covalent modifications, methylation and acetylation. The smallest and the largest molecules such as protein complexes are the most difficult to study in biological systems because of their transient characteristics. Hierarchical time scale differences additionally complicate computational models as open systems tend to be difficult to analyze due to environmental, transport, irreversible, or regulatory constrains. Building a dynamic model of multiple dimensional composite functions at each moment by approximating negativity as a function of mass change is what may be necessary for discovering the causative force underlying oscillations in concentrations and states of small molecules and therefore populations. Is there a mechanism to define species' variability through the physics of small molecules relative to the origin of carbon signaling?

Key – Words: - acetylation, methylation, epigenetics, carbon signaling, asymmetric redox systems, non-coding RNA, heterochromatin, euchromatin, negentropy

1. Introduction:

Resonance theory, as widely accepted method for understanding electron negativity fluctuations theorized by Linus Pauling and the establishment of uncertainty principle by Heisenberg, allows us to capture possible intermediates over the course of a given reaction. Chemical quantum mechanisms are good approximations for determining reactants if endogenously produced intermediates. What were the first organic molecules giving rise to biological primitive systems in the RNA world? What other cluster of elements played crucial role for evolving complex biological systems? One group of researchers suggests that urea must have been present [1, 3]. Urea's density functional properties have not been well established due to its relative functionality as a function of given conditions. [4, 5] Therefore it can act either as electrophile or nucleophile relative to its interference with given set of amino acids and/or other molecules as a function of space. Others focuses on modern analysis for possible carbon metabolites and green house gases role in primordial atmosphere [2,3] In 1950 Edmons Mary, Adelaide Delluva, and Wright Wilson published the metabolism of purines and pyrimidines by growing yeast where lactate was incorporated into pyrimidines. However, accurate mechanism following quantum chemical theory was lacking. As a result it was easily composed that aspartic acid and carbamyl phosphate (never observed intermediate), precursor of carbamoyl

phosphate, formed orotic acid when orotic aciduria was discovered as a disease causing excess excretion of orotate. In 1964 McCarty Kenneth et al suggested arginine as a precursor of pyrimidine synthesis. [6] If pyrimidine synthesis is the origin of carbon signaling, then methylome dynamics will be directly linked to mutation dynamics and redox coupled systems causing glyoxylate asymmetric topological changes. The biological relevant properties of carbon containing molecules are a long standing problem that must consider life as inevitable consequence of expanding biological space.

2. Problem Formulation:

Metabolism has been problematic due to topological constrains and loss of electrons in water molecules. Because regulatory mechanisms are related to reversible covalent modifications, metabolism re-emerged as a flux based constrains.

CAD has been a long standing problem in biochemistry where carbene mechanism transient formation has shown to be nearest to biochemical free energy calculations. [7, 8, 9] It appears that the most proficient enzyme, ODCase catalyzes different substrates as recent mutations combined with high resolution crystallography indicate formation of reversible covalent bond on K72 and C-6 of pyrimidine ring. Cyanide group was shown to be a leaving negative group in opposition to neutral carbon dioxide leaving negative destabilized C-6. [10] What if there is something fundamentally wrong with the entire pathway proposal in regard of substrates? Orotate synthesis mechanism is proposed in Fig. 2 Refutation of the regulatory role mediated by the multi protein known as CAD in mammals, consisted of CPSase, ACTase, ODCase and DHOase mechanisms, one of the most proficient enzymes ever known, is the base for paradigm shift in understanding the causative force for mutation rate, dynamics of reversible covalent modifications and unifying network, free radical, mutation and redox theory through implementing the principle of mass compressibility relative to quantum chemistry and general relativity.

Understanding life dynamics as a function of space/time requires introducing the principle of compressibility of carbon molecules. Linux Paulig proposed the existence of hydranion, but in this work it will be accepted that only carbon anions are functionally relevant for dynamic redox systems as composite functions of negativity in expanded space. Current models do not provide information on reasons for U and T synthesis evolutionary mechanism and they lack explanation on integrating it with key metabolite fluxes, protein conformations and macromolecule dynamics. In this paper U and T are considered being synthesized at the same source under different regulatory forces. The role of glucose on differentiation has been an object for continuous investigation [11]. Parallel to it, studies on branched amino acids has shown interesting clinical results inferring the importance of modern approaches in revealing the dependent and independent axis between carbon and nitrogen interference. [12, 13] Is it possible that the most primitive pathway is the missing link in biophysical chemistry expansion as a function of carbon signaling systems? Even today, carbon's physical property continues to surprise us with its potential capacity conductance and subatomic quasi particle behavior. What are the biological relevant properties of carbon containing molecules is a long standing problem that needs to be explored in a novel approach considering life as inevitable consequence of expanding biological space.

3. Problem Solution:

3.1 Arginase and its centrality in nitrogen metabolism

It was believed that Arginase was an enzyme expressed only in liver cells eliminating nitrogen end products, amonia. It is now well documented that ARGase is expressed in any cell entering S phase.[14] It was confirmed that Arginase expression is linked to cellular signaling and differentiation [15, 16] Moreover the existence of such empirical data sheds light on nitrogen metabolism and its role in mitochondria - cytosol relationship of glucose oxidation and urea synthesis. It is confirmed that oxygen tension has direct effect on arginase expression [17]. Oxidative glycolysis is a paradox important for understanding how small molecule signaling and turnover of biomass happens. Arginase expression in immune cell response has been an object for investigating differentiation effects on genome expression [18]. It is the electromagnetic forces formed by resonance that allows strong nucleophilic properties of nitrogen [19]. NO (nitric oxide) synthesis evolved as competitive form for nitrogen regulation as arginine substrate serving to both urea and NO production. How cell differentiates which pathways are

ISBN: 978-960-474-278-3

activated is a function of genomic fluctuation upon external and internal signaling relative to carbon interference.

3.2 Lactate and its centrality in redox coupled systems.

The biologically relevant form of lactic acid is L which suggests that proteins were derived through lactic acid reduction generating S-S coupled dynamic changes by using pyrimidine synthesis and methylation dynamics. If pyruvate is reduced, negative methyl from C-S will attack alpha C+ and give off electrons to reduce carbon from +2 to +1 generating positive methyl group pulling electrons form cysteine coupled systems of co-enzyme Q coupled to DHO. Moreover this suggests that aspartate/malate shuttle is functionally dependent on methyl transferring systems. This predicts that carbon-carbon bonds are highly transient in the world of biology and the driving force is entanglement of negativity within methyl bound states relative to sulfur containing amino acids, C or M. It is reasonable to assume indirect interference of hydrogen peroxide, highly linked to sulfur bridge dynamics [20, 21, 22]. LDH mechanism is refuted as better accuracy is presented with the involvement of Cysteine coupled systems. This explains the existence of methylated lysine residues on dehydrogenases. How do we measure potential in expanded space?

The spatial localization of LDH and its centrality in cancerogenesis related to genomic instability and mutations have been object of investigation for decades. LDH can be seen as a transformer in classic physical perception, therefore if transformer changes capacitor (heterochromatin) state will change as well. Vit. B12 has been known to participate in single carbon transferring reactions [23] therefore directly involved in proliferation/differentiation dynamics by regulating the synthesis of M. Furthermore the central enzyme regulating one carbon transferring to uracil has been now observed to be non locally dependent on M [24]. It appears that spatially separated structures interfere through so called allosteric regulation. What is the force behind it and how can we compute Warburg paradox of lactate increase as a function of carbon signaling by conformational changes composed of partial carbon fluxes? What is the cause for protein and DNA fluctuations? Methylome genomic fluctuations are seen as a function of carbon signaling. It is reasonable to assume that negative methyl reduces glyoxylate forming lactate via -SS-C-N coupled systems. All of the scenarios of asymmetric oxidation are considered in the derivation of carbon interference PDE. (See derivation) Thus, lactate can be formed even when pyruvate is used for pyrimidine synthesis. This is essential in bending symmetry amplified biological systems. There is no ATP problem as quantity for nucleotide synthesis would provide necessary ATP for kinase, however, cancerous cells are independent greedy “creatures”. Note that it is the same carbon atoms of pyruvate which ends up on histones. Same carbon is in interference and usage for signaling of asymmetric redox independent mass amplified spaces between compartments, which implies that phases of electrons are amplified due to interference overlapping bouncing off from DNA.

3.3 Mechanism for pyrimidine synthesis

The mechanism for pyrimidine synthesis is presented in Fig 1. Note that methyl formation may occur at different conformational changes of the protein ACTase, thus proposing that allosteric regulation is a function of methyl inducing sulfur bond transient formation. Note that bonds are a language to represent distant relationship between atoms with different properties. However, is there an emergent system of particles that cause spatial fluctuations of matter? How can we expand off functional groups to describe chained space of sub-atomic particle interference? The smaller a defined mass is, the larger the defined energy relative to space has been determined through the principle of mass compressibility relative to carbon properties. The abundance of methionines in ACTase has never been attributed as dynamic consequence of carbon signaling. It suggests that PEP regulation is essential for electro-negativity derivation through carbon-sulfur bond dynamics. CPS1 was compared to aldolases giving E value of 0.5 (data not published) suggesting that the formation of C-C bond is a function of nitrogen metabolism and substitution mechanism is not sufficient to determine glyoxylate enzymes similarity to CAD as well as the origin of methyl group synthesis.

3.4 Computation of pyruvate/acetate Oscillator

JDesigner biochemistry introduction program was used by implementing a mesh of indirectly dependent carbon molecules Fig 3. Equation (5) was derived.

dAcetate/dt = + J0 - J2 - J3 + J4 - J21 ; The rate of acetate formation equals the sum of pyruvate decarboxylation and histone deacetylation minus the

ISBN: 978-960-474-278-3

sum of the rate of biomass synthesis and the rate of malate and oxaloacetate formation and equation (6)
dPyruvate/dt = + J2 - J4 - J5 + J12 - J13 + J22 ; The rate of pyruvate formation is directly proportional to the sum of glucose uptake, malate synthase and OAA decarboxylation minus the sum of the rate of pyruvate decarboxylation and pyrimidine synthesis. Aging has been attributed to NADH dependent deacetylases [25] as well as other transcription factors, mainly histone methylases as well as traditionally coupled redox system perturbation studies. It is important for us to determine the cause for cytosolic protein acetylation in order to understand the existence of kinase/phosphatase coupled systems. Kinases motifs are propagated diamond network forward motifs due to the amplifying character of phosphate signaling systems. The symmetry is broken as phosphatases much lesser quantity causes higher negentropy vs enetropy magnitude. How does cross coupling of signaling systems happen? Understanding the evolution of forces determining acetyl/ methyl fluxes may explain entropy in an alternative problem solving way, accounting for redox systems amplifications by including water as a reflection of energy availability psi. Thus, oxidation (using water's activated oxygen) is assumed to be entropic force. This can be achieved when, first, carbon and nitrogen metabolism take principles requiring unidirectional flaw of biomass production in terms of pyrimidine synthesis and second, C-C bond breakage on C-5 is perceived as a function of redox opposing forces as demethylated Cytosine would require input of electrons on C-6 from S to preserve the electronic structure of the pyrimidine ring. The electron pair is essentially the same one coming from methyl-sulfur-sulfur interference. As positive methyl groups are transferred to K and R on histones. This indicates that increase of so called "junk" DNA and variability of introns is a consequence of C-S-N interference driven by acetate/pyruvate oscillator. How computing methylome as a function of cellular state is possible? Transcription factors differentiate species. Oxygen state is a reflection of negentropy (synthetic reactions). Therefore, when perceiving space we can use well established physical concepts in order to determine functionality of chemical resonates in expanded space. The five parts used to describe functional meaning of biological structures in physical parts are generator, resistors, capacitor, semiconductors and transformer
Fig. 5 divided on various scale according to magnitude for permissive negative potential flow and switchers that are key regulatory units. Thus, it is in favor of better visualization and a partial functional characterization. The generator is the site for pyrimidine synthesis, capacitors are heterochromatinized regions of DNA, C-C and C-N bond formation, resistors are euchromatine regions as they will regulate generator output, semiconductors are S-C, LDH complex and Fe-S [26] negativity transferring systems which coupled to proteins are well known in oxidation organelle systems seen as transformers while kinases/phosphatases systems are transistors amplifying carbon signaling It is important to realize that all these biological functionally defined parts are working as an entire unit, cell, composing emergent propeller of amplified entropy/negentropy potential psi, as space expands due to mass compression, reducing carbon mass. The principle of space expansion (compressibility) is taken from general relativity theory and modified as a function of compressing mass. Thus the smaller carbon molecules are, the larger the energetic space they occupy because the faster they travel, so time will slow down as a function of negativity (electron re-localization) How can we measure and define the variables that can describe the function of an entire cell? Can atom by atom method solve the problem?

3.3.1 Unidirectional flaw of matter in open systems

Pyruvate decarboxylation as an irreversible step in carbon catabolism plays a key role in determining oxidative state of the cellular metabolism. Classically acetate has been assigned as molecule entering Krebs cycle, but during past decade acetate has been attributed to cytoplasmic and nuclear protein reversible covalent modifications linked to nitrogen oxidation. Cystene redox systems have been investigated [27] as a possible mechanism for regulating immune response. However, what is the cause for sulfur dynamics? How can one account indirectly of sulfur and determine evolutionary as well as differentiation dynamics? In this paper, oxidation is relative only to electrons on carbon and the first principle introduced is no hydranion formation in NAD dependent reactions. It is rather the relative S-C that delivers electrons. In organic chemistry study in late 70's it was unable to determine absolutism on methyl radicals [28]. Carbon transfers electrons to Sulfur in the Generator space. This is coupled to glyoxylate oxidation to oxalate in which electrons are also transferred to methyl groups breaking S-S bridges and formation of homocysteins. Oxalate has overall strong negative charge, thus readily converted to oxaloacetate. Therefore, understanding forces behind

ISBN: 978-960-474-278-3

the shift from oxidative phosphorilation to glycolitic phosphorilation can be seen outside of the light of traditional energy metabolism if one accounts for distinctive axis of metabolite mass flaw. I have independently proposed that glyoxalate and acetate are substrate of an enzyme forming malate [29] which in turn can be oxidized to pyruvate. My model accounts for this distinct axis independently of a group of systems biologist at Stanford and MIT [30, 31] Pyruvate/Acetate oscillator Fig. 3 predicted the reasons driving the existence of such interaction between glyoxalate cycle, Krebs cycle and glycolysis because carbon metabolism cannot be understood outside the light of nitrogen metabolism and the role of ever growing sulfur containing amino acids, Cys and Met, as a consequence of evolution confirmed by sequence technology data (not published). Guo and Tugarinov identified carbon derived from glycolysis to be found on M by NMR studies. [32] Systems biology evolutionary dynamics confirmed that there is correlation between certain amino acids (M, C and R and K) in evolutionary dynamics. It is reasonable to define properties that may predict this notion of evolutionary dynamics.

3.4 Shifting from inductive to deductive biological chemistry

Understanding dynamic chemistry in deductive manner of spatial jumps from cell-cell signaling to cell to compartments to transient protein complexes, to synthetic/degradation to reversible covalent modification interactions leading to properties that can explain protein fluxes, conformational rearrangements and motif selections is the ultimate goal of Theory of Carbon Signaling (PDE life equations). The oscillator periods, amplitudes and frequencies are dependent on Arginase expression, metabolic balance shifts of redox states, as well as rate of glyoxylate production, the origin of asymmetric biological oxidation. According to TCS model glyoxylate is a byproduct of pyrimidine synthesis, (see mechanism) indicating that for the first time I have demonstrated direct causative force for malate-pyruvate axis as a result of genes building block synthesis, or more simply determined by entropy decrease as synthetic processes can be seen as negentropy force, thus increasing the availability of potential energy stored in the hydrogen-oxygen transient bonds. It is now known that hydrogen resonates between oxygens and mass change is determined as a function of negativity travel. In this paper I will not define negativity as this may pose further implications to theoretical physics which will be an attempt to further justification of subatomic particles.

3.4.1 The link between oxygen consumption and lactate

If peroxide is used for oxidative processes and activating oxygen of water molecules by serine proteases in degradation pathways, I assume increase of entropy due to loss of thermal energy during bond breakage. The physiological capacity of oxygen consumption is proportional to turnover of methyl flux and glyoxylate oxidation. Quanta of emitted infrared waves will be absorbed by carbon in its negative assigned number exiting electrons during travel within S-C semiconductors, affecting transformers capability to reduce oxygen molecules to peroxides. Excitation of electrons will be re-emitting amplified quanta, suggesting that higher oxygen consumption correlates with increase of capacitor's state. This may suggests why mammals evolved as a function of oxygen availability. Then acetate, as a central intermediate of catabolic/anabolic processes is actually a signaling molecule involved in shifting "local" genome from hetero to euchromatin and the expression of caspase systems for degrading matter. Then increase of cytosolic acetate by HDAC would cause increase of glyoxylate synthesis. This implies for reasons of chromatin packing and histone dynamics during S phase. As glyoxalate synthesis is parallel to pyrimidine synthesis, and methylation is an opposing force of acetylation, repression by HDAC requires methyl synthesis, which is also a by-product of pyrimidine synthesis pathway. Therefore, TCS model accounts for integrating metabolomic dynamics with gene expression through differentials of metabolism using basic physical concepts to separate biochemical functions in expanded space of omics.

Another interesting aspect is the effect of urea formation on period of each oscillator cycle. This suggests that nitrogen intake determines lifespan of organisms and high protein food should be taken only to build lean mass or during growth of an organism besides intake of essential amino acids. Increase of this substrate would increase the period of each oscillatory cycle and possibly shift the phase. Then more glucose enters glycolysis the more pyruvate would be produced speeding up nucleotide capacitors potential to accommodate methyl groups. Then time is determined by controlling the travel of methyl groups from

ISBN: 978-960-474-278-3

membrane (outer mitochondrial) to membrane (inner side of nuclear) Thus a prediction of TCS model is increase of Arginase expression must correlate with increase of glycolysis and deacetylation favoring gene reduction, methylation. The importance of covalent modifications has rose to an extend where we must differentiate genomic dynamics through integrative approach of various small molecules as a base of mass change in space and vector determination for biological processes as a function of entropy shifts because signaling peptide sequences are subject to reversible modifications. However, life cannot be integrated without first being differentiated. Water has been traditionally considered as the molecule of life in classic biology due to its observable properties relative to hydrogen bonding. Can we solve problem of oxygen? The nature of the bond seems to evaporate as a function of space as negativity loss in carbon. Many studies have confirmed the change of differentiation as a function of time as input of biomass appears to be important in the compensatory mechanism accommodating for internal energy availability. [33, 34, 35, 36] What in essence is biomass and how can we measure compensatory mechanism? How can we predict the outcome of chained redox system defining spatial fluctuations as mass change due to negativity loss through carbon containing metabolites? It is eminent that pieces of expressible DNA have cumulative effect, and a gene itself is not a functional biological unit, but rather an "element" necessary for a proper cellular state at a given stage in linage development. It rather gives some information onto how metabolic mass changes in particular compartment or series of compartments if deactivated. It is a reflection of methyl/negativity discontinuous flux within boundaries, membranes. However, this does not imply that membranes are absolute boundaries as cells are open systems.

3.4.2 Rules for deriving biological carbon PDE.

1. Break time into n-dimensional systems relative to mass compression of carbon molecules oxidation states Fig. 6

2. Approximate change of mass as a function of negativity (entropy vs. negentropy)

3. Take limit towards 0 and invert trig function to work with it better.

4. Use 1 to input mass change relative to larger space, thus construct composite functions as a function of time/space.

5. Derive explicitly and cancel out negativity represented as numbers where possible to catch time independently.

6. Negativity can be a number representing ratios of mass and their change.

7. If you make a mistake, don't worry, we have multiple systems so it is ok to emerge in different system, thus by n-time we allow mistakes to be taken care by other parts.

8. Introduce natural log to compress mass (numbers) and expand in space.

9. Define the space as open carbon signaling system.

Thus, targeting well understood transferases coupled to transporters of hub metabolites involved in regulative forces of functional motif formation is important aspect of medicine development and the emergence of regenerative medicine. When would regeneration be possible?

3.5 Carbon Signaling- from origin to implications. Theory of Carbon Signaling.

Integration of five partial systems spanning in functional space has been introduced that appear to have discontinuous interactive domains. Theoretical and computational methods were used to define the following postulates.

1. Modified Integration of metabolic fluxes reduced to dynamics of "hub" intermediates of carbon and nitrogen metabolism, pyruvate, malate, acetate, glyoxalate, and urea determining precursor quantity for signaling through covalent reversible modifications. Dynamics of covalent bonds as electron negativity force is determined by carbon-sulfur interaction in space coupled to nitrogen-carbon dynamics from evolutionary metabolomic perspective. Relative oxidation state of carbon is assigned as a chained function of metabolic fluxes.

2. Defining global genomic stability by using intermediate functional carbon group properties

ISBN: 978-960-474-278-3

propagation in space determining protein-small molecule interference by assessment of entropy as a function of chained oxidation systems. Thus, highly differentiated tissues must have highest rate of relative oxidation state of carbon containing metabolites according to PDE as highest rate of oxygen reduction is observed.

3. Cys/Met evolutionary dynamics determined by methyl/acetyl transferring systems coupled to ROS (hydrogen peroxide synthesis and degradation), and electron negativity shifts in carbon, determining synthesis/degradation of macromolecules.

4. Water synthesis and degradation is an effect of negentropic and entropic cause in defined functional space. The role of enzymes in the mechanics of entropy oscillation is to resist capacitors, miRNA and siRNA. Viruses escape when capacitance is diminished as a function of decreased entropy. Oncogenes are interfering with histone acetylases amplifying their expression. Tumor suppressors are methyltransferases.

5. Electron negativity originates from carbon anion reducing one sulfur of S-S bridges, oxidizing the second forming another S-S bridge, or/and reducing Fe, thus reducing oxygen is negentropic force. Nucleoiphilic Sulfur strips off methyl groups from nitrogen, reducing nitrogen, causing expression. Thus, in this paper reader must consider redox systems relative to carbon atoms. Thus carbon reduction happens when keto group is converted to hydroxyl group as carbon negative donates electrons through sulfur coupled systems. Cofactors are transient mediator of electron negativity. No transferring of hydrogen anion involved.

3.5.1Moving from a cyclic to an oscillation model. Fig. 4

Histone deacetylases (NAD dependent, and Zn ion binding activating transfer of Acetyl group bounded K side chain to ADP ribose moiety) transporting Ac to the cytosol, where transient complex formation with Malate synthase occurs, which catalyzes the aldol condensation of glyoxylate with acetyl-CoA to form malate. Malate synthase is a protein of 530 to 570 amino acids whose sequence is highly conserved across species.
Malate dehydrogenase converts the NAD to NADH forming oxaloacetate which is decarboxylated requiring prosthetic group for decarboxylation of side chain carboxyl group. This reaction is dependent on pyruvate kinase which is likely to participate in a complex with malate synthase and OAA decarboxylase. The formation of pyruvate as a product of decarboxylation re-enters the pyrimidine pathway formed by multicomplex CAD, thus self amplifying the synthesis of methyl donors (see mechanism), allowing the methylation of deacetylated histones in order to compact deacetylated chromatine. CAD is multi protein consisted of Carbamoyl Phosphate Synthase, ACTase and DHOase. This is the site where nitrogen and carbon metabolism interfere in a fascinated manner as the rate of urea and pyruvate formation determines the rate of pyrimidine synthesis, methyl donor formation and glyoxylate asymmetric oxidation which is the causative force for HADPH hydrogen peroxide formation and malate synthase. Therefore, the production of glyoxylate drives its own synthesis indirectly. This is managed by opposing forces entropy and negentropy.

. HIF expression and GSSG (glutathione synthesis) are regulatory forces triggering negentropy. HIF factor, helix loop helix is a transcription factor that may be involved in deacetylating and most likely participates with complexes regulating genome stability by methylation, repressing genes involved in degradations. This implies that as the rate of oxygen consumption decreases, hydrogen peroxide increases, (-CH3) will increase, therefore favoring transitional by the energy input at given momentum. C to T transition requires deamination by water attack on C-4. Then negantropy forces the transition of G to A, neutralizing entropy. Thus CG to AT transition is an outcome of two forces opposing in their action. The core entropic step is decarboxylation, complete oxidation. This postulates that genetic repeats are an effect of system comprising inter-compartmental cross talk, an emergent property describing functional space through physical properties of given metabolites and proteins involved in a chain of composite carbon signaling metabolites. Therefore, small molecule-protein interaction determines evolutionary force, as mutations targeting promoters where gene expression is selected is not random but rather determined by environmental constrains. Mutations are determined in a dt moment when input for genomic stability is the output of environmental factors transformed through a chain of resistors. The following three equations predict genomic fluctuations of carbon signaling molecules as a function of oxidation, Note: 1=(C-N) + (C-S), thus computing C-N because C-C of meC in cytoplasm: (see LIFE Equation)
Relationship between oxalate, acetate and methylome.

ISBN: 978-960-474-278-3

1) $1\text{-}[\text{-CH3}] = \left(\left[\text{Ln}\left(\sqrt{1-[\text{Acetate}]^{2}}^{-1} - \sqrt{oxalate}\right)\right] / Ln(O_2)\right) - KO_2$

Relationship between lactate and methylome

2) $1-[-\text{CH}_3] = ([-\text{Ln}(1-[\text{lactate}])] / Ln(O_2)) - \text{KO}_2$

Relationship between glyoxylate and methylome

3) $1-[-\text{CH}_3] = ([\text{Ln}(\text{glyoxytate})] / Ln(O_2)) - \text{KO}_2$

In every case, TF(transcription factors) affect either reductive pathways for lactate and glyoxylate and oxidative for acetate and glyoxylate.

Final conclusions:

1. Evolution is an outcome of ever competing forces: negentropy and entropy. Adaptation is an effect of these forces in the origin of carbon interference and natural selection is an effect of negentropy. Negantropy can be defined as shifting redox systems toward reduction or synthetic forces. Phosphorilation is an opposing entropic force. Deacetylation is an entropic force. Then acetylation is negantropic force (increase of gene expression in general).

2. As differentiation takes place smaller amount of "genes" are expressed, as negentropy increase cause stronger entropy. Entropy increases demethylation increases, causing stronger negentropy and genomic disorder (the case of cancer) However, because disorder is caused by super-order at dt, the initial critical step is negentropic, hypermethylation of tumor suppressors (the case of p53) Cancer is an outcome of antievolutionary force.

3. Calcium is an entropy force that arose as an antiforce of phosphorilation in higher organisms, or it happened when the first glyoxylate was oxidized to oxalate, thus oxalate (readily metabolized or excreted) and calcium must be separated in space. If not pathogenesis occur, or complete spatial disorder by formation of crystal structures.

4. The first base that ever came into existence was C-5 methylated pyrimidine. Sulfur containing molecules coupled to metal ions (Fe) interfered with spatial localization of one carbon signaling molecules.

5. Negentropy force is the formation of C-N bonds. The formation of S-C bonds is the emergent force of negentropy and entropy interference.

6. Negentropy and Entropy are directionality of antimatter fluxes which are discontinuous as leptons fluctuation determines gluon bosonic forces to be asymmetric, thus predicting that carbon has different frequency of gluon forces relative to its oxidation state as methyl, negentropic, will have higher frequency of the bosonic wave, while carbon dioxide higher lambda (period).

ISBN: 978-960-474-278-3

Figures:

F.1

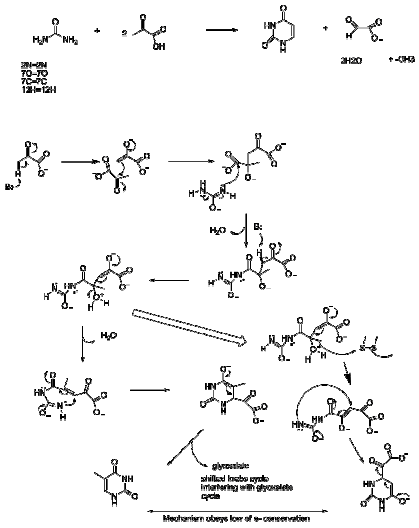


Fig. 2

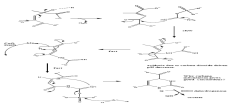


Fig. 3

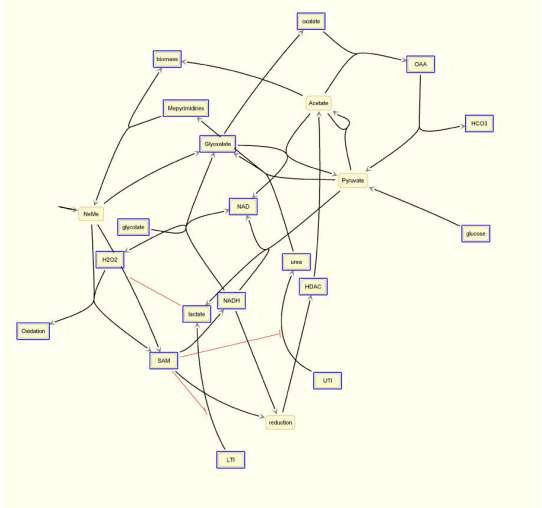
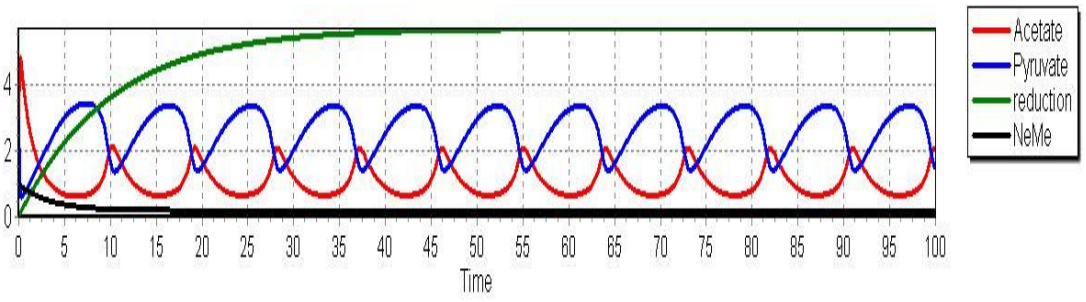


Fig 4

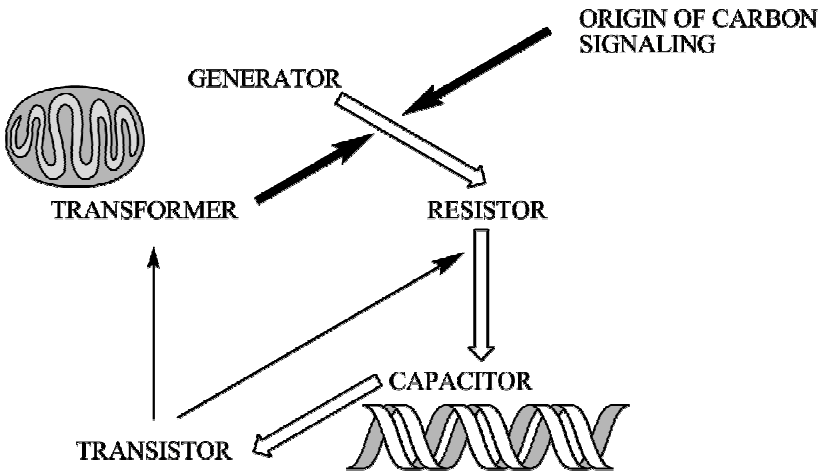


// Differential Equations:

5) dAcetate/dt = + J0 - J2 - J3 + J4 - J21

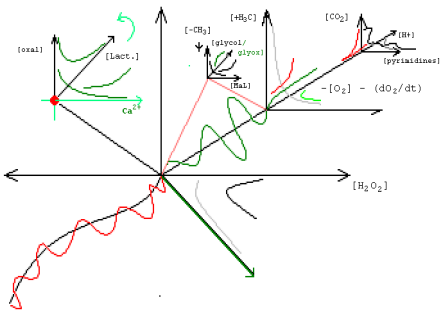
6) dPyruvate/dt = + J2 - J4 - J5 + J12 - J13 + J22

Fig 5



ISBN: 978-960-474-278-3

Fig 6



$$\left(\frac{A^2}{4}\right)-\left(\frac{B^2}{4}\right)=1 \quad , \qquad A,B\neq 2$$

Based on Resonance theory and Redox systems, assume that "e¯" reduce H_2O_2

$$\frac{[-CH_3]^2}{4}-\frac{[H_2O_2]^2}{4}=1 \quad \text{;if} \quad \text{tanxcotx=1}$$

$$\frac{[-CH_3]^2}{4}-\frac{[H_2O_2]^2}{4}=\tan(glu\cos e)^{(-CH_3)}\cot(oxidant)$$

1)because $\frac{[glycolate]}{[glyoxylate]}=\frac{1}{malate}$

AC=Acetate

$$\Rightarrow * \frac{[-CH_3]^2-[H_2O_2]^2}{4}=\tan\left(e^{[O_2][-CH_3]}\right)\frac{\frac{1}{\cos(Ac)}.\cos(glyoxidate)}{\sin\left(\frac{glyoxylate}{glycolate}\right)}$$

if $[H_2O_2]=[\text{glycolate}]^{-1}$ and $[-CH_3]=[\text{lactate}]$, as ↑ S-CH_3(cytosol)=>↑lactate

Rule: inverse functions are used as mass inverses electron negativity.

Rearrange the equation to express the DECORBOXYLATION step on one side the equation as a function of entropy, thus calculating the relationship between Mitochondria /Cytosol/ Nucleous (intercompartment partial carbon fluxes) as a composite redox system of negentropy (synthesis) and arrive at a final equation for explicit differentiation:

ISBN: 978-960-474-278-3

$$\sin^{-1}\left[\frac{glyoxylate}{glycolate}\right].\frac{1}{\tan^{-1}(e^{a_2-CH_3})}.\frac{[lactate]^2-\left[^1 glycolate\right]^2}{4}.\frac{1}{\cos^{-1}[glyoxylate]}=\frac{1}{\cos^{-1}[Acetate]}$$

$$\left(\frac{1}{\sqrt{1-\left[\frac{glyoxylate}{glycolate}\right]}}.\frac{1}{[-CH_3]\left[\frac{1}{1+[E^{O_2}]^2}\right]\left[O_2{}^{-CH_3}\right]}.\frac{1}{\sqrt{1-[glyoxylate]^2}}\right).$$

$$\left[\frac{\left[[lactate]^2+^-[glycolate]^{-2}-\left(2[lactate]-2[glycolate]^{-1}\right)\right]4}{16}\right]=\left(\sqrt{1-[Acetate]^2}\right)^{-1}$$

Use [lactate]^2-[glycolate]^2 as a hole (0) to "jump" to another system (see graph 1) then, rearrange the function again

$$\sqrt{1-\left[\frac{glyoxylate}{glycolate}\right]}^{-1}=\frac{\sqrt{[glycolate]}}{\sqrt{[glycolate-glyoxylate]}} \quad =>$$

$$\frac{\sqrt{glycolate}}{\sqrt{[glycolate-glyoxylate]}}.\frac{1}{[-CH_3]+^+(+CH_3{}^{O_2{}^{[CH_3-1]}})(1+e^{O_2})^{-1}}.\frac{-2[lactate]+^-[glyoxylate]}{4[glyoxylate]}$$

$$=\frac{1}{\sqrt{1-[Acetate]^2}}$$

we approximate the ratio:

$$\frac{\sqrt{[glycolate]}}{\sqrt{[glycolate-glyoxydate]}}=\sqrt{Oxalate}$$

$$\sqrt{[oxalate]}.\frac{1}{[-CH_3]+(+CH_3{}^{O_2{}^{[CH_3-1]}})(1+e^{0_2})^{-1}}.\frac{-[-CH_3]+[glyoxylate]}{2[glyoxylate]}$$

$$=\frac{1}{\sqrt{1-[Acetate]^2}}$$

$$\left(\sqrt{1-[Acetate]^2}\right)^{-1}-\left(\sqrt{[oxalate]}\right)=\frac{1}{[-CH_3]+\left(+CH_3{}^{O_2{}^{-CH_3-1}}\right)(1+e^{0_2})^{-1}}.$$

$$\frac{1+\left(-\left[-CH_3+glyoxylate\right]\right)}{2[glyoxylate]}$$

$$\sqrt{1-[Acetate]^2}^{-1}-\sqrt{[oxalate]}=\frac{[-CH_3]^{-1}+(1+E^{O_2})}{\left(+CH_3{}^{O_2{}^{-CH_3-1}}\right)}.$$

ISBN: 978-960-474-278-3

$$\frac{[glyoxylate]\left([glyoxylate]^{-1}-[-CH_3][glyoxylate]^{-1}+1\right)}{2[glyoxylate]}$$

*Note: 2*X is not X+X, 2 is rather 1+1 or…

$2x\frac{[-CH_3]^2+[H_2O_2]^2}{4}$ = twice the path of an electron pair traveling from: S-CH_3 to H_2O_2

$$\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}=$$

$$\left(\frac{1}{[-CH_3]}+\frac{1+e^{O_2}}{+CH_3{}^{O_2{}^{-CH_3-1}}}\right)\cdot\left(\frac{[glyoxylate]}{2-2([-CH_3]+[glyoxylate])}\right)$$

$$\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}=$$

$$*remove[-CH_3]^{-1}->\frac{1}{[-CH_3]}\left(1+\frac{1+e^{O_2}}{O_2{}^{-CH_3-1}}\right)\cdot\left(\frac{[glyoxylate]}{2-2[CH_3]+2[glyxylate]}\right)$$

$$\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}=$$

$$\frac{1}{[-CH_3]}\left(1+\frac{1+e^{O_2}}{O_2{}^{-CH_3-1}}\right)\cdot\left(2\frac{1}{[-CH_3]}-1+\frac{[glyixylate]}{[-CH_3]}\right)$$

$$\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}=$$

$$\frac{1}{[-CH_3]}\left(1+\frac{1+e^{O_2}}{O_2{}^{-CH_3-1}}\right)\cdot\left(2\frac{1}{[-CH_3]}-1+\frac{[glyixylate]}{[-CH_3]}\right)$$

*2 is mass in negativity, so despite breaking an algebraic rule, for example:

$\frac{2^{e-}\Delta t+x+y}{2^{e-}\Delta t(z+d)}=0$ as the electrons move from –CH_3 and glyoxylate to O_2

$$\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}=$$

$$\frac{1}{[-CH_3]}\left(\frac{[-CH_3][glyoxylate]}{1-[-CH_3+glyoxylate]}\cdot\frac{e^{O_2}}{O_2{}^{-CH_3-1}}\right)$$

$$\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}=$$

$$\left(\frac{e^{O_2}[glyoxylate]}{O_2{}^{-CH_3-1}\cdot[1-lactate]}\right)$$

$$\frac{\left(\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}\right)(1-[lactate])/\Delta t}{[glyoxylate]/\Delta t}=\frac{\left(e^{O_2}\right)/\Delta t}{\left(O_2{}^{-CH_3-1}\right)/\Delta t}$$

ISBN: 978-960-474-278-3

$$Ln\left(\frac{\left(\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}\right)(1-[lactate])/\Delta t}{[glyoxylate]/\Delta t}\right)=Ln\left(\frac{e^{O_2}}{O_2{}^{-CH_3-1}}\right)/\Delta t$$

$$Ln\left(\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}\right)+Ln(1-[lactate])-Ln[glyoxylate]=O_2-Ln\left(O_2{}^{-CH_3-1}\right)$$

$$Ln\left(\sqrt{1-[Acetate]^2}^{-1}-\sqrt{oxalate}\right)+Ln(1-[lactate])-Ln[glyoxylate]+[-CH_3-1]Ln(O_2)=O_2$$

FINAL EQUATION

$$1-[CH_3]=\left\{\left[\left(Ln\left(\sqrt{1-[Acetate]^2}^{-1}-\sqrt{ocalate}\right)-Ln(1-[lactate])+Ln([glyoxylate])\right)\div[Ln(O_2)]\right]\right\}-[O_2]$$

$$1)\ 1-[\text{-CH3}]=\left(\left[\text{Ln}\left(\sqrt{1-[\text{Acetate}]^2}^{-1}-\sqrt{oxalate}\right)\right]/Ln(O_2)\right)-KO_2$$

$$2)\ 1-[-\text{CH}_3]=([-\text{Ln}(1-[\text{lactate}])]/Ln(O_2))-\text{KO}_2$$

$$3)\ 1-[-\text{CH}_3]=([\text{Ln}(\text{glyoxytate})]/Ln(O_2))-\text{KO}_2$$

References:

[1] Robertson MP., Miller SL. "An efficient prebiotic synthesis of cytosine and uracil" *Nature*.1995 Jun. 29; 3759(6534): 772-4. Jul. 19 2006. www.pubmed.com

[2] Dewitt et al. "A View of the Prebiotic Earth's Atmosphere: Greenhouse Gases, Oxidized Organic Haze, and the Anti-Greenhouse Effect" American Geophysical Union, Fall Meeting 2008, abstract #P33D-01

[3] AS. Subbaraman., Kazi ZA, ChoughuleyAS, Chadha MS. "Urea-acetylene dicarboxylic acid reaction: a likely pathway for prebiotic uracil formation." *Orig Life.* 1980 Dec; 10(4): 343-7. Jul. 19 2006.

[4] E. G. Finer, Franks and M. J. Tait. "Nuclear Magnetic Resonance Studies of Aqueous Urea Solution" *Journal of American Chemical Society.* June 28th, 1972

[5] Anthony Maher et al. "Mathematical Modeling of Urea Cycle. A Numerical Investigation into Substrate Channeling" *European Journal of Biochemistry*, 270. 3953-3961 (2003)

[6] McCarty Kenneth et al. " Arginine as a Precursor of Pyrimidines in Strain L-929

Fibroblast Infected with Pleuropneumonia- like Organisms" *The Journal of Biological Chemistry* Feb. 1964

[7] Brain Miller and Richard Wolfenden. "Catalytic Proficiency: The Unusual Case of OMP Decarboxylase" *Annual Review of Biochemistry* 2002

[8] K.N. Houk et al. "What Have Theory and Crysallography Revealed About the Mechanism of Catalysis by Orotidine Monophosphate Decarboxylase" *Top Curr Chem.* 2003. Springer Verlag
Berlin Heidelberg 2004

[9]Callahan and Miller. "OMP Decarboxylase-An Enigma Persist" *Bioorganic Chemistry*, Dec. 2007

[10] Fujihashi et al. "Structural characterization of the molecular events during a slow substrate-product transition in orotidine 5'-monophosphate decarboxylase" *Journal of Molecular Biology* 2009

[11] Hinck L., J.P. Thissen., S. Pampfer., R. Hertogh. "Effect of high concentration of glucose on differentiation of rat trophoblast cells in vitro" *Diabetologia.* 2003

[12] Kalahan C. Satish., Karen Q. Rossi., Lourdes L. Gruca., Dennis M. Super., and Samuel M. Savin. "Relation between transamination of branched-chain amino acids and urea synthesis: evidence from human pregnancy" *AJP-Endocrinology and Metabolism.* 275: E423-E431 Sep. 1998. Jul. 7 2006.

[13] Bizzaro Nicola., Giovanni Mazzanti., Elio Tonutti., Danilo Villalta., and Renato Tozzoli. "Diagnostic Accuracy of the Anti-Citrulline Antibody Assay for Rheumatiod Arthritis" *Clinical Chmestry* 47: 1089-1093, 2001. Sep. 2006.

[14] Morris M. Sidney, Jr. "Regulation of Enzymes of the Urea Cycle and Arginine Metabolism" *Annu. Rev. Nutr.* 2002.22:87-105. Oct 19 2006.

[15] Wei Hua Liu., et al "IL-4 and IL-13 Upregulate Arginase 1 Expression by cAMP and JAK/STAT6 Pathways in Vascular Smooth Muscle Cells" *American Journal of Physiology- Cell Physiology* 279: C248-C256, 2000.

[16] Aoki P. Maria et al. "Cruzipain, a Major Trypanasoma Antigen, Promotes Arginase-2 Expresion and Survival of Neonatal Mouse Cardiomyocytes" *American Journal of Cell Physiology. Sep* 17th 2003.

[17] Louis A. Claudine., et al. "Distinct Arginase Isoforms Expressed in Primary and Transformed Macrophages: regulation by oxygen tension" *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 274:R775-R782, March 1998.*

[18] Bronte Vincenzo and Paula Zanovello. "Regulation of Immune Response by L-Arginine Metabolism" *Nature Reviews/Immunology*, Vol. 5 Aug.

[19] Sergey V Krayatov et al. "A study of the Equilibrium and Kinetics Of Urea Binding by

Biomimetic Dinickel Complex" *Eur.J. Inorg. Chem.* 2003

[20] Juraj Kona and Tore Brink. "A Combined Molecular Dynamic Simulation and Quantum Chemical Study on the Mechanism for Activation of the OxyR Transcription Factor by Hydrogen Peroxide" *Organic and Biomolecular Chemistry.* Aug 2006

[21] Stone James and Tucker Collins. "The Role of Hydrogen Peroxide in Endothelial Proliferative Responses" *Endothelium*, 9;231-238, 2002.

[22] Suryanarayana Vepa, William M. Scribner, Narasimham L. Parinandi, Denis English, Joe G. N. Garcia, and Viswanathan Natarajan **"**Hydrogen peroxide stimulates tyrosine phosphorylation of focal adhesion kinase in vascular endothelial cells" *Am J Physiol Lung Cell Mol Physiol*, Jul 1999;

[23] Shyue-fang Battaglia-Hsua et al. "Vitamin B12 Deficiency Reduces Proliferation and Promotes Differentiation in Neuroblastoma Cell and Up-regulates PP2A, proNGF andTACE" *PNAS* Dec 22, 2009 Vol. 106.

[24] . Randal V. Mauldin and Andrew L Lee. "NMR study of the role of M42 in the solution Dynamics of E.coli dehydrofolate reductase" *Biochemistry*. Article ASAP. Jan 14. 2010

[25]Jeffery Chen and Lu Tian. "Roles of Dynamic and Reversible Histone Acetylation in Plant Development and Polyploidy" *Biochimica et Biophysica Acta* 1769 (2007)

[26] George D. Cody, *et al.* "Primordial Carbonylated Iron-Sulfur compounds and the Synthesis of Pyruvate" *Science* 289, 1337 (2000)

[27] Zhonghua Yan and Ruma Banerjee. "Redox Remodeling as an Immunoregulatory Strategy" *Biochemistry*, 2010

[28] Marynick Dennis and David Dixon. "Electron Affinity of The Methyl Radical: Structrures of CH3+ and CH3-" *PNAS USA* Vol. 74, Feb. 1977

[29] Anstrom David, Karen Kallio and James Remington. " Structure of E.coli malate synthase G;pyruvate:acetyl CoA abortive ternary complex at 1.95 A resolution" *Protein Science.* 2003. Cold Spring Harbor Laboratory Press Nov. 2007

[30] Markus Covert, Nan Xiao, Tiffany Chen and Jonathan Karr. "Integrating metabolic, transcriptional regulatory and signal transduction models in Escherichia Coli" *Bioinformatics* 2008 24(18):2044-2050; doi:10.1093/bioinformatics/btn352

[31] Shaham et al. "Metabolic profiling of the human response to a glucose challenge reveals distinct axes of insulin sensitivity" *Mol Syst Biol.* 2008; 4: 214

[32] 80. Chenyun Guo and Vitali Tugarinov. "Identification of HN-methyl NOEs in large proteins using simultaneous amide-methyl TROSY-based detection" J Biomol NMR (2009) 43:21–30

[33] Guo Lirong et al. "*Reduced Urea Flux Across the Blood-Testis Barrier and Early Maturation in*

the Male Reproductive System in UT-B Null Mice" May 2, 2007

[34.] Berger U., H. Tsukaguchi and M. Hediger. "*Distribution of mRNA for Facilitated Urea Transporter UT3 in the Rat Nervous System"* 25 Nov. 1997

[35] Prichett William et al. "Identification and Cloning of Human Urea Transporter HUT11, Which is Downregulated During Adipogenesis of Explant Cultures of Human Bone" *Journal of Cellular Biochemistry*. 2000

[36] Daniela Bruch-Gerharz et al. "Arginase 1 Overexpression in Psoriasis. Limitation of Inducible Nitric Oxide Synthase Activity as a Molecular Mechanism for Keratinocyte Hyperproliferation " *American Journal of Pathology*. Jan 2003.

ISBN: 978-960-474-278-3