DYNAMICS OF RESOURCE ALLOCATION IN BIOLOGICAL SYSTEMS II: *On cancer cell metabolism*

Imadol V. Jeff-Eke[1]

Abstract

Here we shall apply the approach presented in the paper *Dynamics of resource allocation in biological systems* in considering resource allocation in cancer cell metabolism, specifically, aerobic glycolysis (Warburg effect). Aerobic glycolysis, the metabolic phenomenon of cells utilizing glucose fermentation to lactate even under conditions of ample oxygen availability. We shall consider resource reallocations between processes of two hypothetical cells: a cancer cell and a normal cell. Specifically, we consider reallocation of resources between cancer-related processes of a cancer cell, normal processes of same cancer cell, and processes of a normal cell in attempts to satisfy the high resource requirements for cancer-related processes. In doing this, we draw inferences from the initial work and state hypotheses as pertains to cancer cell metabolism. From this hypotheses, we shall attempt explanation of Aerobic glycolysis. We end by considering genomic instability as a derivation of cancer cell metabolism.

Introduction:

Here we shall apply the approach presented in the paper *Dynamics of resource allocation in biological systems* in considering resource allocation in cancer cell metabolism. Of principal interest is how cancer cells satisfy the relatively high metabolic needs required for their processes under conditions of limited resource content. Although stated for cancer cells, this may also apply to metabolic processes of benign forms of neoplasia. In considering metabolism, we shall also examine aerobic glycolysis (Warburg effect) using the approach outlined in this paper. Aerobic glycolysis, a finding by Otto Warburg et al, that cancer cells facilitate glucose fermentation to lactate even in the presence of ample oxygen supply [**1-4**]. To distinguish between transformation in terms of conformer to regulator changes, and transformation in reference to neoplastic changes, we apply underlined italic characters when referencing the latter. Thus, neoplastic transformation would be considered as neoplastic *transformation*.

We must consider that by the nature of the pathology, cancer-related processes are rather autonomous and thus may neither follow from stimuli nor be elicited in proportion to stimuli. This presents an issue in terms of application of concepts presented in the previous work. However,

[1] Contact: Corresponding author at ivjeffeke@gmail.com

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since resource allocations are the more pertinent matter, we shall circumvent such deficiencies by supposing that these processes follow from unappreciable stimuli. In other words, presenting stimuli are "ghosts" on observation. This is a valid assumption, since whether or not stimuli can be detected by an experimenter has no bearing on actuation of said processes.

A second issue concerns transformation with respect to effects of stimuli on cancer cells. In the paper *Dynamics of resource allocation in biological systems,* primary considerations were of actualized transformations. That is, the system as initially a conditional conformer undergoes change to a conditional regulator with respect to effects of a given stimulus. However, since cancer cells and therefore cancer-related processes of cancer cells can potentially occur indefinitely, as evidenced by the continued propagation of HeLa cell lines [**5**]. The resource requirements for cancer cells and their associated cancer-related processes can be considered substantial. In this sense then, we must consider transformation events of cancer cells as attempted events that do not actualize. In other words, cancer cells and cancer-related processes of cancer cells continuously and indefinitely attempt transformations.

A third issue then concerns how said unappreciable stimuli must present in order to yield such indefinite transformation attempts. For the paper *Dynamics of resource allocation in biological systems,* we considered actualized transformations as would occur for a transient presenting stimulus. That is, the given stimulus presents for a brief period, with proportional effects of such stimulus persisting until actuation of response. Thus if presenting to an initial conditional conformer, then transformation to a conditional regulator must occur in order for actuation of response. Now consider a succession of such transient presenting stimulus occur and at a frequency such that immediately following transformation with respect to effects of the given stimulus and actuation of response, successive transient stimulus presents such that transformation with respect to effects of each presenting stimulus must follow in order for actuation of response to corresponding stimulus. If the noted succession of transient presenting stimulus should occur indefinitely, then the succession of transformation events must also occur so as to allow for response to stimulus. Thus, indefinite succession of transformation events can be considered akin to indefinite transformation attempts. Based on this line of reasoning, the said unappreciable stimuli can be considered to present in succession and at frequencies that allow for an indefinite succession of transformation events. In other words, the given stimuli can be considered to be rather persistent.

Description of representations	Representations
All processes of cancer cell	Process-**C**
All processes of normal cell	Process-**N**
All cancer-related processes of cancer cell	Process-***cp***
All normal processes of cancer cell	Process-***np***

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Transformation with respect to effects of persistent stimulus on a cancer cell: Resource allocation between a cancer cell and a normal cell:

Let us suppose that the total available resource content, $\dot{\mathbf{R}}$, is a constant, and therefore remains unchanged with transformation. Also, suppose that prior-to and following transformation, $\dot{\mathbf{R}}$ is partitioned between two response processes only. These are response processes of a single cancer cell of which we represent as **process-C,** and processes of a single non-cancerous or normal cell of which we represent as **process-N**.

Let the change in resource partition for a response-i be the difference between the resource partitions for the given response for the transformed, $'\mathrm{R}_{Ai}$ and untranformed system, R_{Ai}. That is, $'\mathrm{R}_{Ai} - \mathrm{R}_{Ai}$. We show that the change in resource partition for process-**C**, $'\mathrm{R}_{AC} - \mathrm{R}_{AC}$, equals the negative of the change in resource partition for process-**N**, $\mathrm{R}_{AN} - '\mathrm{R}_{AN}$.

$$\dot{\mathbf{R}} = \mathrm{R}_{AC} + \mathrm{R}_{AN}$$

$$\dot{\mathbf{R}} = '\mathrm{R}_{AC} + '\mathrm{R}_{AN}$$

$$\mathrm{R}_{AC} + \mathrm{R}_{AN} = '\mathrm{R}_{AC} + '\mathrm{R}_{AN}$$

$$'\mathrm{R}_{AC} - \mathrm{R}_{AC} = \mathrm{R}_{AN} - '\mathrm{R}_{AN}$$

Consider that the resource partition for response-i is the sum of the required resource content and a partition remainder.

$$\mathrm{R}_{Ai} = \mathrm{R}_{Ri} + \mathrm{R}_{ri}$$

$$'\mathrm{R}_{Ai} = '\mathrm{R}_{Ri} + '\mathrm{R}_{ri}$$

Thus, the partition remainder is the difference between the resource partition and required resource content.

$$\mathrm{R}_{ri} = \mathrm{R}_{Ai} - \mathrm{R}_{Ri}$$

$$'\mathrm{R}_{ri} = '\mathrm{R}_{Ai} - '\mathrm{R}_{Ri}$$

The change in partition remainder for response-i that occurs with transformation is the sum of the change in resource partition and change in required resource content for the given response.

$$\begin{aligned} '\mathrm{R}_{ri} - \mathrm{R}_{ri} &= '\mathrm{R}_{Ai} - '\mathrm{R}_{Ri} - \mathrm{R}_{Ai} + \mathrm{R}_{Ri} \\ &= '\mathrm{R}_{Ai} - \mathrm{R}_{Ai} + \mathrm{R}_{Ri} - '\mathrm{R}_{Ri} \end{aligned}$$

Thus, for the given processes of the cancer cell,

$$\mathrm{R}_{r\mathbf{C}} = \mathrm{R}_{A\mathbf{C}} - \mathrm{R}_{R\mathbf{C}}$$

$$'\mathrm{R}_{r\mathbf{C}} = '\mathrm{R}_{A\mathbf{C}} - '\mathrm{R}_{R\mathbf{C}}$$

$$\begin{aligned} '\mathrm{R}_{r\mathbf{C}} - \mathrm{R}_{r\mathbf{C}} &= '\mathrm{R}_{A\mathbf{C}} - '\mathrm{R}_{R\mathbf{C}} - \mathrm{R}_{A\mathbf{C}} + \mathrm{R}_{R\mathbf{C}} \\ &= \mathrm{R}_{R\mathbf{C}} - '\mathrm{R}_{R\mathbf{C}} + '\mathrm{R}_{A\mathbf{C}} - \mathrm{R}_{A\mathbf{C}} \end{aligned}$$

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where,

$$\mathrm{R}_{r\mathbf{C}} \ll {}'\mathrm{R}_{r\mathbf{C}}$$

Let, ${}'\mathrm{R}_{A\mathbf{C}} = {}'\mathrm{R}_{R\mathbf{C}}$, thus

$${}'\mathrm{R}_{r\mathbf{C}} = {}'\mathrm{R}_{A\mathbf{C}} - {}'\mathrm{R}_{R\mathbf{C}} = 0$$

and

$$\mathrm{R}_{r\mathbf{C}} \ll 0$$

We can therefore express the change in partition remainder for process-**C** as:

$$-\mathrm{R}_{r\mathbf{C}} = \mathrm{R}_{R\mathbf{C}} - {}'\mathrm{R}_{R\mathbf{C}} + {}'\mathrm{R}_{A\mathbf{C}} - \mathrm{R}_{A\mathbf{C}}$$

Inference-1

We infer from proposition-1: If, following transformation with respect to effects of stimuli for process-**C**, there is no change in resource partition for process-**C** only,

$${}'\mathrm{R}_{A\mathbf{C}} - \mathrm{R}_{A\mathbf{C}} = 0$$

then,

$$-\mathrm{R}_{r\mathbf{C}} = \mathrm{R}_{R\mathbf{C}} - {}'\mathrm{R}_{R\mathbf{C}} + 0$$

Also, since $\mathrm{R}_{r\mathbf{C}} \ll 0$

$${}'\mathrm{R}_{R\mathbf{C}} \ll \mathrm{R}_{R\mathbf{C}}$$

If, following transformation with respect to effects of stimuli for process-**C**, there is no change in required resource content for process-**C** only,

$${}'\mathrm{R}_{R\mathbf{C}} - \mathrm{R}_{R\mathbf{C}} = 0$$

then,

$$-\mathrm{R}_{r\mathbf{C}} = 0 + {}'\mathrm{R}_{A\mathbf{C}} - \mathrm{R}_{A\mathbf{C}}$$

Also, since $\mathrm{R}_{r\mathbf{C}} \ll 0$

$$\mathrm{R}_{A\mathbf{C}} \ll {}'\mathrm{R}_{A\mathbf{C}}$$

Let us now consider process-**N** as affected by transformation with respect to effects of stimuli for process-**C**. That is, how changes in resource parameters for process-**C** affect those for process-**N**.

$$-\mathrm{R}_{r\mathbf{C}} = 0 + {}'\mathrm{R}_{A\mathbf{C}} - \mathrm{R}_{A\mathbf{C}}$$

From the above relationship

$${}'\mathrm{R}_{A\mathbf{C}} - \mathrm{R}_{A\mathbf{C}} = \mathrm{R}_{A\mathbf{N}} - {}'\mathrm{R}_{A\mathbf{N}}$$

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thus,

$$-\mathrm{R}_{r\mathbf{C}} = 0 + \mathrm{R}_{A\mathbf{N}} - {}'\mathrm{R}_{A\mathbf{N}}$$
$$= 0 + \mathrm{R}_{R\mathbf{N}} + \mathrm{R}_{r\mathbf{N}} - {}'\mathrm{R}_{R\mathbf{N}} - {}'\mathrm{R}_{r\mathbf{N}}$$
$$= 0 + \mathrm{R}_{R\mathbf{N}} - {}'\mathrm{R}_{R\mathbf{N}} + \mathrm{R}_{r\mathbf{N}} - {}'\mathrm{R}_{r\mathbf{N}}$$

Inference-2

We infer from proposition-2: If, following transformation with respect to effects of stimuli for process-**C**, there is no change in both the required resource content for process-**C** and process-**N** only,

$${}'\mathrm{R}_{R\mathbf{C}} - \mathrm{R}_{R\mathbf{C}} = 0$$
$${}'\mathrm{R}_{R\mathbf{N}} - \mathrm{R}_{R\mathbf{N}} = 0$$

then,

$$-\mathrm{R}_{r\mathbf{C}} = 0 + 0 + \mathrm{R}_{r\mathbf{N}} - {}'\mathrm{R}_{r\mathbf{N}}$$

Also: since $\mathrm{R}_{r\mathbf{C}} \ll 0$,

$${}'\mathrm{R}_{r\mathbf{N}} \ll \mathrm{R}_{r\mathbf{N}}$$

Inference-3

We infer from proposition-3: If, following transformation with respect to effects of stimuli for process-**C**, there is no change in both the required resource content for process-**C** and partition remainder for process-**N** only,

$${}'\mathrm{R}_{R\mathbf{C}} - \mathrm{R}_{R\mathbf{C}} = 0$$
$${}'\mathrm{R}_{r\mathbf{N}} - \mathrm{R}_{r\mathbf{N}} = 0$$

then,

$$-\mathrm{R}_{r\mathbf{C}} = 0 + \mathrm{R}_{R\mathbf{N}} - {}'\mathrm{R}_{R\mathbf{N}} + 0$$

Also: since $\mathrm{R}_{r\mathbf{C}} \ll 0$,

$${}'\mathrm{R}_{R\mathbf{N}} \ll \mathrm{R}_{R\mathbf{N}}$$

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Transformation with respect to effects of persistent stimulus on processes of cancer cell: Resource reallocation between cancer-related- and normal processes of cancer cell.

Let the total available resource content for the cancer cell, $\dot{\mathbf{R}}_{\mathbf{C}}$, be a constant, and therefore remains unchanged with transformation; where $\dot{\mathbf{R}}_{\mathbf{C}}$ is the sum of sum resource partition for the cancer cell:

$$\dot{\mathbf{R}}_{\mathbf{C}} = \sum \mathrm{R}_{Acp} + \sum \mathrm{R}_{Anp}$$

$$\dot{\mathbf{R}}_{\mathbf{C}} = \sum {}'\mathrm{R}_{Acp} + \sum {}'\mathrm{R}_{Anp}$$

Thus, the total available resource content for the cancer cell, $\dot{\mathbf{R}}_{\mathbf{C}}$ can be considered the resource partition for the cancer cell.

$$\dot{\mathbf{R}}_{\mathbf{C}} = \mathrm{R}_{AC} = {}'\mathrm{R}_{AC}$$

Where,

$$\mathrm{R}_{AC} \equiv \sum \mathrm{R}_{Acp} + \sum \mathrm{R}_{Anp}$$

$${}'\mathrm{R}_{AC} \equiv \sum {}'\mathrm{R}_{Acp} + \sum {}'\mathrm{R}_{Anp}$$

Suppose that prior-to and following transformation, $\dot{\mathbf{R}}_{\mathbf{C}}$ is partitioned between two response processes only. In addition, let us suppose that these are processes of the cancer cell. These are **cancer-related processes of cancer cell** of which we represent as **process-*cp*,** and **normal processes of cancer cell** of which we represent as **process-*np***. Let the change in resource partition for a response-*j* be the difference between the resource partitions for the given response for the transformed, ${}'\mathrm{R}_{Aj}$, and untransformed system, R_{Aj}**.** That is, ${}'\mathrm{R}_{Aj} - \mathrm{R}_{Aj}$**.** We show that the change in sum resource partition for process-***cp***, $\sum {}'\mathrm{R}_{Acp} - \sum \mathrm{R}_{Acp}$, equals the negative of the change in sum resource partition for process-***np***, $\sum \mathrm{R}_{Anp} - \sum {}'\mathrm{R}_{Anp}$.

$$\dot{\mathbf{R}}_{\mathbf{C}} = \sum \mathrm{R}_{Acp} + \sum \mathrm{R}_{Anp}$$

$$\dot{\mathbf{R}}_{\mathbf{C}} = \sum {}'\mathrm{R}_{Acp} + \sum {}'\mathrm{R}_{Anp}$$

$$\sum \mathrm{R}_{Acp} + \sum \mathrm{R}_{Anp} = \sum {}'\mathrm{R}_{Acp} + \sum {}'\mathrm{R}_{Anp}$$

$$\sum {}'\mathrm{R}_{Acp} - \sum \mathrm{R}_{Acp} = \sum \mathrm{R}_{Anp} - \sum {}'\mathrm{R}_{Anp}$$

Where,

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$\sum \mathrm{R}_{Acp}$ = The sum resource partition for cancer-related processes of cancer cell prior to transformations.

$\sum \mathrm{R}_{Anp}$ = The sum resource partition for normal processes of cancer cell prior to transformations.

$\sum {}'\mathrm{R}_{Acp}$ = The sum resource partition for cancer-related processes of cancer cell following transformations.

$\sum {}'\mathrm{R}_{Anp}$ = The sum resource partition for normal processes of cancer cell following transformations.

Consider that the resource partition for response-j is the sum of the sum required resource content and sum partition remainder.

$$\sum \mathrm{R}_{Aj} = \sum \mathrm{R}_{Rj} + \sum \mathrm{R}_{rj}$$
$$\sum {}'\mathrm{R}_{Aj} = \sum {}'\mathrm{R}_{Rj} + \sum {}'\mathrm{R}_{rj}$$

Thus, the sum partition remainder is the difference between the sum resource partition and sum required resource content.

$$\sum \mathrm{R}_{rj} = \sum \mathrm{R}_{Aj} - \sum \mathrm{R}_{Rj}$$
$$\sum {}'\mathrm{R}_{rj} = \sum {}'\mathrm{R}_{Aj} - \sum {}'\mathrm{R}_{Rj}$$

The change in sum partition remainder for response-j that occurs with transformation is the sum of the change in sum resource partition and change in sum required resource content for the given stimulus.

$$\sum {}'\mathrm{R}_{rj} - \sum \mathrm{R}_{rj} = \sum {}'\mathrm{R}_{Aj} - \sum {}'\mathrm{R}_{Rj} - \sum \mathrm{R}_{Aj} + \sum \mathrm{R}_{Rj}$$
$$= \sum {}'\mathrm{R}_{Aj} - \sum \mathrm{R}_{Aj} + \sum \mathrm{R}_{Rj} - \sum {}'\mathrm{R}_{Rj}$$

Thus for the given process-$\boldsymbol{cp}$

$$\sum \mathrm{R}_{\boldsymbol{rcp}} = \sum \mathrm{R}_{\boldsymbol{Acp}} - \sum \mathrm{R}_{\boldsymbol{Rcp}}$$
$$\sum {}'\mathrm{R}_{\boldsymbol{rcp}} = \sum {}'\mathrm{R}_{\boldsymbol{Acp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rcp}}$$
$$\sum {}'\mathrm{R}_{\boldsymbol{rcp}} - \sum \mathrm{R}_{\boldsymbol{rcp}} = \sum \mathrm{R}_{\boldsymbol{Rcp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rcp}} + \sum {}'\mathrm{R}_{\boldsymbol{Acp}} - \sum \mathrm{R}_{\boldsymbol{Acp}}$$

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where,

$$\sum \mathrm{R}_{rcp} \ll \sum {}'\mathrm{R}_{rcp}$$

Let, $\sum {}'\mathrm{R}_{Acp} = \sum {}'\mathrm{R}_{Rcp}$ thus

$$\sum {}'\mathrm{R}_{rcp} = \sum {}'\mathrm{R}_{Acp} - \sum {}'\mathrm{R}_{Rcp} = 0$$

And

$$\sum \mathrm{R}_{rcp} \ll 0$$

We can therefore express the change in sum partition remainder for process-***cp*** as:

$$-\sum \mathrm{R}_{rcp} = \sum \mathrm{R}_{Rcp} - \sum {}'\mathrm{R}_{Rcp} + \sum {}'\mathrm{R}_{Acp} - \sum \mathrm{R}_{Acp}$$

Inference-4

We infer from proposition-1: If, following transformation with respect to effects of stimuli for process-***cp***, there is no change in sum resource partition for process-***cp*** only,

$$\sum {}'\mathrm{R}_{Acp} - \sum \mathrm{R}_{Acp} = 0$$

then,

$$-\sum \mathrm{R}_{rcp} = \sum \mathrm{R}_{Rcp} - \sum {}'\mathrm{R}_{Rcp} + 0$$

Also, since $\sum \mathrm{R}_{rcp} \ll 0$

$$\sum {}'\mathrm{R}_{Rcp} \ll \sum \mathrm{R}_{Rcp}$$

If, following transformation with respect to effects of stimuli for process-***cp***, there is no change in sum required resource content for process-***cp*** only,

$$\sum {}'\mathrm{R}_{Rcp} - \sum \mathrm{R}_{Rcp} = 0$$

then,

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$$-\sum \mathrm{R}_{rcp} = 0 + \sum {}'\mathrm{R}_{Acp} - \sum \mathrm{R}_{Acp}$$

Also, since $\sum \mathrm{R}_{rcp} \ll 0$

$$\sum \mathrm{R}_{Acp} \ll \sum {}'\mathrm{R}_{Acp}$$

Let us now consider process-***np*** as affected by transformation with respect to effects of stimuli for process-***cp***.

$$-\sum \mathrm{R}_{rcp} = 0 + \sum {}'\mathrm{R}_{Acp} - \sum \mathrm{R}_{Acp}$$

From the above relationship

$$\sum {}'\mathrm{R}_{Acp} - \sum \mathrm{R}_{Acp} = \sum \mathrm{R}_{Anp} - \sum {}'\mathrm{R}_{Anp}$$

thus,

$$\begin{aligned} -\sum \mathrm{R}_{rcp} &= 0 + \sum \mathrm{R}_{Anp} - \sum {}'\mathrm{R}_{Anp} \\ &= 0 + \sum \mathrm{R}_{Rnp} - \sum \mathrm{R}_{rnp} + \sum {}'\mathrm{R}_{Rnp} - \sum {}'\mathrm{R}_{rnp} \\ &= 0 + \sum \mathrm{R}_{Rnp} - \sum {}'\mathrm{R}_{Rnp} + \sum \mathrm{R}_{rnp} - \sum {}'\mathrm{R}_{rnp} \end{aligned}$$

Inference-5

We infer from proposition-2: If, following transformation with respect to effects of stimuli for process-***cp***, there is no change in sum required resource contents for process-***cp*** and process-***np*** only,

$$\sum {}'\mathrm{R}_{Rcp} - \sum \mathrm{R}_{Rcp} = 0$$

$$\sum {}'\mathrm{R}_{Rnp} - \sum \mathrm{R}_{Rnp} = 0$$

then,

$$-\sum \mathrm{R}_{rcp} = 0 + 0 + \sum \mathrm{R}_{rnp} - \sum {}'\mathrm{R}_{rnp}$$

Also: since $\sum \mathrm{R}_{rcp} \ll 0$,

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$$\sum {}'\mathrm{R}_{\boldsymbol{rnp}} \ll \sum \mathrm{R}_{\boldsymbol{rnp}}$$

Inference-6

We infer from proposition-3: If, following transformation with respect to effects of stimuli for process-***cp***, there is no change in both the sum required resource content for process-***cp*** and sum partition remainder for process-***np*** only,

$$\sum {}'\mathrm{R}_{\boldsymbol{Rcp}} - \sum \mathrm{R}_{\boldsymbol{Rcp}} = 0$$

$$\sum {}'\mathrm{R}_{\boldsymbol{rnp}} - \sum \mathrm{R}_{\boldsymbol{rnp}} = 0$$

then,

$$-\mathrm{R}_{\boldsymbol{r}\mathbf{C}} = 0 + \sum \mathrm{R}_{\boldsymbol{Rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rnp}} + 0$$

Also: since $\sum \mathrm{R}_{\boldsymbol{rcp}} \ll 0$,

$$\sum {}'\mathrm{R}_{\boldsymbol{Rnp}} \ll \sum \mathrm{R}_{\boldsymbol{Rnp}}$$

Transformation with respect to cancer-related processes of cancer cell: Resource reallocation between cancer-related processes of cancer cell and normal processes of both cancer and normal cell.

We can express the resource partition for the cancer cell as the sum of sum resource partitions for cancer-related processes of cancer cell and normal processes of cancer cell.

$$\mathrm{R}_{\boldsymbol{AC}} = \sum \mathrm{R}_{\boldsymbol{Acp}} + \sum \mathrm{R}_{\boldsymbol{Anp}}$$

$${}'\mathrm{R}_{\boldsymbol{AC}} = \sum {}'\mathrm{R}_{\boldsymbol{Acp}} + \sum {}'\mathrm{R}_{\boldsymbol{Anp}}$$

Thus,

$$\dot{\mathbf{R}} = \mathrm{R}_{\boldsymbol{AC}} + \mathrm{R}_{\boldsymbol{AN}}$$

$$= \sum \mathrm{R}_{\boldsymbol{Acp}} + \sum \mathrm{R}_{\boldsymbol{Anp}} + \mathrm{R}_{\boldsymbol{AN}}$$

$$\dot{\mathbf{R}} = {}'\mathrm{R}_{\boldsymbol{AC}} + {}'\mathrm{R}_{\boldsymbol{AN}}$$

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$$= \sum {}'\mathrm{R}_{\boldsymbol{Acp}} + \sum {}'\mathrm{R}_{\boldsymbol{Anp}} + {}'\mathrm{R}_{\boldsymbol{AN}}$$

We can express the change in sum resource partition for process-$\boldsymbol{cp}$, $\sum {}'\mathrm{R}_{\boldsymbol{Acp}} - \sum \mathrm{R}_{\boldsymbol{Acp}}$, as:

$$\sum \mathrm{R}_{\boldsymbol{Acp}} + \sum \mathrm{R}_{\boldsymbol{Anp}} + \mathrm{R}_{\boldsymbol{AN}} = \sum {}'\mathrm{R}_{\boldsymbol{Acp}} + \sum {}'\mathrm{R}_{\boldsymbol{Anp}} + {}'\mathrm{R}_{\boldsymbol{AN}}$$

$$\sum {}'\mathrm{R}_{\boldsymbol{Acp}} - \sum \mathrm{R}_{\boldsymbol{Acp}} = \sum {}'\mathrm{R}_{\boldsymbol{Anp}} + {}'\mathrm{R}_{\boldsymbol{AN}} - \sum \mathrm{R}_{\boldsymbol{Anp}} - \mathrm{R}_{\boldsymbol{AN}}$$

$$= \sum \mathrm{R}_{\boldsymbol{Anp}} + \mathrm{R}_{\boldsymbol{AN}} - \sum {}'\mathrm{R}_{\boldsymbol{Anp}} - {}'\mathrm{R}_{\boldsymbol{AN}}$$

The change in sum resource partition for process-$\boldsymbol{cp}$ can also be expressed in terms of the sum required resource content and sum partition remainder for process-$\boldsymbol{cp}$.

$$\sum {}'\mathrm{R}_{\boldsymbol{Acp}} - \sum \mathrm{R}_{\boldsymbol{Acp}} = \sum {}'\mathrm{R}_{\boldsymbol{Rcp}} + \sum {}'\mathrm{R}_{\boldsymbol{rcp}} - \sum \mathrm{R}_{\boldsymbol{Rcp}} - \sum \mathrm{R}_{\boldsymbol{rcp}}$$

Thus,

$$\sum \mathrm{R}_{\boldsymbol{Anp}} + \mathrm{R}_{\boldsymbol{AN}} - \sum {}'\mathrm{R}_{\boldsymbol{Anp}} - {}'\mathrm{R}_{\boldsymbol{AN}} = \sum {}'\mathrm{R}_{\boldsymbol{Rcp}} + \sum {}'\mathrm{R}_{\boldsymbol{rcp}} - \sum \mathrm{R}_{\boldsymbol{Rcp}} - \sum \mathrm{R}_{\boldsymbol{rcp}}$$

The change in sum partition remainder for process-$\boldsymbol{cp}$ that occurs with transformation is the sum of the change in sum resource partition and change in sum required resource content for the given process-$\boldsymbol{cp}$.

$$\sum {}'\mathrm{R}_{\boldsymbol{rcp}} - \sum \mathrm{R}_{\boldsymbol{rcp}}$$

$$= \sum \mathrm{R}_{\boldsymbol{Anp}} + \mathrm{R}_{\boldsymbol{AN}} - \sum {}'\mathrm{R}_{\boldsymbol{Anp}} - {}'\mathrm{R}_{\boldsymbol{AN}} - \sum {}'\mathrm{R}_{\boldsymbol{Rcp}} + \sum \mathrm{R}_{\boldsymbol{Rcp}}$$

$$= \sum \mathrm{R}_{\boldsymbol{Rnp}} + \sum \mathrm{R}_{\boldsymbol{rnp}} + \mathrm{R}_{\boldsymbol{RN}} + \mathrm{R}_{\boldsymbol{rN}} - \sum {}'\mathrm{R}_{\boldsymbol{Rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{rnp}} - {}'\mathrm{R}_{\boldsymbol{RN}} - {}'\mathrm{R}_{\boldsymbol{rN}} - \sum {}'\mathrm{R}_{\boldsymbol{Rcp}} + \sum \mathrm{R}_{\boldsymbol{Rcp}}$$

$$= \sum \mathrm{R}_{\boldsymbol{Rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rnp}} + \sum \mathrm{R}_{\boldsymbol{rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{rnp}} + \mathrm{R}_{\boldsymbol{RN}} - {}'\mathrm{R}_{\boldsymbol{RN}} + \mathrm{R}_{\boldsymbol{rN}} - {}'\mathrm{R}_{\boldsymbol{rN}} + \sum \mathrm{R}_{\boldsymbol{Rcp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rcp}}$$

where,

$$\sum \mathrm{R}_{\boldsymbol{rcp}} \ll \sum {}'\mathrm{R}_{\boldsymbol{rcp}}$$

$$\sum \mathrm{R}_{\boldsymbol{rcp}} \ll 0$$

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$$-\sum \mathrm{R}_{\boldsymbol{rcp}} = \sum \mathrm{R}_{\boldsymbol{Rcp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rcp}} + \sum \mathrm{R}_{\boldsymbol{Rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rnp}} + \sum \mathrm{R}_{\boldsymbol{rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{rnp}} + \mathrm{R}_{\mathbf{RN}} - {}'\mathrm{R}_{\mathbf{RN}} + \mathrm{R}_{\mathbf{rN}} - {}'\mathrm{R}_{\mathbf{rN}}$$

Hypothesis 1:
If, following transformation with respect to effects of stimuli for process-***cp***, there are no changes in: partition remainder and required resource content for process-**N**; and sum partition remainder and sum required resource content for process-***np*** only,

$$ {}'\mathrm{R}_{\mathbf{rN}} - \mathrm{R}_{\mathbf{rN}} = 0$$

$$ {}'\mathrm{R}_{\mathbf{RN}} - \mathrm{R}_{\mathbf{RN}} = 0$$

$$\sum {}'\mathrm{R}_{\boldsymbol{rnp}} - \sum \mathrm{R}_{\boldsymbol{rnp}} = 0$$

$$\sum {}'\mathrm{R}_{\boldsymbol{Rnp}} - \sum \mathrm{R}_{\boldsymbol{Rnp}} = 0$$

then,

$$-\sum \mathrm{R}_{\boldsymbol{rcp}} = \sum \mathrm{R}_{\boldsymbol{Rcp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rcp}} + 0 + 0 + 0 + 0$$

Also: since $\sum \mathrm{R}_{\boldsymbol{rcp}} \ll 0$,

$$\sum {}'\mathrm{R}_{\boldsymbol{Rcp}} \ll \sum \mathrm{R}_{\boldsymbol{Rcp}}$$

Hypothesis 2:
If, following transformation with respect to effects of stimuli for process-***cp***, there are no changes in: partition remainder and required resource contents for process-**N**; sum partition remainder for process-***np***; and sum required resource content for process-***cp***,

$$\sum {}'\mathrm{R}_{\boldsymbol{Rcp}} - \sum \mathrm{R}_{\boldsymbol{Rcp}} = 0$$

$$ {}'\mathrm{R}_{\mathbf{rN}} - \mathrm{R}_{\mathbf{rN}} = 0$$

$$ {}'\mathrm{R}_{\mathbf{RN}} - \mathrm{R}_{\mathbf{RN}} = 0$$

$$\sum {}'\mathrm{R}_{\boldsymbol{rnp}} - \sum \mathrm{R}_{\boldsymbol{rnp}} = 0$$

then,

$$-\sum \mathrm{R}_{\boldsymbol{rcp}} = 0 + \sum \mathrm{R}_{\boldsymbol{Rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{Rnp}} + 0 + 0 + 0$$

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Also: since $\sum \mathrm{R}_{\boldsymbol{rcp}} \ll 0$,

$$\sum {}'\mathrm{R}_{\boldsymbol{Rnp}} \ll \sum \mathrm{R}_{\boldsymbol{Rnp}}$$

Hypothesis 3:
If, following transformation with respect to effects of stimuli for process-***cp***, there are no changes in: partition remainder and required resource contents for process-**N**; and sum required resource content for both process-***cp*** and process-***np***,

$$\sum {}'\mathrm{R}_{\boldsymbol{Rcp}} - \sum \mathrm{R}_{\boldsymbol{Rcp}} = 0$$

$${}'\mathrm{R}_{r\mathbf{N}} - \mathrm{R}_{r\mathbf{N}} = 0$$

$${}'\mathrm{R}_{R\mathbf{N}} - \mathrm{R}_{R\mathbf{N}} = 0$$

$$\sum {}'\mathrm{R}_{\boldsymbol{Rnp}} - \sum \mathrm{R}_{\boldsymbol{Rnp}} = 0$$

then,

$$-\sum \mathrm{R}_{\boldsymbol{rcp}} = 0 + 0 + \sum \mathrm{R}_{\boldsymbol{rnp}} - \sum {}'\mathrm{R}_{\boldsymbol{rnp}} + 0 + 0$$

Also: since $\sum \mathrm{R}_{\boldsymbol{rcp}} \ll 0$,

$$\sum {}'\mathrm{R}_{\boldsymbol{rnp}} \ll \sum \mathrm{R}_{\boldsymbol{rnp}}$$

Hypothesis 4:
If, following transformation with respect to effects of stimuli for process-***cp***, there are no changes in: partition remainder for process-**N**; sum required resource content for process-***cp***; sum partition remainder and sum required resource content for process-***np***,

$$\sum {}'\mathrm{R}_{\boldsymbol{Rcp}} - \sum \mathrm{R}_{\boldsymbol{Rcp}} = 0$$

$${}'\mathrm{R}_{r\mathbf{N}} - \mathrm{R}_{r\mathbf{N}} = 0$$

$$\sum {}'\mathrm{R}_{\boldsymbol{rnp}} - \sum \mathrm{R}_{\boldsymbol{rnp}} = 0$$

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$$\sum {}'\mathrm{R}_{Rnp} - \sum \mathrm{R}_{Rnp} = 0$$

then,

$$-\sum \mathrm{R}_{rcp} = 0 + 0 + 0 + \mathrm{R}_{RN} - {}'\mathrm{R}_{RN} + 0$$

Also: since $\sum \mathrm{R}_{rcp} \ll 0$,

$${}'\mathrm{R}_{RN} \ll \mathrm{R}_{RN}$$

Hypothesis 5:

If, following transformation with respect to effects of stimuli for process-***cp***, there are no changes in: required resource contents for process-**N**; sum required resource content for process-***cp***; sum resource partition and sum required resource content for process-***np***,

$$\sum {}'\mathrm{R}_{Rcp} - \sum \mathrm{R}_{Rcp} = 0$$

$${}'\mathrm{R}_{RN} - \mathrm{R}_{RN} = 0$$

$$\sum {}'\mathrm{R}_{rnp} - \sum \mathrm{R}_{rnp} = 0$$

$$\sum {}'\mathrm{R}_{Rnp} - \sum \mathrm{R}_{Rnp} = 0$$

then,

$$-\sum \mathrm{R}_{rcp} = 0 + 0 + 0 + 0 + \mathrm{R}_{r\mathbf{N}} - {}'\mathrm{R}_{r\mathbf{N}}$$

Also: since $\sum \mathrm{R}_{rcp} \ll 0$,

$${}'\mathrm{R}_{r\mathbf{N}} \ll \mathrm{R}_{r\mathbf{N}}$$

Translation of hypotheses to biological outcomes

1. Consider that for the given hypothesis 1, significant reduction in the required resource content for cancer-related processes of the cancer cell, process-***cp***, can potentially manifest as one or a combination of biological phenomena:
    a. **Reduction in respective intensities of stimuli derived from surroundings:** Stimuli that would otherwise modulate process-***cp*** may be directly or indirectly affected by processes such that there are reductions in respective intensities of presenting

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stimuli. Thus, reduction in the extent of process-***cp***. An expected outcome of such diminished responses is reduction in required resource content for process-***cp***. This would increase the likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Two plausible mechanisms by which said reductions in intensities of stimuli can occur are:

i. Degradation of mediator(s) of stimuli prior to interaction with receptor/sensor aspects of process-***cp***.
ii. Sequestration of mediator(s) of stimuli prior to interaction with receptor/sensor aspects of process-***cp***.

b. **Reduction in respective intensities of [perceived] stimuli/modulators:** The ability to "sense" stimuli from the surroundings may be directly or indirectly affected by processes such that there are reductions in respective intensities of stimuli as perceived by the sensor/receptor aspects of process-***cp***. Thus, reduction in the extent of process-***cp*** (e.g. decrease in activity of enzymes) that may derive from stimuli. An expected outcome of such diminished responses is reduction in required resource content for process-***cp***. Thus, an increase in the likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Some plausible mechanisms by which such desensitization to stimuli may be achieved are:

i. Modification of receptors/sensors required for initiation and/or actuation of process-***cp.***
ii. Degradation of receptor/sensor aspects of process-***cp*** with potential reallocation of degradation products to effectors of process-***cp***.
iii. Repression or silencing of genes for receptor/sensor aspects of process-***cp.***

c. **Changes in proportionalities between intensities of presenting stimuli and resource requirements of cancer-related processes of the cancer cell:** The efficiency of effectors of process-***cp*** may be altered by processes, with the expected alteration being a reduction in the quantity of resources utilized by process-***cp*** in actuation of response(s) to given intensities of stimuli. Plausible mechanisms by which utilization of resources may be affected are:

i. Modulation of key effectors of process-***cp*** thus increasing the efficiency of said effectors.
ii. Splicing of mRNA with resultant increase in efficiency of translated effector products for process-***cp***.
iii. Isoform switching involving a switch to more efficient isoforms of effectors for process-***cp***.

2. Consider that for the given hypothesis 2, significant reduction in the required resource content for normal processes of cancer cells, process-***np***, can potentially manifest as one or a combination of biological phenomena:
   a. **Reduction in respective intensities of stimuli derived from surroundings:** Stimuli that would otherwise modulate process-***np*** may be directly or indirectly affected by processes such that there are reductions in respective intensities of presenting

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stimuli. Thus, reduction in the extent of process-***np*** that derive from presenting stimuli. An expected outcome of such diminished responses is reduction in required resource content for process-***np***. This would allow for more resources to be available for reallocation to process-***cp*** and thus increased likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Two plausible mechanisms by which reductions in intensities of stimuli can occur are:

i. Degradation of mediator(s) of stimuli prior to interaction with receptor/sensor aspects of process-***np***.
ii. Sequestration of mediator(s) of stimuli prior to interaction with receptor/sensor aspects of process-***np***.

b. **Reduction in respective intensities of [perceived] stimuli/modulators:** The ability to "sense" stimuli from the surroundings may be directly or indirectly affected by processes such that there are reductions in respective intensities of stimuli as perceived by the sensor/receptor aspects of process-***np***. Thus, reduction in the extent of process-***np*** that may derive from stimuli. The expected outcome of such diminished responses is reduction in required resource content for process-***np***. This would allow for more resources to be available for reallocation to process-***cp*** and thus increased likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Some plausible mechanisms by which such desensitization may be achieved are:

i. Modification of receptors/sensors required for initiation and/or actuation of process-***np*.**
ii. Degradation of receptor/sensor aspects of process-***np*** with potential reallocation of degradation products to receptor/sensor and effector aspects of process-***cp***.
iii. Repression or silencing of genes for receptor/sensor aspects of process-***np*.**

c. **Changes in proportionalities between intensities of presenting stimuli and resource requirements of normal processes of the cancer cell:** The efficiency of effectors of process-***np*** may be altered by processes, with the expected alteration being a reduction in the quantity of resources utilized by process-***np***. This would allow for more resources to be available for reallocation to process-***cp*** and thus increased likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Plausible mechanisms by which utilization of resources may be affected are:

i. Modulation of key effectors of process-***np*** thus increasing the efficiency of these effectors.
ii. Splicing of mRNA with a resultant increase in efficiency of translated effector products for process-***np***.
iii. Isoform switching involving a switch to more efficient isoforms of effectors for process-***np***.

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3. Consider that for the given hypothesis 3, the significant reduction in the partition remainder for process-***np*** can manifest as one or a combination of biological phenomena:
    a. **Decrease in the partition remainder with decreased surplus:** The partition remainder for process-***np*** may be directly or indirectly affected such that resources are reallocated to process-***cp***; with little to no change in quantity of effector aspects of process-***np***. For example, a net flux of metabolites and/or other intermediates and therefore their carbon skeletons may occur from process-***np*** and into process-***cp*** with little to no change in the concentrations of effectors of process-***np***. Thus decreasing the flux of intermediates through process-***np***.

    b. **Decrease in the partition remainder with deficit or increasing deficit.** The partition remainder of process-***np*** may be directly or indirectly affected such that there is a deficit in the partition remainder of process-***np***. Again, in agreement with the conservation laws for energy and mass, for such increase in deficit to occur under conditions of constant total resource content, additional resources must derive from sources not considered to be partitions of the total available resource content for processes of the cancer cell. An example is reduction in quantity of effector aspects of process-***np*** for a fixed quantity of sensor/receptor aspects of process-***np***. The noted reduction being as a result of degradation of effector aspects of process-***np***; with reallocation of breakdown products to process-***cp***. Thus an increase in likelihood of actuation of process-***cp*** under conditions of diminished total resource content.

4. Consider that for the given hypothesis 4, the significant reduction in the required resource content for process-**N** can manifest as one or a combination of biological phenomena:
    a. **Reduction in respective intensities of stimuli derived from surrounding:** Stimuli that would otherwise modulate process-**N** may be directly or indirectly affected by processes, such that there are reductions in respective intensities of presenting stimuli. Thus, reduction in the extent of process-**N** that derive from presenting stimuli. An expected outcome of such diminished responses is a reduction in required resource content for process-**N**. This would allow for more resources to be available for reallocation to process-***cp*** and thus increased likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Two plausible mechanisms by which reductions in intensities of stimuli can occur are:
        i. Degradation of mediator(s) of stimuli prior to interaction with receptor/sensor aspects of process-**N**.
        ii. Sequestration of mediator(s) of stimuli prior to interaction with receptor/sensor aspects of process-**N**.

    b. **Reduction in respective intensities of [perceived] stimuli/modulators:** The ability to "sense" stimuli from the surroundings may be directly or indirectly affected by processes such that there are reductions in respective intensities of stimuli as perceived by the sensor/receptor aspects of process-**N**. Thus, an expected reduction in the extent of process-**N** that may derive from stimuli. The outcome of such

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diminished responses is reduction in required resource content for process-**N**. This would allow for more resources to be available for reallocation to process-***cp*** and thus increased likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Some plausible mechanisms by which such desensitization may be achieved are:

i. Modification of receptors/sensors required for initiation and/or actuation of process-**N.**
ii. Degradation of receptor/sensor aspects of process-**N** with potential reallocation of degradation products to receptor/sensor and effector aspects of process-***cp***.
iii. Repression or silencing of genes for receptor/sensor aspects of process-**N.**

c. **Changes in proportionalities between intensities of presenting stimuli and resource requirements of** process-**N:** The efficiency of effectors of process-**N** may be altered by processes, with expected alterations being reduction in the quantity of resources utilized by process-**N**. This would allow for more resources to be available for reallocation to process-***cp*** and thus increased likelihood of actuation of process-***cp*** under conditions of diminished total resource content. Plausible mechanisms by which utilization of resources may be affected are:

i. Modulation of key effectors of process-**N** thus increasing the efficiency of affected effectors.
ii. Splicing of mRNA with a resultant increase in efficiency of translated effector products for process-**N**.
iii. Isoform switching involving a switch to more efficient isoforms of effectors for process-**N**.

5. Consider that for the given hypothesis 5, the significant reduction in the partition remainder for process-**N** can manifest as one or a combination of biological phenomena:
   a. **Decrease in the partition remainder with decreased surplus:** The partition remainder for process-**N** may be directly or indirectly affected such that resources are reallocated to process-***cp***; with little to no change in quantity of effector aspects of process-**N**. For example, a net flux of metabolites and/or other intermediates and therefore their carbon skeletons may occur from process-**N** and into process-***cp*** with little to no change in the concentrations of effectors of process-**N**. Thus decreasing the flux of intermediates through process-**N**.

   b. **Decrease in the partition remainder with deficit or increasing deficit.** The partition remainder of process-**N** may be directly or indirectly affected such that there is a deficit in the partition remainder of process-**N**. Again, in agreement with the conservation laws for energy and mass, for such increase in deficit to occur under conditions of constant total resource content, additional resources must derive from sources not considered to be partitions of the total available resource content for processes of the normal cell. An example is reduction in quantity of effector aspects of process-**N** for a fixed quantity of sensor/receptor aspects of process-**N.** The noted

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reduction being as a result of degradation of effector aspects of process-**N**; with reallocation of breakdown products to process-***cp***. Thus an increase in likelihood of actuation of process-***cp*** under conditions of diminished total resource content.

These breakdown products may derive from structural and functional polymers such as: Nucleic acids, fatty acids and other lipid derivatives, saccharides, and/or amino acids and/or their polymeric forms (globular and fibrous peptides/proteins). The clinical finding of cachexia in patients with advanced cancers may *partly* reflect such increasing deficits in partition remainder at a global scale.

On the Warburg effect (Aerobic glycolysis):

Here we shall give a brief description of aerobic glycolysis. For extensive discussions and reviews refer to the following cited works. Otto Warburg and colleagues discovered that cancer cells exploit glycolysis, an anaerobic form of glucose breakdown, even in the presence of ample oxygen supply [**1-4**]. The so-called Warburg effects, or in more technical terms aerobic glycolysis: There are many explanations as to why aerobic glycolysis is exploited by cancer cells (refer to [**6**] for a review of the working proposals). An interesting explanation which links aerobic glycolysis to the defining phenotype of tumor cells, cell division, is that glycolysis, as opposed to oxidative phosphorylation, allows for shunting of carbon skeletons into biosynthesis pathways. As these carbon skeletons are essential for neoplastic cell growth and/or division [**7-12**]. Hence the increased preference of tumor cells for glycolysis over oxidative phosphorylation. However, the question to be posed is:

I. Whether the increased flux through the glycolytic pathway occurs because of a requirement for an increased flux of carbon skeletons into biosynthesis pathways. Refer to figure 2A.
II. Whether the increased flux of carbon skeletons into biosynthesis pathways occurs because of a requirement for an increased flux through the glycolytic pathway. Refer to figure 2B.

For the former, the increased flux into biosynthesis pathways is the impetus for-, as opposed to a consequence of-, increased flux through glycolytic pathway. For the latter, the increased flux into biosynthesis pathways is as a consequence of-, as opposed to an impetus for-, increased flux through the glycolytic pathway.

One way to differentiate these possibilities would be to determine whether or not there are other avenues or adjoining pathways that yield flux into biosynthesis pathways. If other such pathways do exist, and if all pathways contribute near evenly to flux, then it is likely that biosynthesis is the impetus. If other such pathways do exist, however, with flux mainly deriving from a fraction of these pathways, then it is likely that flux into pathways for biosynthesis occur as a consequence of increased flux through the said fraction of total pathways. However, this simple scheme can be complicated by phenomena stated in hypotheses 2 and 3.

Based on hypotheses 2 and 3, prolonged, uneven utilization of some pathways over others (figures 2C & 2D) in the context of a limited total available resource content, can eventually diminish flux

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through poorly utilized pathways. As the noted reduction in flux results from reduction in pathway intermediates, and/or reduction in sensor and effector aspects of pathways, with reallocation of carbon skeletons to said aspects of highly utilized processes. Thus with resorption of some pathways, flux into biosynthesis pathways would only derive from those pathways highly utilized for the prolonged duration.

Based on this line of reasoning, aerobic glycolysis should result following prolonged metabolism of glucose under hypoxic to near anoxic conditions. As the utilization of oxidative phosphorylation under conditions of low oxygen tension is contracted. An expected outcome is resorption of sensors and effectors of oxidative phosphorylation. Thus, immediately following restoration of normoxic conditions, utilization of oxidative phosphorylation would remain diminished.

We must reiterate that, based on this line of reasoning, prolonged and significant flux through glycolysis in addition to prolonged exposure to hypoxic conditions, should have previously occurred in order for aerobic glycolysis to later manifest. As this would ensure uneven utilization of the glycolytic pathway over oxidative phosphorylation. Effects of hypoxia on metabolic switch to glycolysis in the context of cancer metabolism is considered in detail in the following reviews [**10**, **13-15**].

ADDITIONAL CONSIDERATION:

A possible relationship between genomic instability and resource parameters for cancer cells.

Based on hypotheses 2 and 3, if highly utilized processes exist under conditions of diminished total resource content, and under such conditions DNA repair processes are poorly utilized (as may result from decreased frequency of DNA base changes or modification), then a potential reduction in sensor and effector aspects of DNA repair processes can occur. With reallocation of carbon skeletons to said aspects of highly utilized processes. The result of such reduction in carbon skeletons of DNA repair processes would be a reduction in the ability of these processes to sense and/or affect correction of DNA mutations when such mutations arise. Thus, a decline in fidelity of DNA repair processes. In the context of decreased fidelity of DNA repair processes, the expected outcome is a greater than normal frequency of mutations. Of DNA segments predisposed to such increase in frequency of mutations, genes for sensors and effectors of DNA repair processes may be involved. In this sense, it is important to revisit the question on the one-sided cause and effect relationships between initial gene mutations and metabolic phenotypes of neoplastic cells, respectively.

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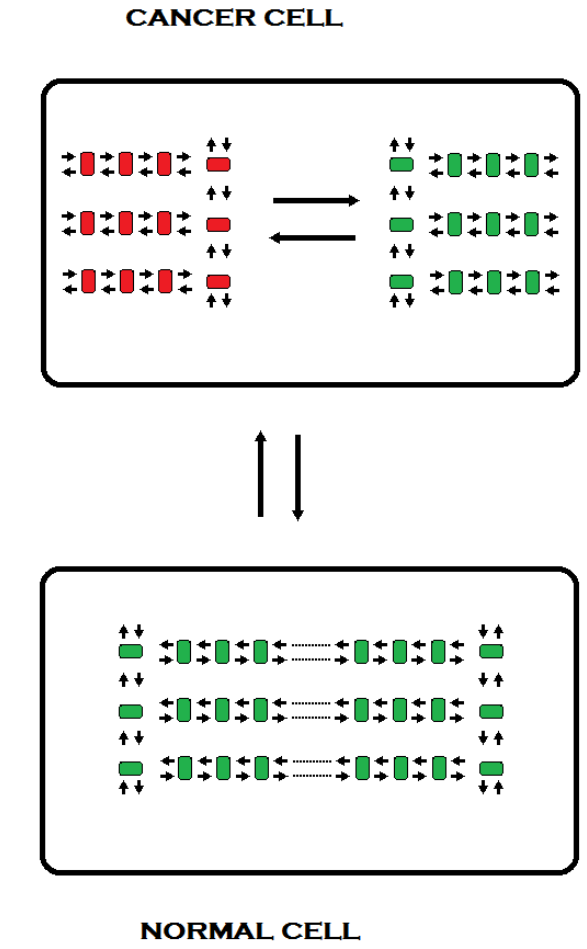
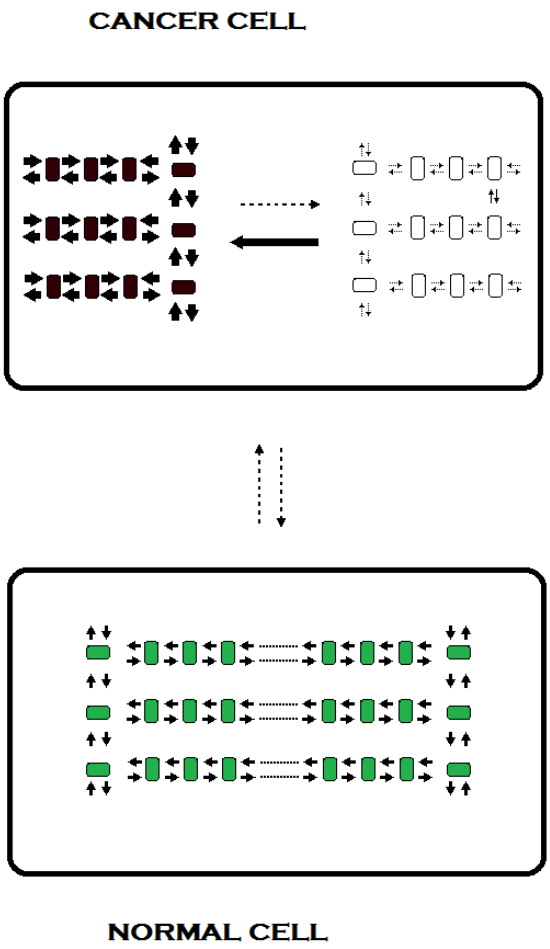


A.



B.

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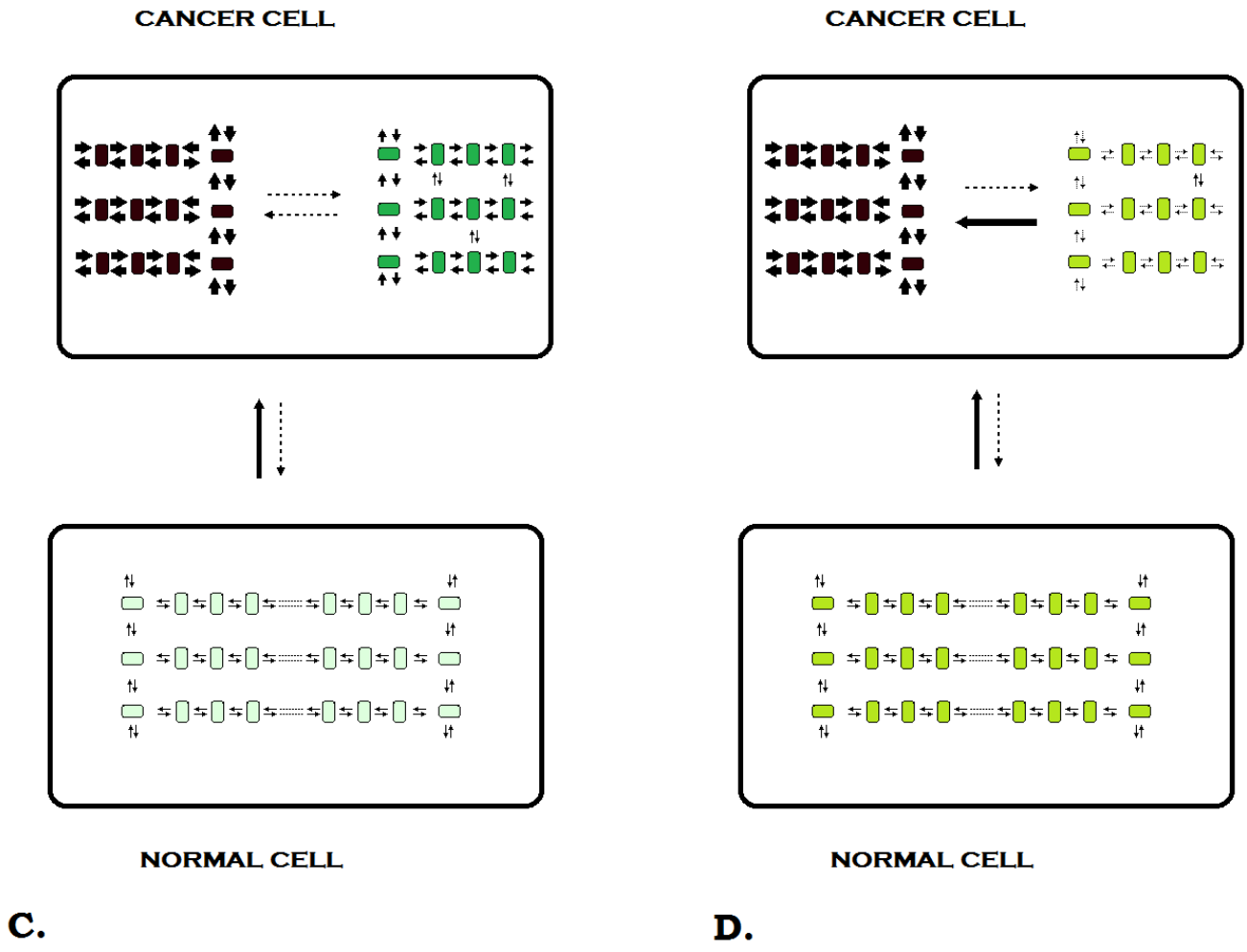

Figure 1: Representation of cancer and normal cell processes. Flux of intermediates within cancer-related processes of cancer cell (Red rectangles), normal processes of cancer cell (green rectangles), and processes of normal cell (green rectangles); with direction of flux indicated (small arrows). Flux of intermediates *between* cancer-related processes and normal processes of cancer cell; with direction of flux indicated (long horizontal arrows). Flux of intermediates *between* processes of cancer cell and processes of normal cell with direction of flux indicated (long vertical arrows). The magnitude of flux is represented as size, thickness and/or continuity of arrows (solid vs dotted). Each color-coded rectangle represents the pool of sensors and effectors at individual steps of each process. The quantity of sensors and effectors in each rectangle is represented as luminance; with darker colors indicating lower luminance and therefore higher quantities of said aspects, and lighter colors indicating higher luminance and therefore lower quantities of said aspects. **Figure 1A.** Depicts relationships between cancer-related processes of cancer cell, normal processes of cancer cell, and processes of normal cell. Note the even exchange of resources for all three processes. Also note the luminance of all rectangles of processes. We shall consider this as the reference for comparison. **Figure 1B**. A representation of hypotheses 2 and 3 only, and depicts a net reallocation of resources from normal processes of cancer cell to cancer-related processes of cancer cell. Reduction in flux at normal process of cancer cell is represented using thin, dotted arrows. Reduction in sensor and effector aspects of normal processes of cancer cell is represented as an increase in luminance, as compared to reference. Increase in flux at cancer-related processes is represented as an increase in thickness of small arrows, as compared to reference. Increase in sensor and effector aspects of cancer-related processes is represented as a decrease in luminance, as compared to reference. Also note the reduction in flux between cancer and normal cell (thin, dotted long vertical arrows). This increases reliance of cancer-related processes on resources of normal processes of

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cancer cell. Hence the significant reduction in sensors and effectors of normal processes –as indicated by the significant increase in luminance of rectangles for normal processes of cancer cell. **Figure 1C**. A representation of hypotheses 3 and 4 only, and depicts a net reallocation of resources from processes of normal cell to processes of cancer cell, notably cancer-related processes. Reduction in flux at processes of normal cell is represented using thin, dotted small arrows. Reduction in sensor and effector aspects of processes of normal cell is represented as an increase in luminance, as compared to reference. Increase in flux at cancer-related processes is represented as an increase in thickness of small arrows, as compared to reference. Increase in sensor and effector aspects of cancer-related processes is represented as a decrease in luminance, as compared to reference. Also note the reduction in flux between cancer-related processes and normal processes of cancer cell (thin, dotted long horizontal arrows). This increases reliance of cancer-related processes on resources of processes of normal cell. However, being that there are more processes of normal cell as compared to normal processes of cancer cell, the reduction in sensors and effectors of processes of normal cell is not as significant. Hence the lower luminance than that of normal processes of cancer cell in figure 1B. **Figure 1D**. Depicts a net reallocation of resources both from processes of normal cell and normal processes of cancer cell to cancer-related processes. Reduction in flux at processes of both normal cell and normal processes of cancer cell are represented using thin, dotted small arrows. Reduction in sensor and effector aspects of processes of normal cell and normal processes of cancer cell is represented as an increase in luminance, as compared to reference. Increase in flux at cancer-related processes is represented as an increase in thickness of small arrows, as compared to reference. Increase in sensor and effector aspects of cancer-related processes is represented as a decrease in luminance, as compared to reference. Since cancer-related processes rely on resources of processes of normal cell and normal processes of cancer cell, the net reduction in sensors and effectors of processes of normal cell and normal processes of cancer cell is far less than the case of either one of these processes alone. Hence the lower luminance than either normal processes of cancer cell or processes of normal cell alone. Compare to figure 1B and figure 1C.

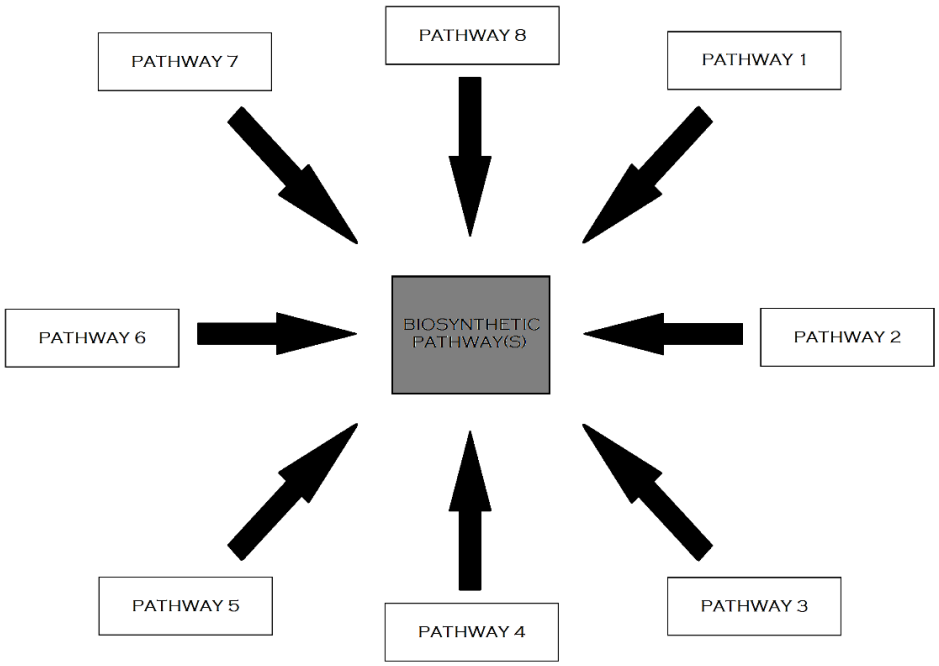

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Figure 2A. Grey-colored boxes represent the impetus for flux. In this scenario, the requirement for increased flux of carbon skeletons for biosynthesis pathways is satisfied by flux (black arrows) from all adjoining pathways.

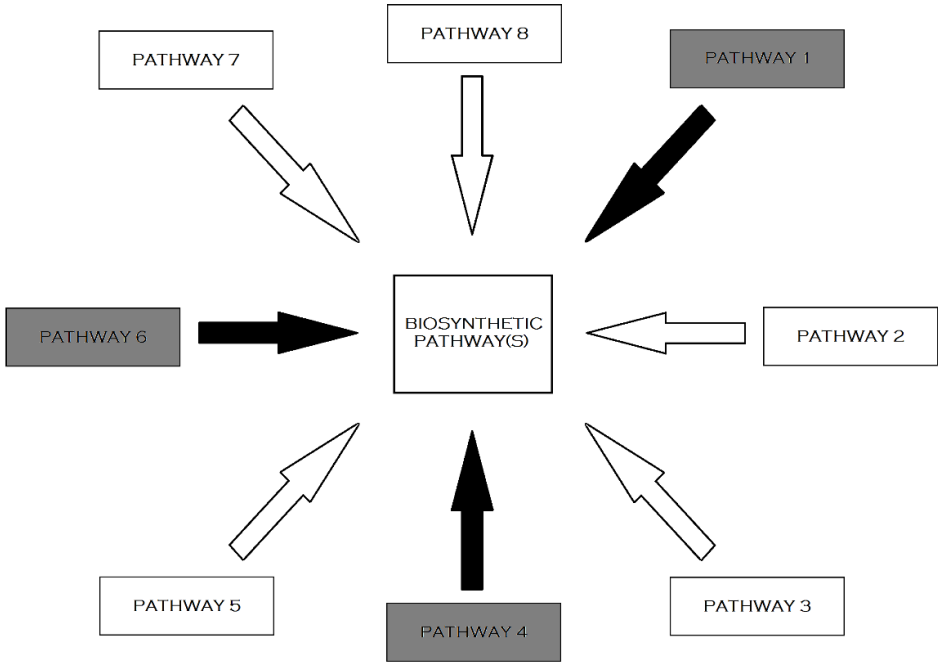

Figure 2B. Grey-colored boxes represent the impetus for flux. In this scenario, the increased flux of carbon skeletons into biosynthesis pathways occurs as a consequence of increased flux (black arrows) from a fraction of adjoining pathways; pathways 1, 4, and 6.

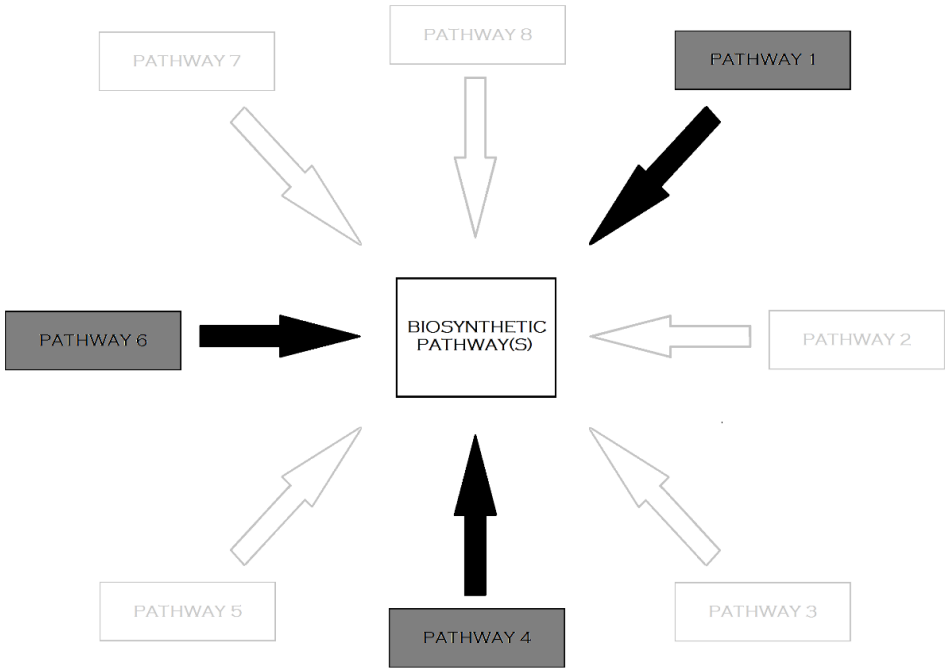

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Figure 2C. Grey-colored boxes represent the impetus for flux. In this scenario, flux of carbon skeleton into and through biosynthesis pathways occur as a consequence of increased flux of carbon skeletons through and from pathways 1, 4, and 6. However, unlike figure 2, prolonged flux through pathways 1, 4, and 6 under conditions of limited resources results in diminished sensor and effector aspects of pathways 2, 3, 5, 7, and 8.

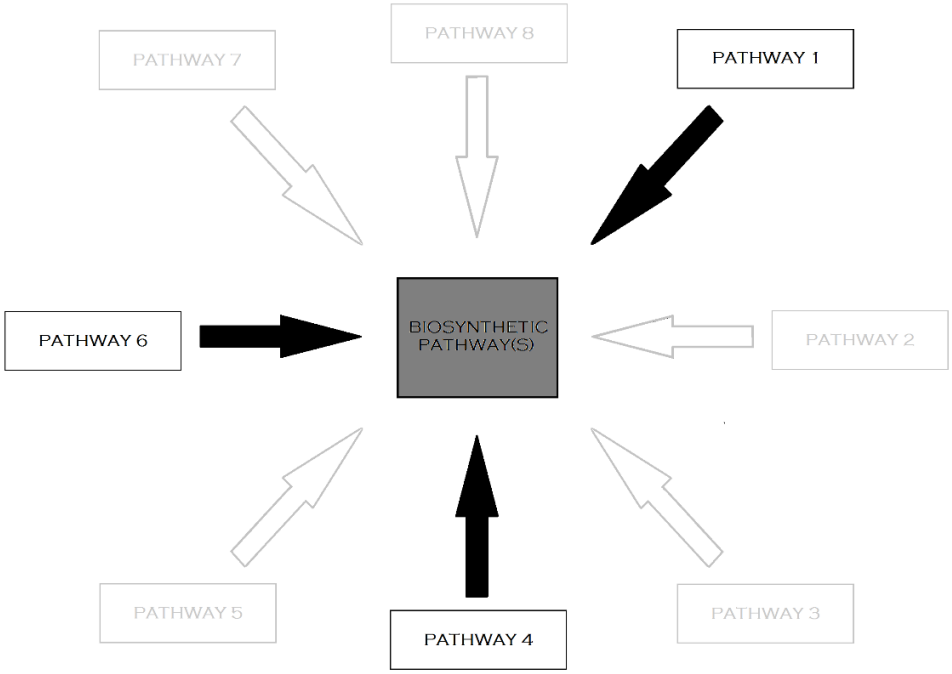

Figure 2D. Grey-colored box represents the impetus for flux. In this scenario, the impetus for flux of carbon skeleton is an increased requirement of flux of carbon skeletons into and through the biosynthesis pathways. This need is thus satisfied by increased flux through and from all pathways. However, unlike figure 1, prolonged flux through pathways 1, 4, and 6 under conditions of limited flux through other pathways results in resorption of sensor and effector aspects of poorly utilized pathways 2, 3, 5, 7, and 8; with reallocation of resources to highly utilized pathways which include pathways 1, 4, and 6.

Reference:

1) Warburg, O. (1925) The metabolism of carcinoma cells. J. *Cancer Res*. 9, 148-163.

2) Warburg, O., Wind, F., & Negelein, E. (1927). The metabolism of tumours in the body. *The Journal of general physiology*, 8(6), 519-530.

3) Warburg, O. 1956b. On the origin of cancer cells. *Science* 123, 309-314.

4) Warburg, O. 1956b. On respiratory impairment in cancer cells. *Science* 124, 269-270.

PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.2533v1 | CC BY 4.0 Open Access | rec: 16 Oct 2016, publ: 16 Oct 2016

5) Finkel, T., Serrano, M., & Blasco, M. A. (2007). The common biology of cancer and ageing. *Nature*, 448(7155). 767-774.

6) Liberti, M. V., & Locasale, J. W. (2016). The Warburg effect: how does it benefit cancer cells? *Trends in biochemical sciences*, 41(3), 211-218.

7) Potter, V. R. 1958. The biochemical approach to the cancer problem; proc. 17, 691-697.

8) Vander Heiden, M.G., Cantley, L.C., Thompson, C. B. (2009), Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 324, 1029-1033.

9) Koppenol, W. H., Bounds, P. L., & Dang, C. V. (2011). Otto Warburg's contributions to current concepts of cancer metabolism. *Nature Reviews Cancer*, 11(5), 325-337.

10) DeBerardinis, R. J., Lum, J. J., Hatzivassiliou, G., & Thompson, C. B. (2008) The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell metabolism*, 7(1), 11-20.

11) Levine, A. J., & Puzio-Kuter, A. M. (2010). The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes. *Science*, 330(6009), 1340-1344.

12) Dang, C. V. (2012). Links between metabolism and cancer. Genes & development, 26(9), 877-890.

13) Semenza, G. L. (2010). HIF-1: Upstream and downstream of cancer metabolism. *Current opinion in genetics and development*, 20(1), 51-56.

14) Hanahan, D., & Weinberg, R. A. (2011). Hallmark of cancer: The next generation. *Cell*, 144(5), 646-674.

15) Cairns, R. A., Harris, I., McCracken, S., & Mak, T. W. (2011, January). Cancer cell metabolism. In *Cold Spring Harbor symposia on quantitative biology* (vol. 76, pp. 299-311). Cold Spring Harbor Laboratory Press.

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