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# Metabolic Reprogramming and Cancer: 2022

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## Abstract

Cancer is a disease that is considered a silent killer. Early therapeutic interventions can lead to a cure for the disease. The causal reasons for cancer are many. At the molecular level, metabolic reprogramming is a process for self-renewal and survival by cancer cells. Dietary constituents are an important factor that leads to metabolic transitions and induces cellular reprogramming. The process is initiated by inducing changes in metabolism leading to the supply of nutrients and energy to the tumour cells, and this is linked to the induction of EMT and VM. Thermodynamic changes that get distinguished in proliferating and non-proliferating cells might also be a possible reason for cellular reprogramming. The entire process of metabolic reprogramming is linked to diet-driven changes and bioenergetics. The work here elucidates in brief the dependency of metabolic reprogramming on different factors, or stages and highlights possibilities for therapeutic interventions as part of cancer therapeutics.

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**Running title:** Metabolic reprogramming in cancer

## Introduction

The silent killer which goes by name of cancer, if detected at an early stage, can lead to a cure by therapeutic intervention with maximum chances. Though model-based year-wise predictions of cancer trends cannot be a possible eye opener as the incidences vary from year to year for manifold reasons, there might be 1.9 million new cancer cases as diagnosed along with 609,360 deaths in 2022 at USA.<sup>[1]</sup> Globally in 2020, there was 10 million death due to cancer.<sup>[2]</sup> The year 2020 reported 18.1 million cancer cases worldwide with 9.3 million in men and 8.1 million in women.<sup>[3]</sup> The incidence of cancer cases worldwide rose to 21 % with 16 % deaths from 2010-19 and cancer incidence in India has increased at an annual

average annual rate of 1.1-2 % during 2010-19.<sup>[4]</sup>

India occupies the third position worldwide in cancer incidences,<sup>[5]</sup> and there are reports of the rise in breast cancer in men in India.<sup>[6][7]</sup> India has reported an estimate of around 40 lakh cancer cases and 22.54 lakh deaths from 2018-2020.<sup>[8]</sup> The increase in the burden of cancer has been linked to socio-demographic index and food intake apart from other factors.<sup>[9]</sup>

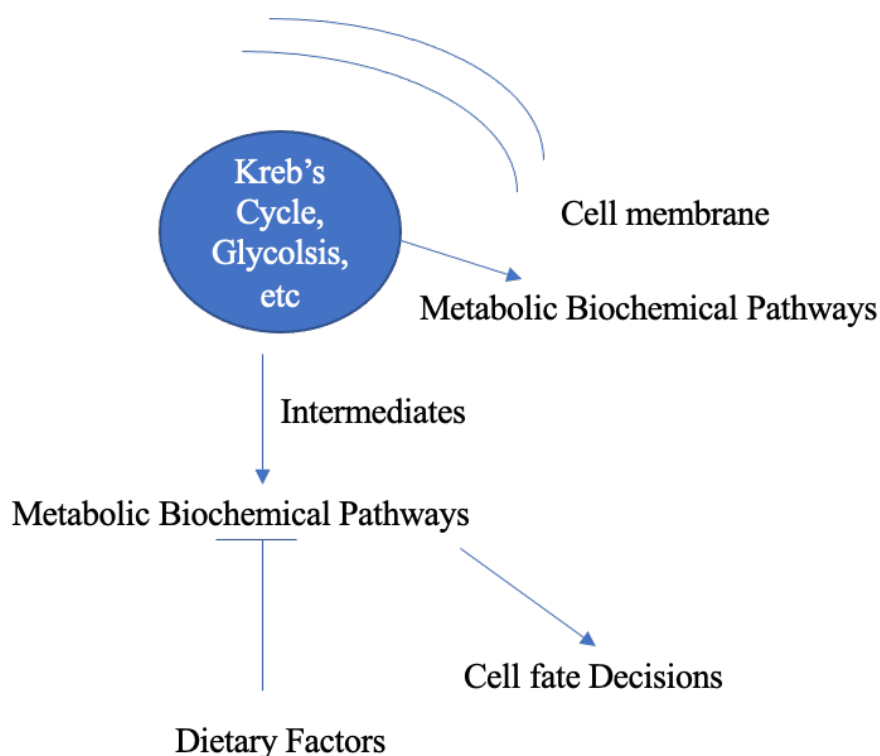
Cancer is a disease that can affect any body part, and a recognized phenomenon of cancer is the very fast creation of abnormal cells growing beyond their usual boundaries, which can lead to metastasis. Early detection and screening can help to reduce mortality due to cancer.<sup>[10]</sup> Diet can be an important component to reducing the cancer aggressiveness and progression,<sup>[6][11]</sup> but it is of high importance that diet as a therapeutic intervention must progress along with the mode of primary treatment. Diet makes cells undergo metabolic programming in normal cells as well as reprogramming in cancer cells, wherein the latter is a hallmark of malignancy!<sup>[12]</sup> Dietary restriction also leads to metabolic reprogramming and can be thought of as a therapeutic approach as the process extends the lifespan of an organism and the process is linked to energy intake restriction without essential nutrient deficiency.<sup>[13]</sup>

The tumour microenvironment (TME) involves the interaction of metabolic reprogramming with tumour cells and non-tumour cells, suggesting therapeutic strategies to target metabolic interventions.<sup>[12]</sup> With the growing incidences of cancer, it is necessary to look into the metabolic reprogramming occurring in cancer cells and the possible dietary interventions along with the first-line therapy as medical care for cancer patients.<sup>[14]</sup> Additionally, targeted therapy adapted in cancer cure can either target tumour cells to be killed, or can help tumour cells to grow in TME. Thus, targeted therapeutics can either act as cytostatic and or as precision medicine, as they act on specific molecular targets.<sup>[15]</sup> Such therapeutics might be influenced by food intake and diet, followed by metabolic reprogramming that also leads to cellular reprogramming. This review summarizes the influence of diet on metabolic reprogramming and possible targets as a therapeutic intervention in cancer cure. The entire process of metabolic reprogramming is dependent upon many factors and processes, or pathways, referred to as 'stages' in the present manuscript, affected by dietary components. Dietary food intake components can be from plant, animal, and microbial sources, and is referred to as 'dietary factors' as food component representative of any food source in this review. Detailed discussion on the subtopics is beyond the scope of this review, and the current review in a concise way is highlighting the stages, and usage of dietary components that can influence metabolic reprogramming and cell fate decisions.

## Metabolic reprogramming

Metabolic reprogramming leads to the development and progression of cancer!<sup>[16]</sup> The TME rich with a heterogenous environment associated with the 'Warburg effect' shows a fast response of tumour cells to hypoxia and hypo-nutrient conditions. The TME is characterized by reduced pH, lessened oxygen apart from various metabolic changes, which combinatory leads to changes in immune cells in the microenvironment, increase in various tumour-related immune cells, decrease in inhibitory cells, and release of various toxic metabolites.<sup>[17]</sup> Intermediates from biochemical pathways also lead to metabolic reprogramming (Figure 1). This leads to changes in tumour cell bioenergetics, and the process named

'metabolic reprogramming' is a necessity for malignancy and tumour progression. Additional metabolic reprogramming of cancer stem cells (CSC) makes CSC show metastatic potential leading to resistance against cancer therapeutics.<sup>[18][19]</sup>



**Figure 1.** Intermediates from the biochemical pathways and metabolic reprogramming, regulated by dietary factors.

Intermediates generated from Kreb's cycle, glycolysis, etc. from biochemical pathways can lead to metabolic reprogramming, as well as biochemical cycles can directly lead to metabolic reprogramming. The process of metabolic reprogramming can be inhibited by dietary factors.

It is not only metabolic changes, but also epigenetic changes that help in the metabolic adaptation of the cancer cells in TME. Additionally, non-tumour cells in TME also undergo metabolic reprogramming.<sup>[12]</sup>

The altered metabolic pathway sustains a pool of nutrients and energy for the cancer cells to grow. Furthermore, metabolic pathway activity in a such cancerous cellular environment is influenced by transcriptional programs involving oncogenes and tumour suppressor genes.<sup>[20]</sup>

## Stages

Metabolic reprogramming induces cellular reprogramming and initiation of cancer in pathological conditions. The process involves phenomenal changes referred to herein as 'stages', or 'steps'. A detailed discussion of the steps is beyond the scope of this review, and a concise view of the stages is discussed below.

## Factors involved in metabolic reprogramming

Advances in biological research have proved that many of the signaling pathways changed by gene mutations regulate cancer cell metabolism, and can lead to conditions, like aerobic glycolysis or the 'Warburg effect'. Reports evidence aberrations in the proto-oncogenes, *Myc* or *Ras* leading to glycolytic phenotype by HIF 1 $\alpha$  – mediated metabolic reprogramming.<sup>[21]</sup> Key regulators of the processes are three transcription factors, namely HIF-1, c-Myc, and p53. As an example, the risk of malignant tumour occurrence increase due to changes in enzyme activity of  $\alpha$ -ketoglutarate-dependent dioxygenase resulting from the increased levels of 2-hydroxyglutarate due to mutations in gene encoding isocitrate dehydrogenase.<sup>[22]</sup> Additionally, metabolic reprogramming of breast cancer cells and fibroblast activation occurs due to the transcription factor POU1F1 by regulating gene encoding lactate dehydrogenase A.<sup>[23]</sup>

An example of complexity arising due to transcription factor defect is MODY resulting due to alterations in *HNF1 $\alpha$* . MODY1 results due to alterations in *HNF4 $\alpha$* , whereas MODY4 is due to mutations in *PDX1* and insulin synthesis defect.<sup>[23][24]</sup> Apart from the internal factors, there are also external factors, like cytokine IL-4/IL-4R signaling leads to elevated uptake of glucose and glutamine via their transporters to stimulate breast cancer cell growth. Furthermore, alteration of functions of metabolic nodes due to IL-6, TNF  $\alpha$ , IL-17, and IL-1 $\beta$  are seen in patients tumourigenic for breast, pancreatic, and colon.<sup>[25]</sup> The IL-6 in TME also activates the JAK-STAT3 pathway for immune, epithelial and endothelial cells.<sup>[26][27][28]</sup> Besides this, cytokines and chemokines can also mediate metabolic interactions between host and tumour cells in TME. There can be hormone receptors also which act as transcription factors, like androgen and estrogen receptors in breast cancer. Metabolite cross-feeding also leads to tumourigenesis.<sup>[29][30]</sup>

The T-cell activation induces transcription factors, HIF 1 $\alpha$  and Myc, and the absence of Myc stops activated glycolysis and glutaminolysis in T cells. HIF 1  $\alpha$  plays role in the regulation of immune cell effector functions, and also plays important role in the maturation of dendritic cells and T cell activation.<sup>[21]</sup>

However, Myc-based metabolism was seen to be linked to the polyamine biosynthesis via glutaminolysis, suggesting a myc-dependent metabolic transcriptome drives metabolic reprogramming in activated, primary T lymphocytes.<sup>[31]</sup> HIF induction leads to the expression of Carbonic anhydrase IX (CA IX), monocarboxylate transporter 4, and programmed death ligand 1, wherein CA IX is needed for tumour progression under conditions of hypoxia.<sup>[21]</sup> Metabolic reprogramming in cancer is helped by another transcription factor, Nrf 2 (Nuclear factor erythroid-2–related factor-2).<sup>[32]</sup>

Thus, disturbances in the metabolic activities due to environment, mutation, and metabolic insults affect transcription at the level of epigenetic and transcriptional activities leading to a significant effect on oncogenesis.<sup>[33]</sup>

The long non-coding RNAs also modulate metabolic reprogramming and cancer progression.<sup>[34]</sup> Researchers also have

observed the role of ubiquitination and deubiquitination in tumour cell metabolic reprogramming, especially dysregulation of these processes leads to cancer.<sup>[35]</sup> Hindrances to mitochondrial apoptosis is an additional player in the cancer initiation and progression.<sup>[36]</sup> Metabolites by themselves can prove to be oncogenic by interfering with cell signaling as well as inhibiting cell differentiation.<sup>[37]</sup>

## Metabolic reprogramming and cytoskeletal changes

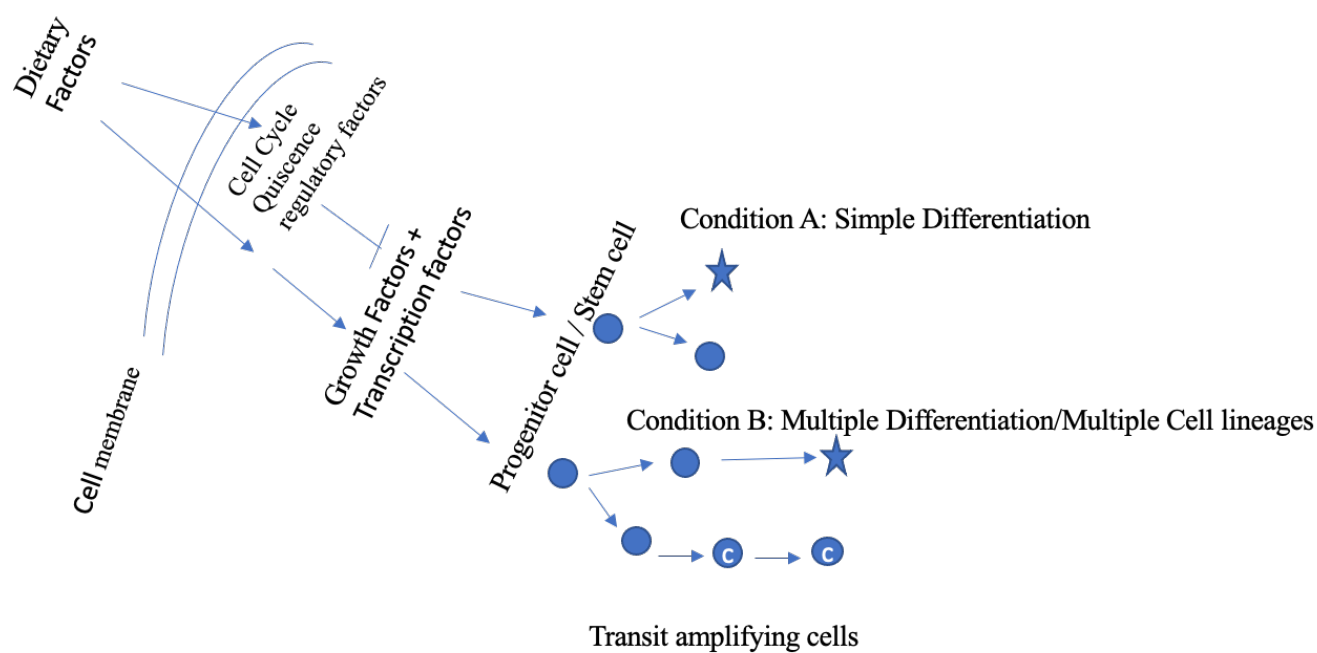
Metabolic reprogramming is a part of physiological cell proliferation and tumourigenesis.<sup>[38]</sup> Cellular growth and proliferation is also linked to changes in cytoskeletal dynamics of a cell. The cytoskeleton also plays important role in tumour cell aggressiveness and EMT.<sup>[39]</sup> Mitochondrial Hsp 90 is one of the important mediators of tumour cell motility when nutrients are limited in human glioblastoma, prostate, lung, breast, melanoma, and fibroblast cell lines, which in turn also acts as the upstream regulator tumour cell bioenergetics. In a nutshell, cytoskeletal dynamics, including the release of cell motility factor, FAK is controlled by metabolic forces.<sup>[40]</sup>

## Cell fate decisions

Cell fate decisions are inter-twinned with metabolic shifts and are essential for the development of pluripotency.<sup>[41]</sup> Metabolic reprogramming also plays important role in cell fate transitions and is essential for cell differentiation at the embryonic stage, as well as in tumour development and progression. It is not only the metabolic networks, but also mitochondrial distribution that acts to regulate the divisional balance between stem cells in asymmetric and symmetric divisions, finally affecting tissue homeostasis.<sup>[42]</sup>

Alterations in metabolic activities can affect post-translational modifications, by affecting gene expression for cell differentiation. This helps in regulating not only the cell fate decisions, but also epigenetic modifications.<sup>[43]</sup>

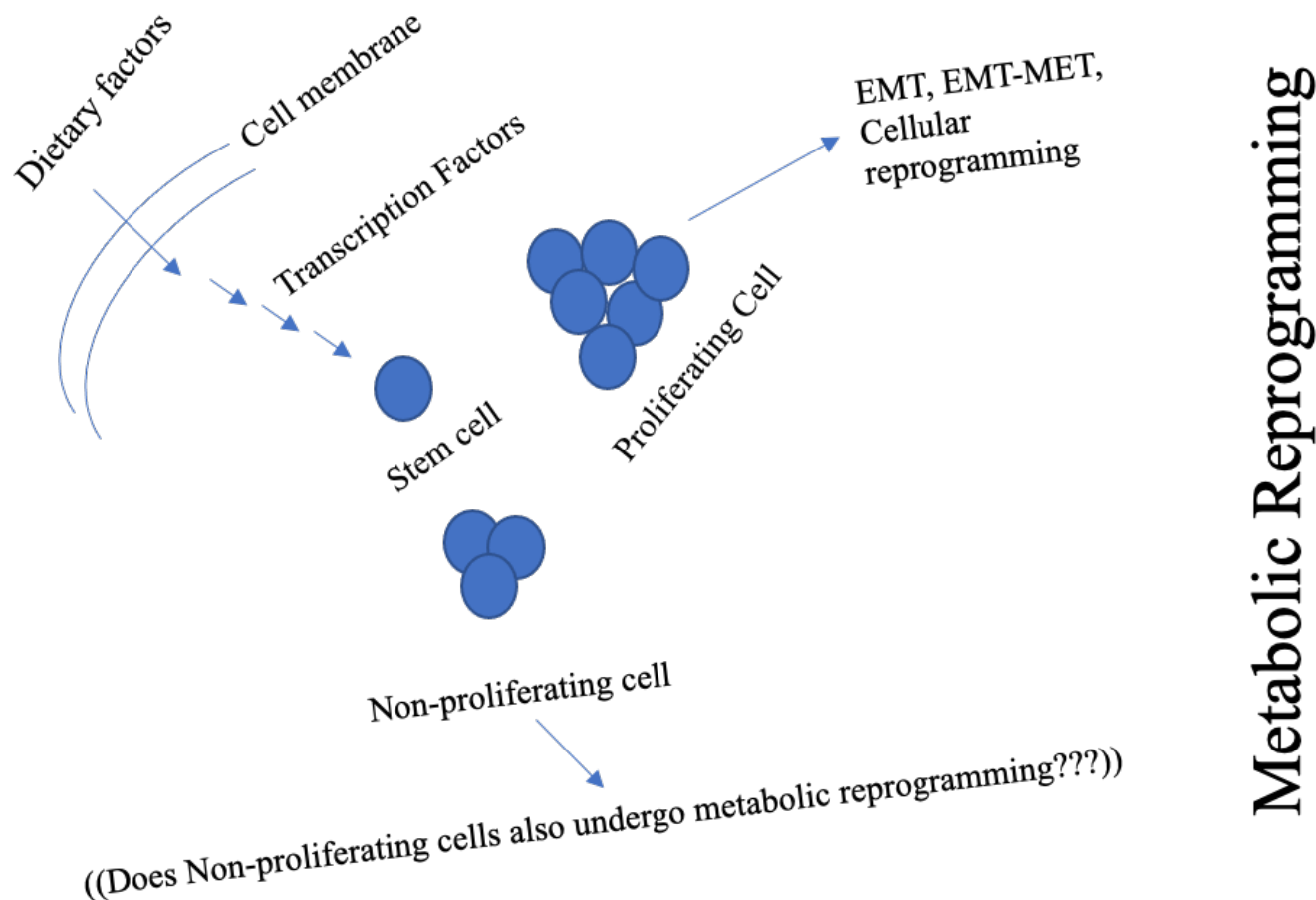
Dietary factors regulate cellular proliferation and cell fate decisions by metabolic shifts, by affecting functions of cell cycle quiescence factors (Figures 2 and 3). These processes lead toward EMT and EMT-MET.



Symbols used for representation of different cell lineages: circles as whole or with 'c' or star shaped: ● ●c ★

**Figure 2.** Illustrative mechanism for dietary factors to regulate cell fate decisions.

Dietary factors can either lead to cellular quiescence or allow cell cycle to proceed leading to the generation of stem cells and multiple cell lineages.



**Figure 3.** Dietary factors regulates proliferation of cells.

Dietary factors can lead to the generation of stem cells via transcription factors, and growth factors, etc. Stem cells can lead further lead to the generation of either proliferating cell, or non proliferating cell. Proliferating cells can undergo EMT, or EMT-MET or cellular reprogramming,, but it is not clear if non-proliferating cells also undergo metabolic reprogramming.

Networking between cell organelles, like lysosomes, also plays a critical role in metabolic transitions and fate decisions of stem cells for defining cell identity.<sup>[44]</sup> In brief, controlling factors for cell fate decisions are: metabolic activities, reactive oxygen species, intracellular pH, and cell morphology.<sup>[45]</sup>

## Metabolic reprogramming and Epithelial-Mesenchymal Transition

The phenomenon of epithelial-mesenchymal transition refers to loss of epithelial cellular characteristics and gain of mesenchymal traits in epithelial cells.<sup>[46]</sup> On the other side, metabolic reprogramming is also linked to the acquirement of EMT traits. The regulatory process of EMT involves specific transcription factors, microRNAs, epigenetic modifications as well as long non-coding RNAs (lncRNAs) and metabolic reprogramming coordinates the transitory process.<sup>[47]</sup> The process is linked to the generation and expression of cancer stem cell features, and changes in metabolic ways enable the survival of tumour cells in changed environmental conditions.<sup>[48]</sup>

Glycolytic enzymes in metabolic reprogramming plays role in EMT induction making use of glycolytic flux. The process of EMT advancement is linked to abnormal lipid metabolism and amino acid metabolism in cancerous cells.<sup>[49][50][51][52]</sup> Furthermore, EMT is also regulated by products from the metabolic pathways by transcription factors in the EMT process as well as epigenetic regulators,<sup>[46]</sup> like some products from the glycolytic pathway can induce EMT, as well as some products from the same glycolytic pathway, can inhibit EMT.<sup>[47]</sup> The process of EMT in metastasis can also involve entry of CTCs in peripheral blood, wherein CTCs can show the presence of hybrid epithelial-mesenchymal markers. Additionally, EMT can also lead to the formation of CSCs,<sup>[53]</sup> which can switch between glycolysis and oxidative phosphorylation.<sup>[54]</sup> Furthermore, CSCs proliferate and grow towards the formation of multiple cell lineages leading to tumour heterogeneity (Figure 2) to express their differentiation potential.<sup>[55]</sup> On the other side, EMT-generated CSCs can switch to MET, and the process is useful in the initiation of pluripotency.<sup>[56][57]</sup> Reprogramming is affected by EMT and metabolic regulatory processes, through different factors like histone modification, and DNA methylation. The importance of metabolism in deciding cell fate is evidenced by the studies of substrate utilization.<sup>[58][59]</sup> Many signaling networks, like Notch, TGF- $\beta$ , and BMP plays role in the regulatory part of the process.<sup>[46][60]</sup> The transcription factor TWIST, part of basic helix-loop-helix (bHLH) transcription factors involved in EMT apart from playing role in the formation of cancer stem cells, functions in lipid metabolism in adipose tissue, and also plays role in inflammation and insulin resistance.<sup>[61]</sup> Metabolic reprogramming has been reported to be involved with type 2 diabetes and breast cancer.<sup>[62]</sup> Another transcription factor involved in EMT, ZEB1 is important in adipogenesis.<sup>[63]</sup> However ZEB 1/2, though influenced by TCA cycle end products, also influences glycolysis and can also divert glycosphingolipid metabolism.<sup>[64][65]</sup> On the other side, miR-200 can inhibit EMT by targeting ZEB 1/ 2.<sup>[66]</sup> Additionally, TP53 can downregulate ZEB 1/ 2 expression by targeting miR 192 and 200.<sup>[67]</sup> The miR200 member(s) can also inhibit signaling networks, like Wnt and Notch pathways.<sup>[68][69]</sup> Apart from this, lncRNAs also play role in the activation, or inhibition, of EMT, and research works are expanding knowledge on their role in metabolism and cancer cell metabolism associated with EMT.<sup>[70][71]</sup> However, EMT can be suppressed also by the OVOL 1 / 2 transcription factors, and OVOL2 and ZEB 1 can mutually repress each other.<sup>[72][73]</sup> Nevertheless, though little is known about the role of transcription factors to suppress MET, FOXA1 can reduce lipid accumulation in human hepatocytes, and interactions between FOXA1 activity and ZEB 1 and SNAIL (Snail belongs to zinc finger protein, SNAI1) can be another way to study cancer cell metabolism.<sup>[47][74]</sup>

## Vascular Mimicry

Vascular mimicry involves the formation of blood vessel-like structures by aggressive tumours and is connected to the process of EMT.<sup>[75][76][77]</sup> One of the reasons for perturbed vascular functions is due to the disturbed arterial blood flow, induction of metabolic reprogramming through HIF-1 $\alpha$  resulting in activation of endothelial cells, vascular inflammation, and atherosclerosis. HIF-1 $\alpha$  is required for disturbed flow-induced metabolic reprogramming in human and porcine vascular endothelium.<sup>[78]</sup>

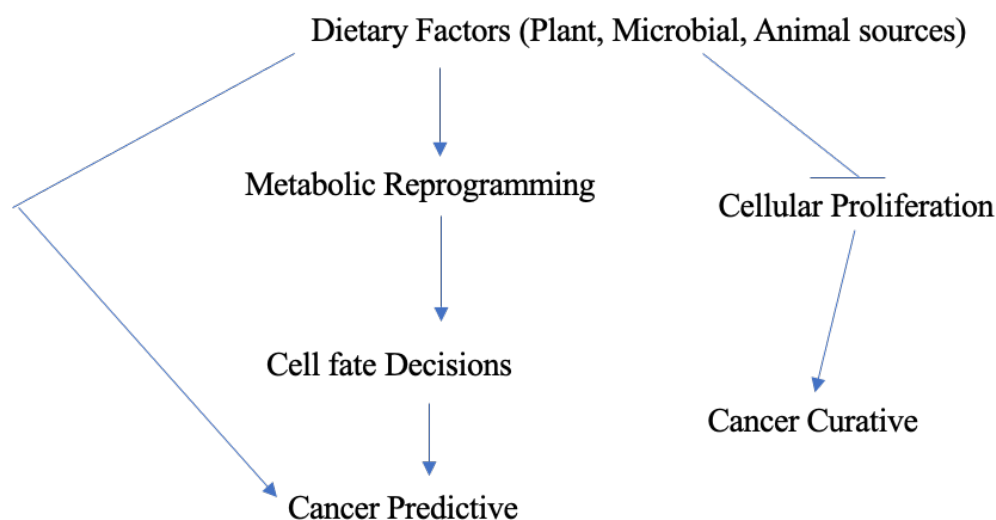


An interaction between EC, VSMC, and immune cells regulates the response between pathological and physiological states.<sup>[79]</sup> Furthermore, nitric oxide is a critical modulator of VEC, and metabolic reprogramming leads toward the migration of VEC in an anoxic environment.<sup>[76]</sup> Factors like LPS, IL-1, and TNF- $\alpha$  activates VEC leading to changed VEC metabolic activities with enhanced glycolysis, upregulated FAS.<sup>[80]</sup> The cumulative effect of activities leads to increased proliferation, migration and VEC dysfunction, and vascular diseases.<sup>[76][81]</sup>

## Dietary components in metabolic reprogramming

The tumour cell in cancer changes their metabolic pathway as they enter metabolic reprogramming which is one of the characteristic features of cancer.<sup>[82]</sup> The purpose is to provide tumour cells with essential energy, signaling intermediate and precursors to support biosynthesis, growth, proliferation, and metastasis.<sup>[83]</sup>

Diet and food intake influence microbial composition and the healthy metabolic activity of the consumer. Plant-based food is understood to help in maintaining a healthy gut microbiota. Food intake is also understood in terms of food ingredients and food supplementation that includes microbial sources also.<sup>[84]</sup> Food intake not only includes components from plant-based sources, but also microbial and animal sources (Figure 4). Gut microbiota shows ecosystem shifts, and is related to metabolic transitions.<sup>[85]</sup>



**Figure 4.** Schematic illustration of therapeutic importance of dietary factors in metabolic reprogramming.

Dietary factors can either help in therapeutics for cancer cure or can help in prediction of cancer occurrence.

Diet and nutrition are also two of the major essential requirements to control cancer cell metabolism.<sup>[86]</sup> Gut microbiome

undergoes shifts in changes with regard to diet consumption and lifestyle and can result in a change in gut microflora composition. The gut microbiome due to diet changes can affect tumour development, progression, and therapy.<sup>[87][88]</sup> Cell motility in malignant cancers is affected by EMT signalling. Dietary components, like luteolin and quercetin, can reduce EMT signalling and inhibit metastasis in cervical cancer.<sup>[89]</sup> Gut microbiota is influenced by dietary components. A high fiber diet can lead to the generation of short-chain fatty acids that offers manifold health benefits.<sup>[90]</sup><sup>90</sup> However, fatty acids, like palmitic acid and a high-fat diet also lead to cancer and EMT by activating TGF- $\beta$  and  $\beta$ -catenin.<sup>[91][92]</sup> Reports evidence the ability of dietary energy balance to modulate EMT and cancer progression.<sup>[93]</sup>

Resveratrol found in grapes, peanuts, cranberries, etc. was seen to inhibit EMT factors and TNF- $\beta$ -induced factors for tumour progression.<sup>[94][95][96]</sup> Similarly, silibinin, a flavonolignan found in milk thistle (*Silybum marianum*) was reported to modulate levels of EMT markers and stop EMT, and remove colorectal CSCs by blocking the Wnt/  $\beta$ -catenin signaling pathway.<sup>[97][98]</sup> The nucleus sourced  $\beta$ -catenin is a transcriptional activator of EMT target genes and stem cell markers.<sup>[99]</sup> Zerumbone, from the Zingiberaceae family, was reported to upregulate miR-200c and inhibit cancer progression, EMT, and CSC functions.<sup>[99][100][101]</sup>

Fucoxanthin, belonging to marine carotenoids and abundant in macro- and microalgae was also reported to induce apoptosis and inhibit EMT and CSC invasion.<sup>[102][103]</sup> The EMT-related markers are also regulated by scutellarein, derived from apigenin and found in *Scoparia dulcis*, *Artemisia douglasiana*, as well as by tetramethyl ether found in *Acacia carneorum*, *Acacia fasciculifera*, and *Pongamia pinnata*,<sup>[104][105]</sup> and by cyclopamine, a steroidal alkaloid isolated from the corn lily (*Veratrum californicum*).<sup>[106][107][108]</sup>

The TGF  $\beta$  signaling is also linked to cancer metabolism and EMT.<sup>[109]</sup> Nanoparticle-coated  $\alpha$ -mangostin ( $\alpha$ -Mangostin, a natural xanthonoid found in bark and dried sap of *Garcinia mangostana* L.) could inhibit colorectal cancer growth and EMT by downregulating GSK3 $\beta$ / $\beta$ -catenin /CDK6 signaling pathway.<sup>[110][111][112]</sup> Curcumin obtained from turmeric and analogues of curcumin modulated signaling network, miRNAs and EMT and anticancerous effect on colorectal cancer stem cells.<sup>[113][114]</sup> Additionally, triptolide suppressed EMT by downregulating EMT transcription factors.<sup>[115]</sup> Low folate metabolic stress in the colon by reprogramming Hh pathway transdifferentiated human colon adenocarcinoma cells to EMT with deep tissue invasion.<sup>[116]</sup> Baicalin, a natural flavonoid observed in *Scutellaria* spp. could inhibit EMT by stopping the TGF $\beta$ /Smad pathway.<sup>[117][118][119]</sup> Thus natural plant-derived chemicals can not only modulate different stages of cancer progression but also can inhibit EMT.

## Phenomenal relatedness of the processes in metabolic reprogramming

Though not common in all cancer types, in the majority of tumorous conditions EMT drives the development of cancer.<sup>[120][121]</sup> Epithelial-mesenchymal transition is also a part of the developmental process and irrespective of development or disease, EMT involves complex networking of pathways and different factors.<sup>[122][123]</sup> The process of EMT initiation and advancement is dependent upon many signaling molecules, like EGF, FGF, HGF, TGF  $\beta$ , BMP, SHH, Notch, and Wnt signaling pathway, etc., as well as  $\beta$ -catenin–dependent canonical and  $\beta$ -catenin–independent

noncanonical WNT signaling pathways.<sup>[124][125][126]</sup> A few of these signaling networks are in turn modulated by dietary, or food components. The transcription factor family, SNAIL can not only change epithelial cell polarity, but also inhibit apoptosis and cell cycle, as well as induce the formation of CSCs. However, TGF  $\beta$  in turn induces SNAIL expression not only in cellular development, but also in organ development. The TGF  $\beta$  again can be inhibited by Baicalin.<sup>[119]</sup> The transcription factor, Twist also drives the development of CSC phenotypes, and due to the levels of expression of Twist in specific precursor cell types, is useful as a cancer biomarker.<sup>[47]</sup> However, triptolide can down-regulate SNAIL, Twist, and Slug (Slug: Zinc finger transcription factor).<sup>[115]</sup>

## Targeted therapeutic interventions

Therapeutic intervention is a necessity for curing cancer. Understanding of the therapeutic intervention needs study in the appropriate cell lines followed by studies in model systems with final clinical trial studies. Of all the types of cancer, there are numerous reports about studies on breast cancer. This is not only with regard to the growing importance of breast cancer of all types of cancer, but also there are advantages to the availability of negative and positive breast cell lines for experimentation. Different therapeutic approaches can be adapted for cancer cure, wherein targeted therapy can be practised along with the standard therapeutic approaches.<sup>[15]</sup> Targeted therapy can act on specific molecular targets, and exemplarily targets can be the cell cycle molecules, like cyclins.<sup>[127][128]</sup> The other targets that can be used are: *IGF-1R*, *Pin-1*, *Nicastrin*, *SHIP 2*, *Syndecan 1*, and pro-inflammatory cytokines.<sup>[129]</sup> The metabolic pathway products can be also used for targeted therapy.<sup>[130]</sup> Chemical cell death kinase inhibitors and miRNA can be also used in targeted therapy.<sup>[131][132][133]</sup> Recent reports evidence the usage of miRNA for metabolic reprogramming of chimeric antigen receptor T-cells.<sup>[134]</sup>

Mitochondria plays important role in tumour metabolism. Another important target for therapeutic purposes can be Parkin, an E3 ubiquitin ligase, a regulator of mitochondrial integrity, which not only plays role in the early onset of Parkinson's disease but also in cancer.<sup>[135]</sup>

Metabolic remodeling is a necessity for the cells to support energy for cytoskeletal remodeling needed for cellular responses, cell migration, EMT, and changes in cell morphology. The process is linked to the rearrangement of actin bundles and the binding of glycolytic enzymes to actin fibres.<sup>[136]</sup>

Actin interacts with three of the glycolytic enzymes, PFK-1, aldolase, and GAPDH, wherein binding of PFK-1 to actin is by electrostatic forces.<sup>[137][138]</sup> and binding is dependent upon ADP concentrations over ATP concentration but independent of its substrate, F-6-P (fructose-6-phosphate). In turn, aldolase binds preferentially to F-actin, whereas GAPDH binds directly to F-actin.<sup>[136]</sup> Cell migration and proliferation need energy, nutrients, and metabolic activities, and metabolic activities in proliferating cells differ from that in non-proliferating activities.<sup>[38][136]</sup> Intracellular transport in cancer metabolism is also linked to cytoskeletal dynamics and functioning.<sup>[139]</sup> Furthermore, the use of VM inhibitors along the standard anti-angiogenesis treatment and drugs targeting hypoxia signaling might be of help in angiogenesis treatment.<sup>[77]</sup>

## Thermodynamic constraints

Thermodynamic constraints and their consequences have been well studied in microorganisms. Understandings from those studies can help understand more about the metabolic constraints in mammalian cells. Metabolic reprogramming may lead to the development of thermodynamic constraints.<sup>[140]</sup>, which might be beneficial for the proliferating cells and can be hypothesized to distinguish between proliferating and non-proliferating cells and this might lead them to be far away from equilibrium.<sup>[141]</sup> This needs to be investigated in the mammalian cell line experimentations. There are enumerable studies in this regard to understand the physiology of microorganisms and their survival in a niche. Studies in metabolic networks can be related to the maximum entropy production.<sup>[142]</sup> This understanding might be possible for reinforcement of the knowledge from microbial syntrophy studies, wherein this refers to a process of metabolic interaction between microbial partners in an environmental condition.<sup>[143]</sup> Metabolic interactions can also modulate metabolic rates.<sup>[144]</sup>

## Conclusion and future directions

Somatic cells can be reprogrammed to iPSCs by use of defined transcription factors, and the process is called somatic cell reprogramming.<sup>[145]</sup> The process can be hypothesized to be regulated by dietary factors, or diet inducible factors. Despite the fact that the MET is an essential requirement for reprogramming, the sequential process of EMT-MET at the initiation stage of reprogramming can increase reprogramming efficiency.<sup>[46][57]</sup> The reports from Liu et al. 2013 revealed that temporary EMT can generate iPSCs with an efficiency of 600% at the basal level. The regulatory process of EMT also involves the functioning of noncoding RNAs like miRNA.<sup>[133]</sup> However, it is not known whether the functioning of those miRNAs is in turn being influenced by diet/dietary factors. Reprogramming can shed new light on the therapeutical approaches to cancer.<sup>[57]</sup> It is the metabolic shift that regulates EMT in metastasis apart from the pathway metabolites that control epigenetically.<sup>[58][146]</sup> The phenomenon of drug treatment resistance has been also linked to EMT.<sup>[147][148]</sup> Thus, EMT by itself can be an addressing factor to study and cure drug resistance.<sup>[47]</sup> Vascular mimicry has been also linked to EMT.<sup>[75]</sup> This leads to the question if vascular mimicry can also be regulated by metabolic reprogramming, which needs to be studied. There are numerous reports about the usage of plant and microbial products with antimicrobial properties that can be possibly used for therapeutic purposes, and it might be possible to use many of them for metabolic reprogramming.<sup>[149][150]</sup> Metabolites can transcriptionally regulate genes, and metabolic reprogramming can be predictive for cancer detection, and might be therapeutic as part of cancer precision medicine.<sup>[30][151]</sup> Cytokines and TNF- $\alpha$  can play role in cancer pathogenesis as well as cancer prediction (Figure 4).<sup>[152][153][154][155]</sup> Dietary phytochemicals are evidenced to regulate EMT.<sup>[156]</sup> Additionally, derived cytokines can play role in abnormal glucose and lipid metabolism.<sup>[157][158]</sup> Furthermore, Krebs's cycle intermediate, citrate plays role in both immunity and inflammation.<sup>[159]</sup> In recent reports, the therapeutical side of metabolic reprogramming also evidences the use of fibroblasts in the microenvironment of pacemaker cardiomyocytes at the sinoatrial node to drive metabolic

reprogramming.<sup>[160]</sup> Cells in higher eukaryotes can either proliferate or show senescence. Both of these states are regulated by extrinsic and intrinsic stimuli and environmental factors.<sup>[161][162]</sup> Dietary factors provide growth factors and other necessities for influencing the states and can be hypothesized to regulate cellular proliferation or senescence mechanisms (Figures 2 and 3). Proliferation, including in nerve cells leads to the generation of transit-amplifying cells (TAC).<sup>[163][164][165]</sup> Senescence can be triggered by stress, and stress induced by serum deprivation can lead to a quiescent stage (G<sub>0</sub> phase of the cell cycle).<sup>[166][167][168]</sup> Both senescence and proliferation are important in tissue regeneration which can be modulated by dietary factors.<sup>[169][170]</sup>

Lastly to state, it is the diet that makes cells undergo metabolic reprogramming.<sup>[171]</sup> This is also because dietary phytochemicals targets signaling pathways of cancer stem cells, which prospects the development of phytomedicines and pharmaceutical development for cancer therapeutics.<sup>[95][172][173]</sup>

Though there are significant advances achieved in the studies of EMT and metabolic reprogramming, the unanswered questions need to be looked in:

1. Can diet/dietary factors be the driving force to initiate EMT and metabolic reprogramming?
2. Will dosage or quantum of diet in terms of energy and diet/dietary component initiate EMT and metabolic reprogramming?
3. Can the transcription factors and other factors including noncoding RNAs involved in EMT, EMT-MET, metabolic reprogramming, and cell fate decisions be decided by specific dietary components qualitatively and quantitatively?
4. Can the gut microflora also influence cell fate decisions?
5. In the situation where somatic reprogramming is linked to EMT, can conditional reprogramming be linked to influences from dietary factors as well as EMT and EMT-MET?

A defined answer to the questions can help in therapeutic interventions in cancer and can be of help in situations where resistances to therapies arise. Understanding the metabolic decisions will be a major hallmark to understand development and disease biology.

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## Appendix-I

### List of Abbreviations Used And their Expanded Form

Abbreviations	Expanded form
TME	Tumour Microenvironment
<i>Myc/c-Myc</i>	Myelocytomatosis/c- Myelocytomatosis
<i>Ras</i>	Rat sarcoma virus
HIF-1	Hypoxia inducible factor-1
p53	protein 53
POU1F1	pituitary-specific POU-homeo domain transcription factor
HNF	Hepatocyte Nuclear Factor
MODY	Maturity-onset diabetes of the young
TNF $\alpha$	Tumour necrosis factor- $\alpha$
JAK-STAT	Janus kinase/Signal transducers and activators of transcription
EMT	Epithelial Mesenchymal Transition
MET	Mesenchymal Epithelial Transition
CTC	Circulating Tumour Cells
CSC	Cancer Stem Cells
TGF $\beta$	Transforming Growth Factor $\beta$
BMP	Bone morphogenetic proteins
ZEB	Zinc Finger E-box-binding homeobox 1
TCA cycle	Tricarboxalic acid cycle/ Krebs' cycle
miRNA/miR	microRNA
OVOL	Ovo like protein
FOXA1	Forkhead box protein A1
EC	Endothelial cells
VSMC	Vascular smooth muscle cell
VEC	Vascular Endothelial Cell Function
LPS	Lipopolysaccharide
IL	Interleukin
FAS	Fatty acid synthase
Hh	Hedgehog
Smad	Suppressor of Mothers against Decapentaplegic
EGF	Epidermal Growth Factor
FGF	Fibroblast Growth Factor
HGF	Hepatocyte Growth Factor
SHH	Sonic Hedgehog
<i>IGF-1R</i>	insulin-like growth factor 1 receptor
<i>Pin-1</i>	Peptidylprolyl Cis/Trans Isomerase, NIMA-Interacting 1
<i>SHIP 2</i>	SH2-domain-containing inositol phosphatase 2
PFK-1	Phosphofructokinase-1
GAPDH	Glucose-3-phosphate dehydrogenase

CDH1	Glyceraldehyde-3-phosphate dehydrogenase
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
VM	Vascular Mimicry

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