



## CANCER PROTEIN METABOLISM: REVIEW ON ETIOLOGY, PROGRESSION AND MANAGEMENT

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### ABSTRACT

Altered metabolism is one of the hallmarks of cancer cells. Cell cycling and protein synthesis are both key physiological tasks for cancer cells. In recent years, interest has been renewed as clear that many of the signaling pathways that are affected by genetic mutations and the tumor microenvironment have a profound effect on core metabolism of cancer cells. Metabolic alterations in cancer cells are numerous and include aerobic glycolysis, reduced oxidative phosphorylation and the increased generation of biosynthetic intermediates needed for cell growth and proliferation. Furthermore, accelerated protein turnover seen in many cancer patients and whole body protein turnover is increased with advancing stage of disease. Cancer cells alter their consumption and the way they process sugars, fats, amino acids and other energy sources to satisfy the demands of continuous proliferation. The possible effects of specific amino acid, methionine, asparagine, arginine, tyrosine and glutamine, etc. on protein cancer metabolism are discussed. Evidences confirm a contribution of proteins in all cancer stages and describe metabolism of protein in cancer and how amino acids can be targeted to management or initially prevent different types of cancer. Several studies suggest that people who eat more red meat have higher risk for developing colorectal cancer than those who eat less red meat, but avoiding processed meats is even more important for cancer prevention. In this review we summarize the role of proteins in cancer etiology, metabolism, its complication, prevention and treatments.

**KEYWORDS:** protein, cancer, metabolism, etiology, complications, prevention and treatment.

### INTRODUCTION

Cancer is a generic term for a large group of diseases that can affect any part of the body.<sup>[1]</sup> Cancer is not just one disease, but a large group of almost 100 diseases. Cancer has existed for all of human history. The earliest written record regarding cancer is from circa 1600 BC in the Egyptian Edwin Smith Papyrus and describes cancer of the breast.<sup>[2]</sup> This view of the disease was first formulated by the English surgeon Campbell De Morgan between 1871 and 1874.<sup>[3]</sup> In 1915, cancer was induced for the first time in rabbits by coal tar applied to skin. During the last decades of the 20th century, surgeons developed new methods for cancer treatment by combining surgery with chemotherapy and/or radiation.<sup>[4]</sup> Scientists have learned more about cancer in the last 2 decades than had been learned in all the centuries. Furthermore, preceding cancer research is advancing on so many fronts examples: more targeted therapies, immunotherapy, more on cancer genetics, nanotechnology, robotic surgery, expression profiling and proteomics.<sup>[5]</sup>

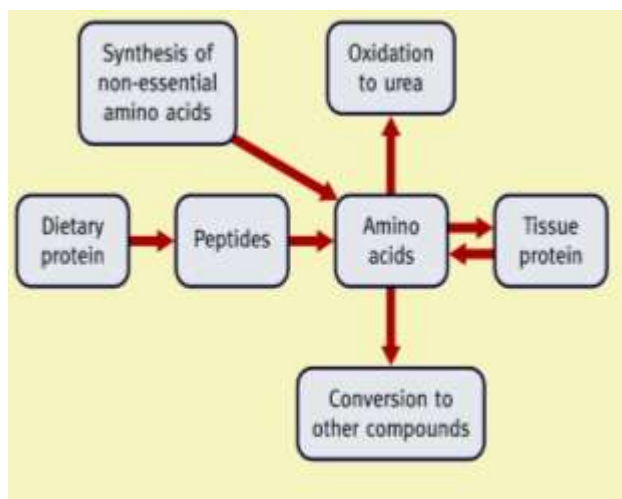
A protein is a linear polymer of amino acids linked together by peptide bonds. Proteins, the working molecules of a cell, carry out the program of activities encoded by genes. This program requires the coordinated effort of many different types of proteins.<sup>[6]</sup> Each day, humans turnover 1% to 2% of their total body protein, principally muscle protein. High rates of protein degradation occur in tissues that are undergoing structural rearrangement. While approximately 75% of the amino acids liberated by protein degradation are reutilized, the remaining excess free amino acids are not stored for future use. Amino acids not immediately incorporated into new protein are rapidly degraded.<sup>[7]</sup> The goal of the current review is elucidate the role of abnormal protein metabolism in cancer states: etiology, progression and cancer complication related to protein metabolism. Moreover, the treatment and dietary guidelines for prevention using safe protein natural products.

### Protein metabolism in normal cells

One of the first steps in the breakdown of amino acids is the removal of the amino group. This involves a

transamination reaction, often with alpha-ketoglutarate as the acceptor.<sup>[8]</sup> The breakdown of a few amino acids involves nothing more than the reversal of the reactions responsible for their synthesis. Glutamate, for example, may shed its amino group in any of numerous possible transamination reactions, and the resulting alpha-ketoglutarate can be utilized through the Krebs cycle. Some other amino acids require a much larger number of reactions and may depend on several vitamin cofactors. The complete oxidation of tryptophan, for example, takes more than 20 steps and requires adequate supplies of thiamin, riboflavin, vitamin B6, niacin, pantothenate, lipoate, iron and magnesium.<sup>[9]</sup> However, leucine and lysine cannot be converted to glucose and under these circumstances they give rise to acetoacetic acid, so they are classified as ketogenic amino acids. The ketogenic amino acids are those that are metabolized only to acetyl CoA, while those that are metabolized to tricarboxylic acid cycle intermediates are glucogenic. Tryptophan, methionine and cysteine produce pyruvate and so can be either ketogenic or glucogenic. Phenylalanine and tyrosine are metabolized to fumarate plus acetoacetate and are thus both ketogenic and glucogenic, as isoleucine.<sup>[10]</sup>

Nutritional studies revealed that all or a portion of the carbon skeleton of every amino acid is convertible either to carbohydrate, fat, or both fat and carbohydrate.<sup>[7]</sup> Under certain circumstances, such as starvation, diabetes or a high-fat diet, the body may need to synthesize glucose from amino acids rather than oxidizing them directly. Urea is formed in the liver by a series of reactions known as the urea cycle. Urea biosynthesis occurs in four stages: (1) transamination, (2) oxidative deamination of glutamate, (3) ammonia transport and (4) reactions of the urea cycle.<sup>[7]</sup> Glutamine and asparagine are the amidation products of their respective dicarboxylate amino acid precursors. Arginine, ornithine, citrulline, and proline start from glutamate; net synthesis occurs only in the intestinal wall. The precursor for routine synthesis is cysteine.<sup>[11]</sup>



**Figure 1: Overview of the main processes of amino acid metabolism.**<sup>[10]</sup>

### Metabolism of methionine

Methionine is an essential amino acid must be provided by protein diet. Methionine breakdown starts with its conversion to S-adenosylmethionine (SAM). S-adenosylhomocysteine (SAH), in turn, serves as a donor of methyl groups. Methionine breakdown products are recycled back to form methionine by two pathways: remethylation of homocysteine and conversion of methylthioadenosine (MTA) to methionine. SAM and SAH are the substrate and product of methyltransferase reactions. A decrease in the SAM: SAH ratio often indicates decreased cellular methylation potential.<sup>[12]</sup>

### Abnormal metabolism (etiological role)

#### Methionine: methylation deficiency in cancer

Since folate is so closely related to the one-carbon metabolism and a choline/methionine deficiency alone is able to generate a folate deficiency, it seems likely that a combined folate, choline and methionine deficient diet will have a stronger carcinogenic effect compared to either a folate deficient or a preformed methyl deficient diet.<sup>[13]</sup> In humans, hypomethylation has been observed in DNA from colon tissue, both benign colon polyps and malignant carcinoma, compared to adjacent normal tissue.<sup>[14]</sup> A comparison of normal and neoplastic tissue from the same patient showed hypomethylation in a specific CCGG site in the third exon of c-myc.<sup>[15]</sup>

#### DNA methylation in carcinogenesis

Differential patterns of DNA methylation in cancer have been recognized for more than two decades.<sup>[16]</sup> Hypermethylation of promoter regions, which is associated with transcriptional silencing, is at least as common as actual DNA mutation as a mechanism for the inactivation of classical tumor suppressor genes in human cancers.<sup>[17]</sup> Additionally, a number of candidate tumor suppressor genes that are not commonly inactivated by mutation are transcriptionally silenced by this mechanism.<sup>[18]</sup> Genes associated with tumorigenesis can be silenced by this epigenetic mechanism. The crucial properties required to generate the characteristic malignant attributes associated with cancer are the ability to replicate without limitation, indifference to positive growth signals, disregard for growth inhibitory factors, evasion of programmed cell death, sustained angiogenesis, and the ability to invade and metastasize.<sup>[19]</sup> Although both global hypomethylation and regional DNA hypermethylation are well documented in cancer, the mechanisms behind these events remain unclear, particularly the paradox of why some DNA remains hypomethylated in the presence of increased DNA methyltransferase activity and expression. It has been suggested that the deregulation of DNA methyltransferases might lead to genome-wide hypomethylation in cancers.<sup>[20]</sup> Hypermethylation is associated with the inactivation of virtually all pathways involved in the cancer process, including DNA repair, cell cycle regulation, apoptosis, carcinogen metabolism, hormonal response and cell adherence.<sup>[21]</sup>

### DNA damage; poly (ADP-Ribose) polymerase activity and NAD Levels

DNA damage can be caused either by imbalance of the nucleotide pool because of a shift of scarce methyl groups to SAM synthesis and away from purine and pyrimidine formation<sup>[22]</sup> by oxidative damage<sup>[23]</sup>, or hypomethylation.<sup>[24]</sup> Moreover, James et al<sup>[25]</sup> showed evidence of DNA damage by measuring increased amounts of DNA-strand breaks in spleen cells of rats fed a methyl/folate-deficient diet. DNA strand breaks in turn act as stimulating event for poly (ADP-ribose) polymerase (PARP), a nuclear enzyme, which catalyzes the formation of poly ADP-ribose polymers from NAD.<sup>[26]</sup> The folate/choline methionine deficiency acts as a complete carcinogen. The effect of a low folate level on the purin/pyrimidine balance leading to DNA strand breaks and mutations might cause initiation and the increased proliferation and cell death might cause promotion.<sup>[13]</sup>

### Asparagine

Asparagine is an amino acid (a building block of proteins) that is found in many vegetables, with higher concentrations in some varieties of potatoes. When heated to high temperatures in the presence of certain sugars, asparagine can form acrylamide. High-temperature cooking methods, such as frying, baking, or broiling, have been found to produce acrylamide.<sup>[27]</sup> Studies in rodent models have found that acrylamide exposure poses a risk for several types of cancer.<sup>[28]</sup> Neoplastic pathogenesis by chemicals is a complex process which can be divided into three distinct stages, from an operational point of view. These are: initiation, promotion and progression.<sup>[29]</sup> Changes in gene expression also take place during the promotion stage, with selective proliferation of initiated cells and the development of preneoplastic cells.<sup>[30]</sup> During initiation and promotion, apoptosis and cell proliferation can occur at different rates, while remaining balanced. During progression, this balance is modified and from there malignancy arises<sup>[31]</sup> (figure2).

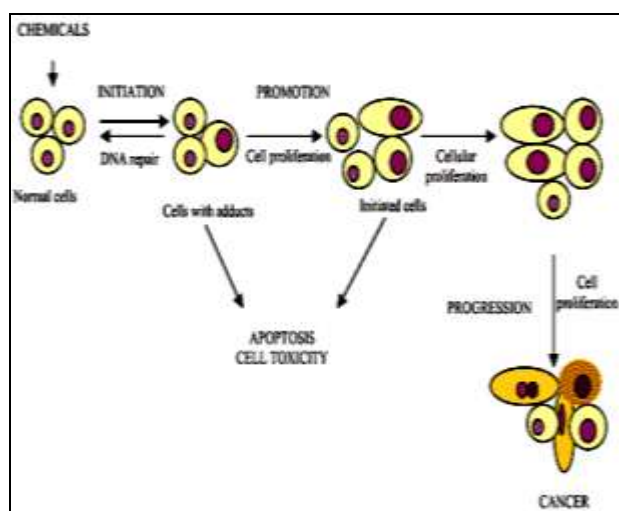


Figure 2: Chemical carcinogenesis stages and the occurrences involved in each one.<sup>[32]</sup>

### 2.1.3 -One-carbon metabolism (De novo serine and glycine metabolism)

An intermediate in glycolysis, 3PG (3-phosphoglycerate), can be oxidized to form 3-phosphohydroxy-pyruvate (pPYR). This reaction is the initial and committed step for de novo (that is, originating from glucose) serine biosynthesis.<sup>[33]</sup> Thus, carbon derived from glucose can be shunted from glycolysis into de novo serine metabolism and then into the folate cycle. It has been known for many years that this pathway correlates with tumorigenesis. Further extensive work by Snell and colleagues showed that flux through this branch point in glycolysis correlated with cancer progression in rat carcinoma models. Recent studies using isotope tracing with <sup>13</sup>C-labelled glucose showed that a subset of cancer cells diverted a substantial amount (approximately 10%) of 3-phosphoglycerate away from glycolysis and into one-carbon metabolism through phosphoglycerate dehydrogenase (PHGDH).<sup>[34]</sup> PHGDH was also found to be overexpressed in the triple-negative subtype of breast cancer.<sup>[35]</sup>

### Glutamin

Transglutaminase 4 is the prostate - specific transglutaminase, although it is also expressed in a number of other tumour cell lines. The mRNA for the human enzyme undergoes differential splicing in the development of benign prostate hyperplasia and prostate cancer.<sup>[36]</sup>

### Arginine

Arginase control arginine availability for nitric oxide synthesis and polyamine synthesis. Imbalance between nitric oxide and polyamine synthesis is a factor in colon cancer.<sup>[37]</sup>

**Glycine:** glycine N - methyltransferase is inhibited by methyl tetrahydrofolate. The development of liver cancer is a result of activation of the Ras and JAK/STAT signalling pathways due to hypermethylation of inhibitors of the pathways. They also show abnormal methylation of histones.<sup>[38]</sup>

### Tryptophane

Carcinoid is a tumour of the enterochromaffin cells that normally synthesize 5 - hydroxytryptophan and 5 - hydroxytryptamine.<sup>[39]</sup>

### Tyrosine

Albinism is a genetic disorder in which production of the photoprotective pigment melanin is impaired. One cause of the disease is a defect in the gene for tyrosinase. Affected persons have visual impairment and are at increased risk for skin cancer.<sup>[40]</sup>

### Mutations of proto-oncogenes

Proto-oncogenes are a group of genes that cause normal cells to become cancerous when they are mutated.<sup>[41]</sup> Mutations in proto-oncogenes are typically dominant in nature and the mutated version of a proto-oncogene is

called an oncogene. Often, proto-oncogenes encode proteins that function to stimulate cell division, inhibit cell differentiation, and halt cell death. Today, more than 40 different human proto-oncogenes are known. Oncogenes arise as a result of mutations that increase the expression level or activity of a proto-oncogene.<sup>[42]</sup>

### Classification of oncogenes

Oncogenes can be categorized into 5 groups in terms of the biochemical and functional properties of protein products of proto-oncogenes. These groups are growth factors, growth factor receptors, signal transducers, transcription factors, and others.<sup>[43]</sup> Mutations of proto-oncogenes cause sustained activity of the genes in table 1.<sup>[44]</sup>

**Table 1: Some proto-oncogenes and their functions, mutations and associated cancers.**<sup>[44]</sup>

PROTO-ONCOGENE	FUNCTION	MUTATION	CANCER TYPE
<b>ABL</b>	Nonreceptor tyrosine kinase activity	Translocation t(9;22); forms fusion gene (BCR-ABL)	Chronic myelogenous leukemia, acute lymphoblastic leukemia
<b>ERBB2 (also called Her-2/Neu)</b>	Receptor synthesis	Amplification or overexpression	Breast carcinoma (marker of aggressiveness; amplified in 25% of breast cancers)
<b>C-MYC</b>	Nuclear transcription	Translocation t(8;14)	Burkitt lymphoma
<b>N-MYC</b>	Nuclear transcription	Amplification	Neuroblastoma, small cell carcinoma of lung
<b>RAS</b>	Guanosine triphosphate signal transduction	Point mutation	Accounts for 15%–20% of all cancers; 90% pancreatic carcinomas; 50% of endometrial, colon, thyroid cancers; 30% lung adenocarcinoma and myeloid leukemias; bladder cancer; breast and cervical cancer
<b>RET</b>	Receptor synthesis	Point mutation	Multiple endocrine neoplasia IIa/IIb syndromes; leukemia
<b>SIS (PBGFB)</b>	Growth factor synthesis	Overexpression	Osteogenic sarcoma, astrocytoma

### Apoptosis effect

The role of apoptosis (programmed cell death) in normal physiology is as significant as that of its counterpart, mitosis. It demonstrates a complementary but opposite role to mitosis and cell proliferation in the regulation of various cell populations. It is estimated that to maintain homeostasis in the adult human body, around 10 billion cells are made each day just to balance those dying by apoptosis.<sup>[45]</sup> Apoptosis is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development and chemical-induced cell death. Inappropriate apoptosis (either too little or too much) is a factor in many human conditions including neurodegenerative diseases, ischemic damage, autoimmune disorders and many types of cancer.<sup>[46]</sup>

The mechanisms of apoptosis are highly complex and sophisticated, involving an energy-dependent cascade of molecular events (Figure 3). To date, research indicates that there are two main apoptotic pathways: the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway. However, there is now evidence that the two pathways are linked and that molecules in one pathway can influence the other.<sup>[47]</sup>

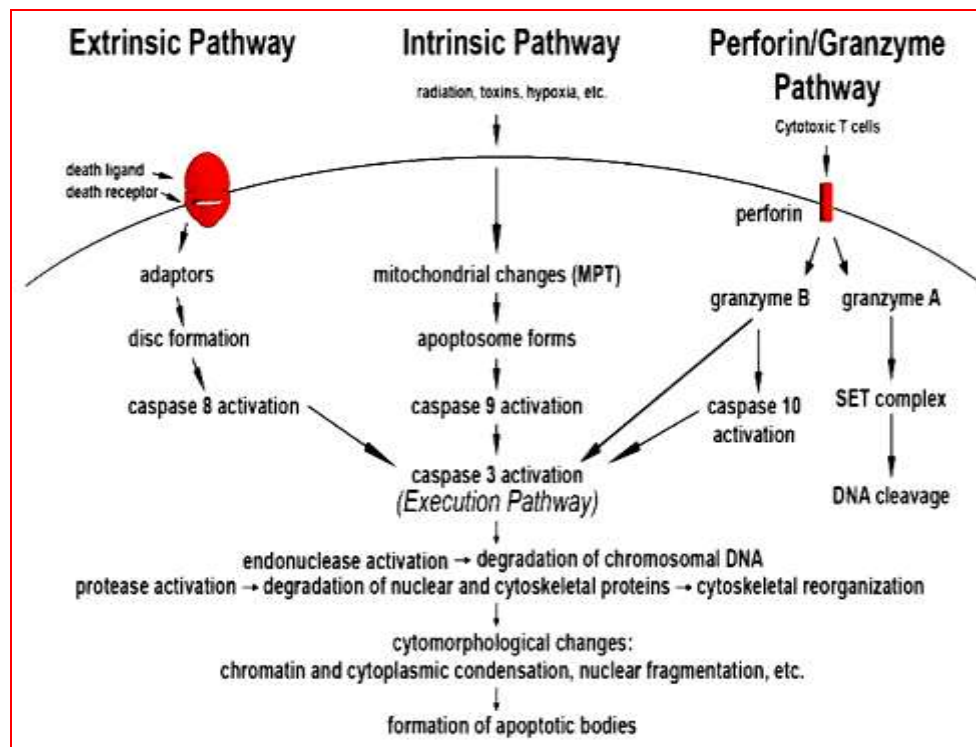


Figure 3: Mechanism of apoptosis.<sup>[46]</sup> Schematic representation of apoptotic events. The two main pathways of apoptosis are extrinsic and intrinsic as well as a perforin/granzyme pathway. Each requires specific triggering signals to begin an energy-dependent cascade of molecular events. Each pathway activates its own initiator caspase (8, 9, 10) which in turn will activate the executioner caspase-3. However, granzyme A works in a caspase-independent fashion. The execution pathway results in characteristic cytomorphological features including cell shrinkage, chromatin condensation, formation of cytoplasmic blebs and apoptotic bodies and finally phagocytosis of the apoptotic bodies by adjacent parenchymal cells, neoplastic cells or macrophages.

Bcl-2 is the first member of the Bcl-2 family of proteins to be discovered in B-cell lymphomas, hence the name bcl (b-cell lymphoma). As a consequence of its relocation next to a strong promoter, oncogenic activation of the Bcl-2 gene occurs. Over-expression of the anti-apoptotic protein Bcl-2 leads to insufficient apoptotic turnover and accumulation of B-cells. This translocation is not only found in most cases of follicular B-cell lymphomas but also in other types of cancer such as gastric, lung and prostate. All anti-apoptotic members of the Bcl-2 family may function as oncogenes, and pro-apoptotic members act as tumor suppressor genes.<sup>[49]</sup>

The heat shock proteins can inhibit the release of cytochrome c, which is essential for the formation of the apoptosome (protein structure formed in the process of apoptosis cleave procaspase), from the mitochondria.<sup>[48]</sup> The heat shock protein Hsp70 blocks apoptosis mainly by the inhibition of Bax (pro-apoptotic member of Bcl-2 family of proteins) activation and as a result preventing the release of pro-apoptotic factors from mitochondria.<sup>[50]</sup> The human IAP (Inhibitor of apoptosis proteins) family is composed of eight proteins. Some of IAP proteins are directly involved in apoptosis regulation.<sup>[51]</sup>

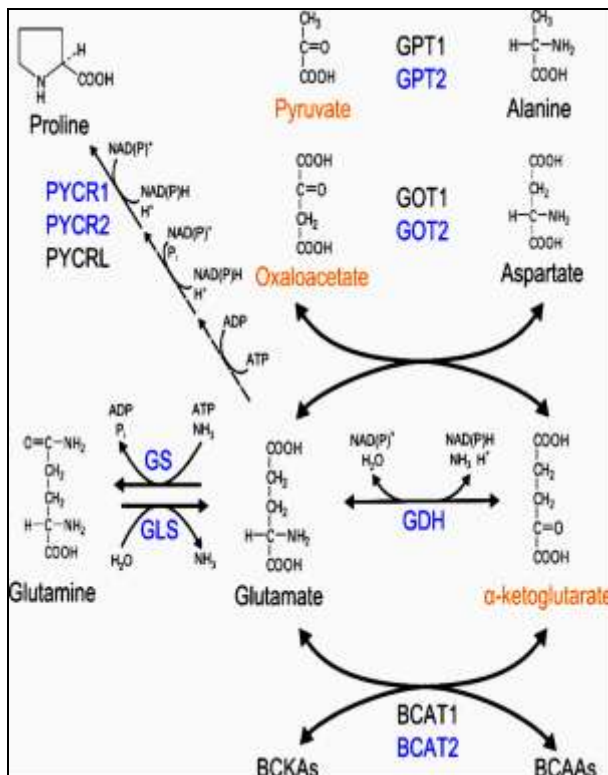
#### Abnormal metabolism during cancer development Albumin

The retention of albumin in tumors has since been observed in various experimental solid tumors (e.g., sarcoma, ovarian carcinoma, Novik of hepatoma, etc.) using radiolabeled or dye complexed serum albumin.<sup>[52]</sup> Tumors cells endocytosis and lysosomally break proteins down to constituent amino acids, which are then used as an energy and nitrogen source. Moreover, studies have suggested that the hypoalbuminemia evident in cancer patients is a result of albumin catabolism by the tumor.<sup>[53]</sup> Macropinocytosis of albumin provides nutrients to sustain cancer cell proliferation.<sup>[54]</sup>

#### Glutaminolysis and reductive carboxylation

The importance of glutamine as a nutrient in cancer derives from its abilities to donate its nitrogen and carbon into an array of growth-promoting pathways.<sup>[55]</sup> The requirement for glutamine is particularly true in cancer cells, many of which display oncogene-dependent addictions to glutamine in culture.<sup>[56]</sup> Glutamine catabolism begins with its conversion to glutamate in reactions that either donate the amide nitrogen to biosynthetic pathways or release it as ammonia. The latter reactions are catalyzed by the glutaminases (GLSs), of which several isozymes are encoded by human genes GLS and GLS2.<sup>[57]</sup> Glutamate, the product of the GLS reaction, is a precursor of glutathione, the

major cellular antioxidant. It is also the source of amino groups for nonessential amino acids like alanine, aspartate, serine and glycine, all of which are required for macromolecular synthesis. In glutamine-consuming cells, glutamate is also the major source of  $\alpha$ -ketoglutarate, a TCA (tricarboxylic acid) cycle intermediate and substrate for dioxygenases that modify proteins and DNA. During avid glucose metabolism, the transamination pathway was predominates.<sup>[58]</sup> When glucose is scarce, glutamate dehydrogenase (GDH) becomes a major pathway to supply glutamine carbon to the TCA cycle and is required for cell survival.<sup>[59]</sup> Metabolism of glutamine derived  $\alpha$ -ketoglutarate in the TCA cycle serves several purposes: it generates reducing equivalents for the electron transport chain (ETC) and oxidative phosphorylation, becoming a major source of energy<sup>[60]</sup> and it is an important anaplerotic nutrient, feeding net production of oxaloacetate to offset export of intermediates from the cycle to supply anabolism.<sup>[61]</sup> Glutamine oxidation also supports redox homeostasis by supplying carbon to malic enzyme, some isoforms of which produce NADPH. In tumor de novo glutamine synthesis in the liver and surrounding tissues is likely critical for tumor cell growth.<sup>[62]</sup>



**Figure 4: Coordination of carbon and nitrogen metabolism across amino acids.<sup>[63]</sup> Glutamate and aKG are key substrates in numerous transamination reactions and can also serve as precursors for glutamine, proline and the TCA cycle. Mitochondrial enzymes catalyzing these reactions are highlighted in blue and TCA cycle intermediates are highlighted in orange (pyruvate enters the TCA cycle as acetyl-CoA or oxaloacetate).**

### Proline

Mitochondrial proline metabolism and synthesis are critically important for tumor cells, at least in part due to the unique, modifiable chemical properties it provides to proteins. Proline is synthesized from glutamine or urea cycle derived ornithine via the intermediate pyrroline-5-carboxylate (P5C). P5C is then converted to proline via the NAD(P)H-dependent enzyme pyrroline-5-carboxylate reductase (PYCR), which exists in three isoforms: PYCR1, PYCR2 and PYCR3 (Figure 4).<sup>[64]</sup> The formation of reactive oxygen species (ROS) accompanying the oxidation of proline has been linked to a number of downstream events. Others have suggested that the generation of ROS through complex III is the source of mitochondrial ROS used for signaling because ROS is released into the intermembranous space.<sup>[65]</sup> From this site, ROS can be transferred out of the mitochondria to regulate various targets. POX expression is induced by the tumor suppressor p53 and ectopic expression of POX in DLD-1 colon cancer cells induces cell cycle arrest and reduces tumor burden in xenograft models.<sup>[66]</sup>

### Aspartate and asparagine

Aspartate can be generated from the TCA intermediate oxaloacetate by glutamate-mediated transaminase activity (figure 4); thus, the biosynthesis of aspartate and downstream metabolites is intimately tied to mitochondrial activity. Aspartate transaminases, which bidirectionally convert aspartate and alpha-ketoglutarate (AKG) to oxaloacetate (OAC) and glutamate, are important for the growth of human pancreatic adenocarcinoma (PDAC). Oncogenic k-ras gene (KRAS), the most common mutation in PDAC, redirects glutamine metabolism toward aspartate production in a number of settings. This metabolic reprogramming is thought to facilitate regeneration of NADPH for reductive biosynthesis and redox homeostasis as well as  $\text{NAD}^+$  for maintaining glycolysis.<sup>[67]</sup> Additionally, aspartate and glutamine are the precursors for asparagine, which is synthesized in the cytosol by asparagine synthetase (ASNS). ASNS expression is required for the survival of cultured glioma and neuroblastoma cell lines.<sup>[68]</sup> Finally, aspartate is a key initiator of pyrimidine synthesis and donates nitrogen for purine synthesis via adenylosuccinate synthetase, further highlighting the role of mitochondrial aspartate metabolism in tumor cell biosynthesis.<sup>[63]</sup>

### Alanine

Alanine production via alanine transaminases, which transfer an amino group between glutamate and pyruvate to yield alanine and  $\alpha$ KG, not only provide proteinogenic alanine but also  $\alpha$ KG for TCA cycle activity (Figure 4). Indeed, secretion of alanine is higher in melanoma cell lines compared to normal melanocytes and is quite significant in human colon carcinoma tumors.<sup>[69]</sup>

### Serine, Glycine, One-carbon metabolism

Glycolysis provides ATP and energy in most cell types, but cancer cells extensively use glycolysis to sustain anabolism, which is necessary for tumor growth. Serine biosynthesis is a component of these glycolysis-diverting pathways. The glycolytic intermediate 3-phosphoglycerate is converted to serine following a three-step enzymatic reaction. Cancer cells use phosphoglycerate dehydrogenase (PHGDH) and NAD to oxidise-10% of the 3-phospho-glycerate generated from glycolysis into the serine precursor 3-phosphohydroxypyruvate.<sup>[70]</sup> Subsequent enzymes in the pathway convert 3-phosphohydroxypyruvate into serine via transamination (PSAT1) and phosphate ester hydrolysis (PSPH) reactions. PHGDH expression is normally upregulated in triple-negative breast cancer and in melanoma.<sup>[71]</sup> In these tumors, the genomic locus on human chromosome 1p12 that encodes PHGDH is subject to frequent amplification, even though no oncogenes are included in this region.<sup>[72]</sup> These analyses suggest that tumors containing amplification of PHGDH might exploit serine biosynthesis activity. Therefore, PHGDH upregulation and serine biosynthesis can be necessary and/or sufficient to sustain cancer growth and oncogenic transformation. Through these pathways the serine synthesis pathway is a major contributor of TCA intermediates; it is responsible for approximately half of the anaplerotic flux to the TCA cycle.<sup>[73]</sup>

De novo synthesis of serine plays a crucial role as supplier of precursors for several biosynthetic pathways. Indeed, serine can be converted to glycine by the enzyme serine hydroxyl methyl transferase (SHMT).<sup>[74]</sup> This reaction represents a major source of methyl groups for the one-carbon pools that are required for the biosynthesis of GSH, proteins, purines and DNA/histones methylation.<sup>[75]</sup> Therefore, SHMT occupies a critical position at the convergence of two key pathways for chemotherapeutic intervention: serine/glycine metabolism and nucleotide biosynthesis.<sup>[76]</sup> Within the cell, two isoforms of SHMT are present. SHMT1 is localized in the cytoplasm, whereas SHMT2 is present in the mitochondria. Interestingly, c-Myc directly regulates the expression of both *shmt1* and *shmt2* genes.<sup>[77]</sup> Several experimental evidences indicate that glycine uptake and catabolism can promote tumorigenesis, indicating that glycine metabolism could be a potential target for therapeutic intervention.<sup>[78]</sup>

For one-carbon metabolism, the integration is carried out through the donation of carbon units from specific amino acids. These carbon units are distributed via a series of chemical reactions for use in diverse cellular processes that include cellular biosynthesis, regulation of redox status, regulation of epigenetics through nucleic acid and protein methylation and genome maintenance through the regulation of nucleotide pools. Loss-of-function mutations in enzymes that are involved in these pathways can lead to growth defects both in animals and

in humans, underscoring the role of one-carbon metabolism in modulating cell growth.<sup>[79]</sup>

### Arginine

Although arginine is a dispensable (nonessential) amino acid for healthy humans, it is conditionally essential under certain physiological conditions or disease state.<sup>[80]</sup> For example, many tumors are dependent on exogenous arginine for growth as they lack the enzyme argininosuccinate synthetase 1 (ASS1).<sup>[81]</sup> ASS1 catalyzes the conversion of citrulline into argininosuccinate in an ATP-dependent manner, completing one of the last steps in the arginine biosynthetic pathway.<sup>[82]</sup> Loss of ASS1 prevents the production of arginine and may lead to arginine depletion. Osteosarcoma and bladder cancer cell lines expressing low levels of ASS1 failed to grow in an arginine-free medium, indicating that ASS1 behaves as a tumor suppressor.<sup>[83]</sup> In addition, TAMCs express high levels of another enzyme in the arginine metabolism, arginase 1 that hydrolyses arginine into urea and ornithine and sustains tumor growth by providing precursors for polyamine synthesis.<sup>[84]</sup> However, TAMCs can arrest cytotoxic T cell proliferation and induce T cell dysfunction by more than one mechanism, including generation of nitric oxide from arginine by nitric oxide synthase.<sup>[85]</sup>

### Tryptophan

Tryptophan catabolism in cancer is increasingly being recognized as an important micro-environmental factor that suppresses antitumor immune responses. It has been proposed that the essential amino acid tryptophan is catabolized in the tumor tissue by the rate-limiting enzyme indoleamine-2,3-dioxygenase (IDO) expressed in tumor cells or antigen-presenting cells. This metabolic pathway creates an immunosuppressive milieu in tumors and in tumor draining lymph nodes by inducing T-cell energy and apoptosis through depletion of tryptophan and accumulation of immunosuppressive tryptophan catabolites.<sup>[86]</sup>

### Relationship between protein, lipid and carbohydrate metabolism in cancer

Cancer cells often display a high rate of glucose consumption, even under oxygen-rich conditions, a process termed aerobic glycolysis or 'Warburg effect'.<sup>[87]</sup> Warburg postulated that increased energy production by aerobic glycolysis in cancer cells was a consequence of impaired mitochondrial oxidative metabolism.<sup>[88]</sup> However, it is now evident that tumor rarely exhibit mitochondrial defects and that most cancer cells still rely on oxidative phosphorylation to produce the majority of their energy.<sup>[89]</sup> Moreover, aerobic glycolysis is not exclusive to tumor cells, but is also a common feature of proliferative normal cells.<sup>[90]</sup> The primary function of elevated aerobic glycolysis is to generate biomass by diverting glycolytic intermediates towards the biosynthesis of macromolecules (nucleotides, lipids, proteins) required for rapidly proliferating tumor cells

(figure 5).<sup>[91]</sup> An alternative model of cancer metabolism called the ‘reverse Warburg effect’ has been described more recently. In this model, glycolytic stromal cells under oxidative stress generate lactate, ketone bodies, glutamine and fatty acids that are taken up by metastatic tumor cells to generate energy through the oxidative mitochondrial metabolism.<sup>[92]</sup> While this phenomenon may have relevance to the anti-tumor effect of natural antioxidants.<sup>[93]</sup> Increased amino acid consumption resulting from overexpression of cell surface transporters in tumor cells provides an alternative to glucose. Most notably, glutamine is utilized as a source of nitrogen and carbon to generate biosynthetic components and for mitochondrial metabolism, essential for growth, proliferation and survival (figure 5).<sup>[94]</sup>

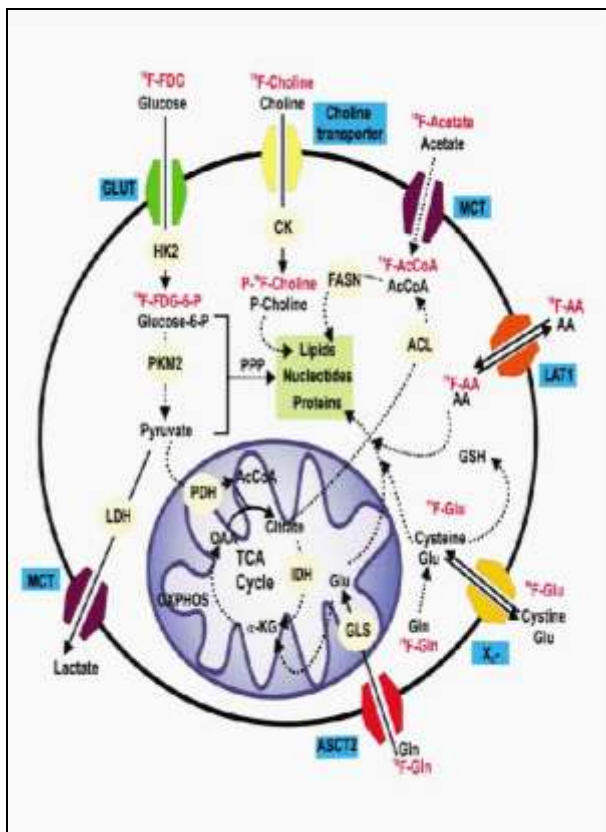


Figure 5 Schematic of key metabolic pathway in cancer.<sup>[95]</sup>

HK2=hexokinase2; PKM2=pyruvate kinase m2; LDH=lactate dehydrogenase PDH=pyruvate dehydrogenase; IDH=isocitrate dehydrogenase; GLS=glutaminase; ACL=atp-citrate lyse; FASN=fatty acid synthase; CK=choline kinase; GLUT=glucose transporter; MCT=monocarboxylate transporter; LAT1=system 1 amino acid transporters; ASCT2=systeme ASCT glutamine transporter; Xc=glutamate transporters; 18F-FDG-6-PHOSPHATE; GLUCOSE-6-P=glucose-6-phosphate; PPP=pentose phosphate pathway; AcCoA=acetyl CoA; a-KG=α-ketoglutarate; OAA=oxaloacetate; OXPHOS=oxidative phosphorylation; TCA cycle=tricarboxylic acid cycle; Gln=glutamine; 18F-Glu=18F-labelled glutamate

analogues; GSH=glutathione; AA=amino acids; 18F-AA=18F-labelled amino acid analogues; P-choline=phosphocholine.

Alterations in lipid biosynthetic pathways also have been described in cancer.<sup>[96]</sup> Unlike most normal cells, tumor cells reactivate de novo lipid synthesis.<sup>[97]</sup> Fatty acid synthesis contributes to many aspects of transformation, including survival under oxidative and energy stress, maintenance of high glycolytic rate, growth and proliferation.<sup>[96]</sup> Among other alterations, the expression of fatty acid synthase, an enzyme essential for fatty acid synthesis, is increased in several cancers including breast and prostate tumors.<sup>[98]</sup> Perhaps the most significant development in recent years is the realization that metabolic reprogramming is intimately linked to oncogenic signaling. Activation of oncogenic pathways, or the loss of tumor suppressors, increases glycolysis by upregulating the expression of glucose transporters and/or several of the glycolytic enzymes.<sup>[99]</sup> Induction of the transcription factor HIF-1 under hypoxia leads to increased expression of fatty acid synthase, thereby promoting lipogenesis for membrane formation and energy storage.<sup>[96]</sup> PI3 kinase/AKT signaling can activate ATP-citrate lyase, which converts cytoplasmic citrate into acetyl-CoA to promote lipid synthesis.<sup>[99]</sup> The characterization of cooperative interactions between metabolic and oncogenic has identified several key molecular targets for diagnostic imaging and/or therapy and prompted the development of several metabolic inhibitors, many of which are already under pre-clinical evaluation.<sup>[100]</sup>

### Complication of abnormal protein metabolism in cancer

#### Angiogenesis and metastasis

The proximity of a cancer cell to a blood vessel determines its fate, whereas cancer cells located farther than 150 μm from a vessel undergo programmed cell death.<sup>[101]</sup> Tumor growth to a size beyond a few millimeters in diameter leads to hypoxia and nutrient deprivation, which activate the ‘‘angiogenic switch’’ and allow tumors to progress.<sup>[102]</sup> Cancer cells produce cytokines and growth factors that act in an autocrine manner to promote their own expansion, and in a paracrine fashion to convey information to quiescent adjacent cells. Angiogenesis diminishes the metabolic pressures associated with unrestricted cancer cell division and increases the likelihood of cancer cell dissemination. The tumor microenvironment becomes enriched in vascular endothelial growth factor (VEGF), a primary mediator of pathological angiogenesis.<sup>[103]</sup>

#### Mechanisms of tumor induced angiogenesis

The mechanism includes; degradation of the basement membrane by proteases, migration of the endothelial cells into the interstitial space and sprouting, proliferation of the tip cells and lumen formation, formation of anastomoses and establishment of blood flow.<sup>[104]</sup>

Endothelial cells have major role in tumor angiogenesis. It is observed that blood vessels are primarily formed by endothelial cells.<sup>[105]</sup> Endothelial cells contain F actin and non-muscle myosin filaments called as cytoskeleton cables that contract in response to growth factors.<sup>[106]</sup> Furthermore, growth factors released by tumor cell and tumor microenvironment induce formation and reorganization of these endothelial filaments. Reorganized endothelial cells then divide continuously to form a migration column, a rope like sequence to form hollow tubes, to allow blood flows. Endothelial cells adhere to each other to form a lumen while the basement membrane is formed. Finally, the blood vessel sprouts fuse with each other, to form a circulatory system.<sup>[107]</sup>

Remodeling of the extracellular matrix proteins (ECM) is an integral component of the angiogenic process. A variety of mechanisms have been documented about how the ECM plays a pivotal role in regulating angiogenesis.<sup>[108]</sup> Major ECM proteins that promote angiogenesis include collagen, laminin and fibronectin. Collagen IV and laminin are predominate proteins of the basal lamina, a 50nm wide ECM that provides structural support for endothelial cells and creates a separation from the adjacent perivascular cells. The majority of ECM proteins mediate angiogenesis through arginine-glycine-aspartic acid (RGD) motifs, which bind to integrins that mediate outside in signaling.<sup>[109]</sup>

One mechanism for driving angiogenesis results from the increased production of vascular endothelial growth factor (VEGF) following up-regulation of the hypoxia-inducible transcription factor.<sup>[110]</sup> VEGF and its receptors play a pivotal role in normal and pathologic angiogenesis. Activation of the VEGF/VEGF-receptor (VEGFR) axis triggers multiple signaling networks that result in endothelial cell survival, mitogenesis, migration and differentiation, and vascular permeability and mobilization of endothelial progenitor cells (EPCs) from the bone marrow into the peripheral circulation.<sup>[111]</sup>

### Metastasis

Metastases represent the end products of a multistep cell-biological process termed the invasion-metastasis cascade, which involves dissemination of cancer cells to anatomically distant organ sites and their subsequent adaptation to foreign tissue microenvironments. Each of these events is driven by the acquisition of genetic and/or epigenetic alterations within tumor cells and the co-option of nonneoplastic stromal cells, which together endow incipient metastatic cells with traits needed to generate macroscopic metastases.<sup>[112]</sup> A higher number of patients will also have micrometastases that would be beyond conventional detection techniques. Thus, metastasis is the most life threatening event in patients with cancer. The process is composed of a number of sequential events which must be completed in order for the tumor cell to successfully metastasize, the so called metastatic cascade. This process contributes to the complexity of cancer as a multiplex disease. During the

metastatic cascade, changes in cell-cell and cell-matrix adhesion are of paramount importance.<sup>[113]</sup>

Within the primary tumor, there is clonal proliferation of cells that develops the capacity to invade and metastasize. First key step in invasion is for malignant cells to lose their cell-to-cell adhesion molecules (cadherins). Second key step is for cell receptors to attach to laminin (a glycoprotein) in the basement membrane and to release metalloproteinases (e.g., collagenases, stromelysins, gelatinases) to degrade the basement membrane and other enzymes to degrade the interstitial connective tissue. Third key step is for cell receptors to attach to fibronectin and other proteins in the extracellular matrix (ECM) and to break it down.<sup>[44]</sup> The blood vessel within the tumor's vicinity can then provide a route for the detached cells to enter the circulatory system and metastasize to distant sites.<sup>[114]</sup> Transport; the movement through the bloodstream is "one-way", tumor cells travel singly or as clumps with platelets, called emboli, in the direction of blood flow. Emboli may protect tumor cells from sheer forces inside the bloodstream.<sup>[49]</sup> Extravasation; once the tumor cell has arrived at a likely point of intravasation, it interacts with the endothelial cells by undergoing biochemical interactions develops adhesion to the endothelial cells to form stronger bonds, and thus penetrates the endothelium and the basement membrane. The new tumor can then proliferate at this secondary focus.<sup>[115]</sup> Metastatic colonization; last stage of metastasis and involve the establishment of a progressively growing tumor at a distant site, involving the formation of new blood vessels as an essential process to provide nutrients and oxygen.<sup>[49]</sup>

### Proteins of metastasis

Several evidences show that osteopontin (OPN) is involved in different processes associated with malignancy such as increased cellular migratory and invasion, increased metastasis, protection from apoptosis.<sup>[116]</sup> OPN signaling pathways mediate tumor progression and metastasis by: 1- Inhibition of apoptosis; 2-Extracellular matrix invasion; 3- Tumor cell adhesion and migration; 4-Evasion of host immunity; 5- Neovascularization.<sup>[117]</sup>

Galectin-3 expression is related to neoplastic transformation and progression toward metastasis in breast<sup>[118]</sup>, colon, stomach and thyroid.<sup>[119]</sup> Galectin-3 expression was shown to increase migration and/or invasion of melanoma<sup>[120]</sup>, lung cancer<sup>[121]</sup>, sarcoma<sup>[122]</sup> and gastric cancer.<sup>[123]</sup>

Fibroblast activation protein  $\alpha$  (FAP $\alpha$ ) is a transmembrane serine protease and is highly expressed on cancer associated fibroblasts present in >90% of human epithelial neoplasms.<sup>[124]</sup> Furthermore, FAP plays a role in matrix digestion and invasion through its gelatinase activity.<sup>[125]</sup> FAP $\alpha$  secrete peptides can cleave native ECM proteins, including collagen I, collagen IV,

fibronectin, laminin and gelatin.<sup>[126]</sup> Also, FAP $\alpha$  have a prominent role in tumor invasion, metastasis and angiogenesis.<sup>[127]</sup>

Actin associated proteins have well-defined functions in tumor cell invasion, such as filopodia, lamellipodia and invadopodia.<sup>[128]</sup> Malignant cancer cells utilize their intrinsic migratory ability to invade adjacent tissues and the vasculature and ultimately to metastasize. Recently, several studies revealed that molecules that link migratory signals to the actin cytoskeleton are upregulated in invasive and metastatic cancer cells.<sup>[129]</sup> An epithelial-mesenchymal transition (EMT) is a biologic process that allows a polarized epithelial cell, to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype, which includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and greatly increased production of ECM components.<sup>[130]</sup> Activation of an EMT program has been proposed as the critical mechanism for the acquisition of malignant phenotypes by epithelial cancer cells.<sup>[131]</sup>

A critical aspect of invasive and metastatic behavior involves adhesive interactions of tumor cells with other cells or extracellular matrix through the integrin family of cell surface receptors.<sup>[132]</sup> Keller and Brown showed frequent association of bone metastasis with advanced prostate cancer is determined by integrin-mediated interaction of metastatic cancer cells and bone microenvironment.<sup>[133]</sup> Tumor cell expression of ( $\alpha$ v $\beta$ 3,  $\alpha$ v $\beta$ 5,  $\alpha$ 5 $\beta$ 1,  $\alpha$ 6 $\beta$ 4) integrins correlated with metastatic progression in melanoma, breast carcinoma, prostate and pancreatic and lung cancer.<sup>[134]</sup>

### Cachexia

Cancer cachexia was defined as a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Its pathophysiology characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. The agreed diagnostic criterion for cachexia was weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (body-mass index [BMI] <20 kg/m<sup>2</sup>) or skeletal muscle mass (sarcopenia).<sup>[135]</sup> Thus, patients suffer of severe muscle wasting, ongoing catabolism, low performance status, and metastatic disease. At this stage, the goal of therapy is palliation of symptoms and reduction in distress for both patient and family.<sup>[136]</sup>

### Energy expenditure

Increased energy expenditure would also contribute to the wasting process. About 70% of the total energy expenditure in sedentary people arises from the resting energy expenditure (REE). The REE in cancer patients is

strongly determined by the type of tumor. Thus, REE is elevated in patients with both lung<sup>[137]</sup> and pancreatic cancer<sup>[138]</sup>, while there is no increase in REE in patients with gastric and colorectal cancer.<sup>[137]</sup> These observations may reflect how close the patients were to death at the time of measurement, since malnourished patients near death show an increased REE, which could relate to the utilization of the last skeletal muscle mass.<sup>[139]</sup>

### Protein metabolism in cachexia

Cachexia is characterized by a specific loss of skeletal muscle, while the non-muscle protein compartment is relatively preserved. This loss can be very large, thus in lung cancer patients who had lost 30% of their pre-illness stable weight there was a 75% fall in skeletal muscle protein mass. This leads to a general muscle weakness (asthenia) and death from immobility and hypostatic pneumonia.<sup>[140]</sup>

Muscle wasting is important in the pathophysiology of cachexia and a major cause of fatigue in patients.<sup>[141]</sup> Accelerated or exaggerated loss of skeletal muscle mass distinguishes cachexia from weight loss that is due solely to reduced energy intake. Several groups of investigators have suggested that actomyosin, actin and myosin are selectively targeted for degradation in clinical conditions associated with cachexia. Acharyya *et al.*<sup>[142]</sup> wrote that "cachectic factors are remarkably selective in targeting myosin heavy chain." In mice with colon-26 tumors, they found that 2 markers of inflammation that are typically elevated with cachexia, tumor necrosis factor- $\alpha$  and interferon- $\gamma$ , reduce the expression of myosin. These data suggest that myosin is a specific target and that both protein-degradative and synthetic pathways are influenced. Selective targeting of skeletal muscle is at least in part due to the systemic inflammation that frequently accompanies clinical conditions associated with cachexia. It also appears that the rate of muscle protein degradation is up-regulated. Nuclear transcription factor  $\kappa$ B (NF- $\kappa$ B) activation may be an important regulator of skeletal muscle proteasome expression and protein degradation. Inhibitors of NF- $\kappa$ B completely attenuated protein degradation in murine myotubes and the NF- $\kappa$ B inhibitor resveratrol significantly attenuated weight loss and muscle protein degradation in mice bearing the MAC16 tumor.<sup>[143]</sup>

Cachexia is also associated with a reduction in circulating anabolic hormones. Testosterone concentrations are greatly reduced in patients with cachexia, resulting in a down-regulation in the rate of muscle protein synthesis. Although circulating growth hormone and insulin-like growth factor-I (IGF-I) appear to be unchanged (compared with normal concentrations) in patients with heart failure, Hambrecht *et al.*<sup>[144]</sup> described a resistance of skeletal muscle to the influence of growth hormone, including a 52% reduction in expression of IGF-I and IGF-I receptor.

Although delivery of nutrition in patients with cachexia may provide energy and amino acids for protein synthesis, in certain cachectic conditions, providing energy and protein maintains weight but not muscle mass.<sup>[145]</sup> In these patients, weight loss occurred when delivery of energy was less than total energy expenditure that increased as a result of a substantial increase in basal metabolic rate.<sup>[146]</sup>

### Proteins and prevention of cancer

#### Limit consumption of processed meats and red meats

Reduce eating meat and dairy products higher intake of red meat, especially processed meat, has been associated with greater risk of colorectal cancer in many prospective studies and in a meta-analysis of these studies.<sup>[147]</sup> Although consumption of meat during midlife or later has generally not been associated with risk of breast cancer, a positive relation has been seen with intake in adolescence and early adult life.<sup>[148]</sup> Minimize consumption of processed meats such as bacon, sausage, luncheon meats and hot dogs. Moreover, choose fish, poultry, or beans as an alternative to red meat (beef, pork and lamb). Additionally, prepare meat, poultry and fish by baking, broiling, or poaching rather than by frying or charbroiling.<sup>[149]</sup> Additionally, in October, 2015, 22 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of the consumption of red meat and processed meat. IARC has classified processed meat as a carcinogen, something that causes cancer. And it has classified red meat as a probable carcinogen, something that probably causes cancer. IARC is the cancer agency of the World Health Organization.<sup>[150]</sup>

### Soy Products

Soy and foods derived from soy are an excellent source of protein and contains several phytochemicals, and is a rich source of isoflavone phytochemicals, which have weak estrogenic activity and may protect against hormone-dependent cancers. There is growing evidence from epidemiologic studies that the consumption of traditional soy foods such as tofu may decrease the risk of cancers of the breast, prostate, or endometrium, and there is selected evidence for a risk reduction of some other cancers.<sup>[151]</sup>

### Proteins and treatment of cancer

#### Suppressor protein; P53

P53 is known as a tumor suppressor gene important for maintenance of genomic integrity. In addition, P53 is regulated by MDM2 protein which participates in p53 rapid degradation. The activation and accumulation of p53 is a response to cellular stress such as DNA damage. Activated p53 is a sequence specific DNA-binding transcription factor and some target genes of its transcriptional activity are important for cell-cycle arrest or for inducing apoptosis.<sup>[152]</sup> Interactions between MDM2 and p53 with small-molecule inhibitors (Table 3) is targeted in cancer therapy to activate p53.<sup>[153]</sup>

Numerous strategies have been devised to correct a dysfunctional p53-regulatory pathway. Small-molecule inhibitors of the p53–MDM2 interaction, p53 gene therapies and drugs that act as chaperones by binding to mutant p53 and restoring its function are some of the approaches currently in clinical trials (Table 2). A breakthrough in the field was the development of nutlin, the first small-molecule inhibitor of the p53–MDM2 interaction.<sup>[154]</sup>

**Table 2: P53 activators currently in clinical trial.**<sup>[153]</sup>

Compound(drug)	Mechanism of action	Company
RG7112 (also known as RO5045337)	Small-molecule MDM2 antagonist	Roche
PRIMA-1MET (also known as APR-246)	Reactivation of mutant p53	Aprea

**Table 3: Compounds that bind to MDM2 or mutant p53**

Compounds (drug)	Mechanism of action	Refs
Nutlin 3a, RG7112, RG7388, Ro-2443	binding to MDM2	[155]
PRIMA-1MET (also known as APR-246)	protein folding	[156]

### Amino acid metabolic enzymes targeted in cancer therapy

Recent advances in amino acid metabolism have revealed that targeting amino acid metabolic enzymes in cancer therapy is a promising strategy for the

development of novel therapeutic agents. There are currently several drugs in clinical trials that specifically target amino acid metabolic pathways in tumor cells (table 4).<sup>[157]</sup>

**Table 4: Amino acid metabolic enzymes targeted in cancer therapy.**

Amino acid metabolism	Targeted enzyme	Drug design	Cancer type	Ref
Arginine	ASS1, Arginine deaminase	ADI-PEG20	HCC (non resectable and metastatic)	[158]
Tryptophan	IDO	Indoximod and docetaxel	Various metastatic solid tumors	[159]
Serine	PHGDH	Neuraminidase enzyme (NA)	Melanoma and breast cancer cell lines (SkBr3, MCF7)	[35]
Glycine	SHMT1	NA	Accelerated lymphomagenesis	[160]
Glutamine	Glutamine-dependent Enzymatic steps	L-DON2, azaserine2	Various animal and human xenografted tumors	[161]
Leucine, Isoleucine, Valine	BCATc	NA	U-87MG glioblastoma cells with BCATcsh RNA; tumor site-intracerebral transplantation	[162]

### 3- Anti-angiogenic therapy

Few anti-angiogenic drugs could prove to be efficient enough for being considered as candidates for monotherapy, ongoing preclinical and clinical trials are providing growing evidence that this therapeutic approach would yield best result when conjugated with conventional therapy, precisely with standard

chemotherapy (Table 5).<sup>[163]</sup> Bevacizumab or Avastin is a humanized monoclonal VEGF antibody against soluble VEGF and has been investigated in numerous preclinical and studies (table 5). Small receptor tyrosine kinase inhibitors are a leading class of anti-angiogenic drugs which have undergone extensive investigation.<sup>[164]</sup>

**Table 5: Inhibitor angiogenesis drugs and target molecule.**

Drug	Target	References
Vandetanib	VEGFR-1,-2,-3,EGFR	[164]
Sunitinib	VEGFR-1,-2,PDGFR	[164]
Bevacizumab	VEGF-A	[165]
Marimastat	MMP-1,-2,-3,-7,-9	[165]
Etaracizumab	Integrin $\alpha$ V	[166]
Prinomastat	MMP-2,-9	[167]
Rebimastat	MMP-1,-2,-8,-9,-13,-14	[168]
Neovastat	MMP-2,-9,-12,VEGF	[164]

### Targeting tyrosine kinases agents

Targeted therapy refers to a new generation of anticancer drugs that are designed to interfere with a specific molecular target, usually a protein with a critical role in tumor growth or progression. This approach differs from the more empirical approach used in conventional cytotoxic chemotherapy, which has remained the mainstay of anticancer drug use over the past several decades.<sup>[169]</sup> Targeted therapy has the potential to reduce

or eliminate many of the present problems in the field of cytotoxic chemotherapy, such as the production of serious host-cell toxicity. Several types of targeted therapy are available, but this review focuses in particular only on small molecule tyrosine kinase inhibitors. Have been approved for use in cancer therapy, and several others are in various stages of clinical trials. (Table 6) provides a summary of these agents and their use in cancer therapy.<sup>[170]</sup>

**Table 6: Tyrosine kinase inhibitors for treatment of cancer**

Inhibitor	Tyrosine Kinase Target	reference
Gefitinib (Iressa)	ErbB1 (EGFR)	[171]
Lapatinib (GW-572016)	ErbB2	[172]
Canertinib (CI-1033)	EGFR (nonselective)	[173]
Semaxinib (SU5416)	VEGFR-2 c-IT FLT-	[174]
Vatalanib (PTK787/ZK222584)	VEGFR-1 (Flt-1)	[175]
Sutent (SU11248)	VEGFR	[176]
Sorafenib (BAY 43-9006)	B-Raf	[177]
Leflunomide (SU101)	PDGFR	[178]

### Conclusions and perspectives

Cancer cells must rewire cellular metabolism to satisfy the demands of growth and proliferation. Recently,

researchers begun to understand the precise biologic nature of these changes and that these altered metabolic processes can be a fundamental driver of tumor growth,

rather than simply being a consequence of the cancer. There is clearly a great deal to be learned about the interrelation of glucose and glutamine metabolism in support of cell growth and proliferation, and how nutrient metabolism is coordinated to support successful cell growth/proliferation. There is mounting evidence for cross-talk between signaling pathways and metabolic control in every multicellular organism studied. Our understanding of tumor protein metabolism continues to evolve as advances in several modeling strategies and integrated strategies for use in therapeutic studies. Therefore, the ultimate goal is to design treatment strategies that affect several protein metabolism pathways that slow tumor progression, improve the response to therapy and result in a positive clinical outcome. Moreover, if we are not able to eradicate cancer in the future decades, there is still much great effort should be done to prevent cancer occurrence with healthy diet and change our lifestyle.

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None Declared.

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