MINIREVIEW

GLYCOLYSIS, GLUTAMINOLYSIS AND CELL PROLIFERATION

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GLYCOLYSIS AND GLUCOSE METABOLISM

Since the original observation that a high rate of aerobic glycolysis is a hallmark of malignant cells (Warburg, 1926), considerable effort has been devoted to elucidation of the role of glycolysis in normal and transformed cell proliferation. Many explanations have been put forward to explain the high flux of glucose to lactate in proliferating normal and transformed cells (Warburg, 1926; Papaconstantinou et al., 1963; Gregg, 1972; Singh et al., 1974a, b; Wenner, 1975; Racker, 1976; Sols, 1976; Wang et al., 1976; Weinhouse, 1976; Fagan and Racker, 1978; Hume et al., 1978; Lazo and Sols, 1980; Eigenbrodt and Glossmann, 1980). However, none have been conclusive enough to determine whether the high glycolytic rate is essential for cell growth or a consequence of other metabolic processes that occur during cell proliferation.

It has been clear for some time that gross defects in respiration are neither a general property of tumor cells and proliferating normal cells nor the cause of a high rate of glycolysis. Many tumor cells and proliferating normal cells, that exhibit a sufficiently high rate of aerobic glycolysis to result in stochiometric conversion of glucose to lactate, consume oxygen normally and are equipped with adequate levels of mitochondrial enzymes that are necessary to completely oxidize pyruvate (Gregg, 1972; Roos and Loos, 1973; Weinhouse, 1976; Donnelly and Scheffler, 1976; Pederson, 1978; Hume et al., 1978). Several important recent observations using isolated cells in culture have shed more light on the role of glucose metabolism in normal and abnormal cell proliferation and in the expression of the malignant cell phenotype.

Glucose transport and pool sizes. Although glucose transport increases during normal cell proliferation and constitutively in some transformed cells, the increase in membrane transport and the intracellular pool size of glucose have been dissociated from increase in the rate of DNA synthesis and cell growth (Barsh and Cunningham, 1977). Others have cast doubt on the significance
of differences in rates of membrane transport in normal and virally-transformed cells because of technical problems in differentiating rate of glucose uptake from glucose metabolism (Romano, 1976).

**Specific mutations in glucose metabolism.** Mutants have been isolated with a reduced rate of glucose uptake and with lesions at specific points in the glycolytic pathway. Variants of Chinese hamster ovary cells were induced that transported either 2-deoxy-glucose or 3-O-methylglucose (glucose analogues) at 20 percent the normal rate (Pouységur et al., 1980). Variants have also been induced that were deficient in glucosephosphate isomerase and phosphoglycerate kinase activities (Pouységur et al., 1980; Morgan and Faik, 1980). These mutations reduced lactate production from glucose to less than 10 percent of the wild-type value (Pouységur et al., 1980) yet the mutants survive, proliferate and exhibit malignant cell properties in the case of transformed cells. Although these results do not eliminate segments of the glycolytic pathway upstream or downstream from the mutations as essential to cell proliferation and the malignant phenotype, they cast doubt on the essential role of a high rate of glucose uptake and flux of glucose to lactate through the complete pathway.

**Glucose limitation experiments.** Glucose limitation experiments in vitro suggest that the quantitative requirement for glucose for growth of cells that exhibit high rates of glycolysis in the presence of high glucose is much lower than expected (Eagle et al., 1958; Graff et al., 1965; Renner et al., 1972; Rheinwald and Green, 1974; Hume et al., 1978). Limitation of external glucose or substitution of it with other hexoses resulted in a marked reduction in lactate formation without a proportional decrease in rate of proliferation of a number of normal and tumor cells in culture. These studies cast further doubt on the essential requirement for a high rate of flux of glucose to lactate and the derived energy in cell proliferation. However, since low levels of glucose or other carbohydrate were still required for cell proliferation, an essential role of glucose and segments of the glycolytic pathway in provision of essential precursors and some of the fuel for cell proliferation cannot be eliminated.

**Pentose metabolism.** At low glucose concentrations or in the presence of other hexoses where the glycolytic rate is diminished but cell proliferation continues, flux of hexose carbons through the pentose phosphate cycle to ribose and nucleic acids is considerable (Renner et al., 1972; Reitzer et al., 1979; 1980). In some cultured cells, an external pentose source completely replaced the hexose requirement for proliferation. Normal diploid human fibroblasts were able to undergo a limited number of cell divisions without glucose utilization if the medium contained hypoxanthine, thymidine, uridine and glycine (Zielke et al., 1976). Under certain conditions, high levels of uridine or cytidine (>100 μM) completely replaced the carbohydrate requirement for continuous proliferation.
of HeLa and several other cell types (Wice et al., 1981). Under the conditions, almost 90 percent of the metabolized uridine released its uracil and 23 percent of the ribose carbon appeared in nucleic acids (Wice et al., 1981). A significant amount of ribose carbons from uridine appeared as CO$_2$ (13-24%), apparently by recycling through the non-oxidative arm of the pentose cycle to fructose-6-phosphate, back to glucose-6-phosphate, and then through the oxidative arm of the pentose cycle (Wice et al., 1981). The appearance of ribose carbons in pyruvate and lactate was undetectable. Thus, the essential function of glucose in tumor cells and normal cells that proliferate may be to provide anabolic substrates rather than fuel for cell proliferation. These observations have led some authors to conclude that the high rate of glucose uptake and aerobic glycolysis observed in both proliferating normal and tumor cells is a consequence of an overall "metabolic strategy" of the proliferating cell to maintain high cytosolic levels of glucose-6-phosphate, fructose-6-phosphate and triosephosphates (Hume et al., 1978; Eigenbrodt and Glossmann, 1980). Glucose-6-phosphate, fructose-6-phosphate and triosephosphates are precursors for synthesis of ribose, fructose-6-phosphate for glucosamine-6-phosphate and triosephosphates for serine, glycine, and glycerol, all of which are essential for macromolecule and lipid biosynthesis during cell proliferation.

GLUTAMINE METABOLISM

Glutamine as a respiratory fuel. The realization that a high rate of glucose flux through the energy yielding steps of glycolysis is unessential for the proliferation of some cell types has lead to a re-examination of the role of sources other than carbohydrate that may fuel cell proliferation. Next to carbohydrate, amino acids are the most abundant source of reduced carbon in mammalian plasma and cell culture media that is available for oxidative metabolism. Glutamine is the most abundant single amino acid in plasma, tissues in general, and cell culture media (Van Slyke et al., 1943; Ham and McKeohan, 1979). It has long been known that various neoplasms have an enormous demand for glutamine, however, this was largely explained as a requirement for glutamine for protein and an amino group donor for nucleic acid precursors (Roberts and Borges, 1955; Rabinovitz et al., 1956; Roberts et al., 1956; Roberts and Simonsen, 1960). Glutaminase activities showed a good correlation with the growth rates and degree of malignancy of several rat tumors (Knox et al., 1967; 1969; Linder-Horowitz et al., 1969). A correlation between glutamine- and glutamate-dependent respiration in isolated tumor mitochondria, the activity of mitochondrial glutaminases and the malignancy of hepatomas suggested that glutamine may be an important respiratory fuel for tumors (Kovačević and Morris, 1972; Regan et al., 1973). Several other early reports also hinted that glutamine may be a respiratory fuel in normal cells that can proliferate in vivo as enterocytes (Finch and Hird, 1960; Neptune, 1965), reticulocytes (Rapoport et al., 1971) and lens epithelium (Trayburn and van Heyningen, 1973).
More recently, vascular perfusion studies of intact rat intestine revealed that small intestinal mucosal cells selectively removed glutamine from the perfusate (Windmueller and Spaeth, 1974). Only 14% of glutamine carbons appeared in acid-insoluble material in the tissue while 57% appeared rapidly back into the perfusate as CO₂. Perfusate glutamine accounted for 32% of the total CO₂ produced even though the perfusate contained 10 to 15 mM glucose. About 19% of glutamine carbons appeared in the perfusate as lactate (Windmueller and Spaeth, 1975). Experiments using isolated cells in primary culture have confirmed that glutamine is extensively oxidized in non-proliferating rat and chicken enterocytes (Watford et al., 1979). Both tumor cells and other normal cells that proliferate in culture generally exhibit a high glutamine requirement (Eagle et al., 1956; Ham et al., 1977; Ham and McKeehan, 1979). This has also largely been explained as a requirement for protein and nucleic acid biosynthesis (Levintow et al., 1957; Salzman et al., 1957) as well as instability of glutamine under cell culture conditions (Gilbert et al., 1949; Tritsch and Moore, 1962; Griffiths and Pirt, 1967; Wein and Goetz, 1973). In 1972, Stoner and Merchant noted that cultures of mouse L-M strain fibroblasts utilized glutamine far in excess of the requirement for synthesis of cellular components. About 55% of glutamine carbons utilized by cells appeared as CO₂. It was estimated that the quantity of glutamine oxidized provided up to 35% of the energy requirement for cell proliferation, even though glucose was present at high levels in the culture medium. More recent studies have confirmed with different normal and tumor cell types in culture that a major fate of glutamine carbon is CO₂ and that the oxidation of glutamine provides up to 40% of the energy requirement for proliferating fibroblasts and HeLa cells, even when the glucose content of the medium is high (Donnelly and Scheffler, 1976; Zielke et al., 1976; Zielke et al., 1978; Reitzer et al., 1979). Glutamine can supply essentially all of the cellular requirements for energy when the supply of glucose is extremely low (Zielke et al., 1976; Reitzer et al., 1979; Wice et al., 1981). It is important to note here that all culture media in which the glucose limitation experiments discussed earlier were carried out probably contained high levels of glutamine. These results clearly implicate glutamine as a potentially important respiratory fuel for tumor cells and normal cells with proliferative potential in vivo and in vitro, even when glucose is present.

Glutaminolysis---the path from glutamine to pyruvate. In addition to CO₂ (35-60%) and macromolecules (15-25%), carbon from the skeleton of glutamine in most glutamine-utilizing systems appears mainly in glutamate (14-18%) and lactate (10-20%) (Stoner and Merchant, 1972; Windmueller and Spaeth, 1974; Reitzer et al., 1979; Zielke et al., 1980). Glutamine carbons distribute among other cellular organic acids in amounts that vary from 0.1% to 2% of the glutamine utilized. The fact that lactate is a major product of glutamine metabolism suggests a linear pathway for partial oxidation of glutamine to pyruvate that I propose to call "glutaminolysis"
(fig. 1). Such a linear pathway is analogous in many facets to glycolysis which describes the partial oxidation of glucose to pyruvate (lactate).¹

![Glutaminolysis pathway diagram](image)

**Fig. 1.** Glutaminolysis - the pathway of glutamine to pyruvate. [H] indicates reducing equivalents available for conversion to energy. Single arrows indicate probable irreversible reactions. Step 7 may consist of multiple steps described in the text.

Glutamine, like glucose, enters cells on a specific plasma membrane carrier (Kilberg et al., 1980). Removal of the 5-amide group of glutamine (fig. 1:1) is probably the "hexokinase step" of glutaminolysis. Similar to the phosphorylation of glucose, all known mammalian glutamine 5-amidotransferase reactions, whether the acceptor of the amino group (R₁-X in fig. 1) is aspartate, 5-phosphoribosylpyrophosphate, 5-phosphoribosylformylglycinamide ribonucleotide, xanthylc acid, fructose-6-phosphate, bicarbonate ions, UTP, desamido-NAD⁺ or H₂O are essentially irreversible (Meister, 1962; 1965). Similar to the hexokinase step of glycolysis, amidotransferase reactions, except where H₂O is the acceptor (simple glutaminase activity), require ATP either directly or in prior activation of the amido group acceptor (i.e., 5-phosphoribosylpyrophosphate). Fructose-6-phosphate is also an exception. Just as the phosphorylation of glucose traps glucose carbons intracellularly, the conversion of glutamine to glutamate by glutamine amidotransferases or glutaminases probably sequesters glutamine carbons as glutamate inside the cell. Glutamate and other dicarboxylic acids cross plasma membranes relatively poorly (Eagle et al., 1956; Hems et al., 1968). This is supported by experiments that show that glutamate is taken up and oxidized much less effec-

¹The term of glycolysis is most used to describe the linear pathway of glucose to lactate. The pathway of glucose to pyruvate is referred to more specifically as the Embden-Meyerhof pathway. Presently, I use glutaminolysis to describe the path of glutamine to pyruvate until more quantitative data becomes available on the fate of glutamine-derived pyruvate in different cell types.
tively than glutamine when applied to glutamine-utilizing systems in equal amounts in the medium (Rapoport et al., 1971; Trayburn and van Heyningen, 1973; Lavietes et al., 1974; Windmueller and Spaeth, 1975; Lazo, 1981). These properties suggest the removal of the 5-amide group of glutamine as a candidate for the committed step in glutaminolysis and for a control point of the pathway. The reversible conversion of the 2-amino group of glutamate to 2-oxoglutarate (fig. 1:2) is likely the second step in glutaminolysis. The reaction requires a 2-oxocarboxylic acid acceptor as co-factor if aminotransferase activity is involved or NAD(P)⁺ if glutamate dehydrogenase (EC 1.4.1.3) is involved (R₂= H in fig. 1). Liver and kidney cells have a means to remove both amino groups of glutamine in reverse order to steps 1 and 2 (fig. 1) by the combined activities of glutamine aminotransferase (glutamine + 2-oxoglutaramate) and ω-amidase (2-oxoglutaramate → 2-oxoglutarate) (Cooper and Meister, 1973). Both steps are essentially irreversible and lie far toward 2-oxoglutarate production because of the rapid non-enzymatic cyclization of 2-oxoglutarate to 5-hydroxy-2-pyrrolidone-5-carboxylate and the irreversibility of the ω-amidase reaction. The presence of these two enzymes in tumor and proliferating normal cell types that utilize glutamine as a respiratory fuel has not been reported.

Similar to the third step of glycolysis that is catalyzed by phosphofructokinase (Bloxham and Lardy, 1973), the third step of glutaminolysis is probably also irreversible and a candidate for regulatory control (fig. 1:3). The conversion of 2-oxoglutarate to succinyl-CoA by the mitochondrial 2-oxoglutarate dehydrogenase complex in glucose-oxidizing tissues is sensitive to Ca²⁺, ADP, ATP, H⁺, the ratios of [NAD⁺]/[NADH] and [succinylCoA]/[CoASH] (Denton and McCormack, 1980; Williamson and Cooper, 1980; Hansford, 1980; McCormack and Denton, 1981). Glutaminolysis presumably proceeds in the mitochondria of glutaminolytic cells by the conversion of glutamine-derived 2-oxoglutarate to succinylCoA by 2-oxoglutarate dehydrogenase activity. Two reversible, energy yielding steps convert succinylCoA to fumarate (fig. 1:4,5) followed by a reversible hydratase reaction that results in malate (fig. 1:6). Just as the Embden-Meyerhof pathway ends with the essentially irreversible conversion of phosphoenolpyruvate to pyruvate that is catalyzed by pyruvate kinase, glutaminolysis may end with the essentially irreversible conversion of malate to pyruvate (fig. 1:7). Recently, it has become apparent that a variety of tumor cells and normal cells with proliferative potential possess a mitochondrial NAD⁺-linked isozyme of malic enzyme [L-malate: NAD⁺ oxidoreductase (decarboxylating)] (Hansford and Lehninger, 1973; Lin and Davis, 1974; Mandella and Sauer, 1975; Sauer and Dauchy, 1978; Sauer et al., 1980; Nagel et al., 1980; McKeehan and McKeehan, 1982). A unique feature of the isozyme is that it works with either NAD⁺ or NADP⁺, catalyzes the irreversible decarboxylation of malate to pyruvate and does not catalyze the decarboxylation of oxalacetate at low pH. This is in contrast to
other mammalian isozymes of malic enzymes (Simpson et al., 1968; Lin and Davis, 1974). In addition, NAD\textsuperscript{+}-linked malic enzyme exhibits properties of a regulatory enzyme that is expected of the pacemaker enzyme at the end of a pathway (e.g., pyruvate kinase and glycolysis). Succinate, fumarate and isocitrate have been identified as positive activators and ATP and ADP as competitive inhibitors (in respect to malate) of NAD(P)\textsuperscript{+}-linked malic enzyme (Sauer, 1973; Lin and Davis, 1974; Mandella and Sauer, 1975). Although mitochondrial NAD(P)\textsuperscript{+}-linked malic enzyme is a good candidate for the irreversible conversion of malate to pyruvate, until more data is available, other more complicated possibilities for conversion of glutamine-derived malate to pyruvate must be left open (Windmueller and Spaeth, 1974; Zielke et al., 1980). An alternate irreversible conversion of glutamine-derived malate to pyruvate may occur by conversion of malate to oxalacetate and then phosphoenolpyruvate within the mitochondria. Phosphoenolpyruvate may then exit the mitochondria and be converted to pyruvate by cytosolic pyruvate kinase activity. Alternatively, malate derived from glutamine may exit the mitochondria for conversion to cytosolic pyruvate by extramitochondrial NADP\textsuperscript{+}-dependent malic enzyme (EC 1.1.1.40). However, this isozyme of malic enzyme catalyzes a reversible reaction (Simpson et al., 1968). Both glutaminolytic intestinal cells and cultured human fibroblasts are enzymatically equipped to carry out these conversions (Windmueller and Spaeth, 1974; Sumbilla et al., 1981; McKeehan et al., 1982).

Although glycolysis occurs exclusively in the cytosol of most mammalian cells (Lehninger, 1975), data from cell types studied so far suggest that glutaminolysis may occur exclusively in the mitochondrial compartment or may be divided between both cytosolic and mitochondrial compartments. Mouse ascites tumor and rat hepatoma cells have the capacity to completely oxidize glutamine carbons to acetyl\textsubscript{CoA} and \textsubscript{CO}_2 within the mitochondria (Sauer and Dauchy, 1978; Sauer et al., 1980). This is thought to be facilitated by mitochondrial, phosphate-dependent glutaminase (L-glutamine aminohydrolase; EC 3.5.1.2) (Linder-Horowitz et al., 1969; Knox et al., 1969; Kovacević, 1974) which converts glutamine to glutamate and \textsubscript{NH}_4\textsuperscript{+}, followed by oxidation of glutamate to malate (fig. 1), and conversion of malate to pyruvate by the NAD(P)\textsuperscript{+}-linked malic enzyme described above. Glutamine- or malate-derived pyruvate both effluxes from and is decarboxylated to acetyl\textsubscript{CoA} by pyruvate dehydrogenase in isolated mitochondria of hepatoma and ascites cells (Sauer and Dauchy, 1978; Sauer et al., 1980). The compartmentation of the two-step conversion of glutamine to 2-oxoglutarate (fig. 1:1,2) has not yet been established in other normal and transformed glutaminolytic cell types. Dependent on the amino group acceptor, either step may occur in the cytosol through glutamine amidotransferase activities (glutamine to glutamate) (Meister, 1962; 1965) and cytosolic aminotransferases (glutamate to 2-oxoglutarate). It is almost certain that the intermediate steps in glutaminolysis (2-oxoglutarate to malate) occur in the mitochondria.
since the enzymes involved (except fumarase, Janski and Cornell, 1980) are a segment of the tricarboxylic acid cycle which is strictly mitochondrial in cells that utilize glucose as major respiratory fuel (Lehninger, 1975). As described above, the most attractive candidate for the conversion of glutamine-derived malate to pyruvate is the mitochondrial NAD(P)+-linked malic isozyme, however, alternate possibilities may involve exit of glutamine-derived malate or phosphoenolpyruvate from the mitochondria for conversion to pyruvate in the cytosol. In cells where both the cytosol and mitochondrial matrix compartments of cells participate in glutaminolysis, then the influx/efflux of intermediates across mitochondrial membranes may be key steps of the pathway and subject to regulatory control (LaNoue and Schoolwerth, 1979).

Can cells proliferate in the absence of glutaminolysis? Since only specialized cells synthesize glutamine from glucose or other precursors and glutamine is required directly for translational protein synthesis, glutamine limitation experiments in cell culture similar to those described for glucose are difficult. The anabolic role of glutamine in amidotransferase reactions that yield glutamate is likely indispensable to cell proliferation. Free ammonium ions cannot substitute for the 5-amido group of glutamine in mammalian purine, pyrimidine, glucosamine and asparagine biosynthesis (Levintow, 1957; Salzman et al., 1957; Meister, 1962). However, mutants of presumably glutaminolytic cultured fibroblasts have been isolated with defects that cause a reduction in rate of oxygen uptake and oxidation of tricarboxylic acid cycle intermediates (DeFrancesco et al., 1974; Franchi et al., 1981). Such mutants still proliferate in vitro (usually at a reduced rate) and exhibit a high dependence on external glucose and glycolysis. DeFrancesco et al. (1974) also noted an increased dependence of mutant cell proliferation on external CO2/HCO3- and asparagine. Franchi et al. (1981) demonstrated that transformed cell mutants with reduced rates of oxygen uptake were also tumorigenic in immunosuppressed hosts, although the mutants initially formed tumors at a reduced rate and took longer to develop than wild-type cells or glycolytic mutants. These results suggest that a high rate of flux of glutamine carbons to pyruvate through the energy-producing steps of glutaminolysis (fig. 1) may be unessential to cell proliferation and expression of the malignant phenotype, if the supply of glucose and other anabolic substrates (or precursors) otherwise provided by glutaminolysis is adequate.

Conclusion. A common property of a number of tumor cells and normal cells that can proliferate when appropriate is a high rate of glucose metabolism to pyruvate and lactate (glycolysis) with little or no oxidation of pyruvate and a high rate of metabolism of glutamine carbons to carbon dioxide, pyruvate and lactate through oxidative pathways (glutaminolysis).

Interest in the role of glycolysis in normal and tumor cell proliferation has concentrated on its role in energy production
with less attention on its role in supplying anabolic precursors for biosynthesis. Conversely, studies on the role of glutamine have focused on its role in biosynthesis with less attention on its role as a respiratory fuel. The strategy of the proliferating cell may be to maintain simultaneously high rates of glycolysis and glutaminolysis. The advantages for supply of both anabolic substrates and energy for cell proliferation under both aerobic and anaerobic conditions are obvious. A high simultaneous flux of both glucose and glutamine through the energy-yielding segments of glycolysis and glutaminolysis, respectively, appears unessential to cell proliferation. Dependent on external conditions (or mutations), cells can rely on the energy-produced from either pathway when the other is reduced. Except in specialized cells, glucose and glutamine probably play essential anabolic roles in cell proliferation that cannot be replaced by the other. Glutamine is uniquely essential in amidotransferase reactions for purine, pyrimidine, asparagine and glucosamine biosynthesis. Glutamine may also supply the bulk of cellular glutamate, aspartate and acetylCoA (for cholesterol and fatty acid synthesis) in cells where entry of glucose carbons into the mitochondria is limited. Glutamine may also contribute cytosolic triosephosphates for serine, glycine and glycerol biosynthesis in glutaminolytic cells that have adequate activities of mitochondrial malate dehydrogenase for conversion of glutamine-derived malate to oxalacetate and phosphoenolpyruvate carboxykinase for conversion of the oxalacetate to phosphoenolpyruvate (McKeehan et al., 1982). Except in specialized cells with sufficient fructose bisphosphatase activity to yield fructose-6-phosphate from fructose-1,6-diphosphate derived from glutamine-derived triosephosphates, glucose or other carbohydrate is likely the unique source of ribose and glucosamine for macro-molecule synthesis.

The results reviewed here pose new questions concerning the regulation of normal cell proliferation by the supply of energy and anabolic substrates and the unregulated proliferation of transformed malignant cells.

1. What are the enzymes of glutaminolysis, their co-factors, activators, inhibitors and subcellular location, in different normal cell types that can proliferate? Both in vivo and in vitro studies are needed. However, cultured cells offer the opportunity to study, under defined and controlled conditions, different isolated cell types that compose a single tissue.

2. What is the effect of the external environment, proliferative state and malignant transformation on glutamine uptake, the activity of the enzymes and level of intermediates of glutaminolysis in different cellular compartments? Are the anabolic and energy-yielding sequences of both glutaminolysis and glycolysis affected differently by the above conditions?

3. Do the anabolic and energy-yielding segments of glycolysis and glutaminolysis sense the activity of the other? If so, what are the sensors and are the sensory mechanisms altered during
cell proliferation by hormone growth factors or by malignant transformation? A full understanding of the above questions should lead to better understanding of control of normal cell proliferation and new strategies to control abnormal cell proliferation.

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