Nuclear receptors and the Warburg effect in cancer

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Abstract

In 1927 Otto Warburg established that tumours derive energy primarily from the conversion of glucose to lactic acid and only partially through cellular respiration involving oxygen. In the 1950s he proposed that all causes of cancer reflected different mechanisms of disabling cellular respiration in favour of fermentation (now termed aerobic glycolysis). The role of aberrant glucose metabolism in cancer is now firmly established. The shift away from oxidative phosphorylation towards the metabolically expensive aerobic glycolysis is somewhat counter-intuitive given its wasteful nature. Multiple control processes are in place to maintain cellular efficiency and it is likely that these mechanisms are disrupted to facilitate the shift to the reliance on aerobic glycolysis. One such process of cell control is mediated by the nuclear receptor superfamily. This large family of transcription factors plays a significant role in sensing environmental cues and controlling decisions on proliferation, differentiation and cell death for example, to regulate glucose uptake and metabolism and to modulate the actions of oncogenes and tumour suppressors. In this review we highlight mechanisms by which nuclear receptors actions are altered during tumorigenic transformation and can serve to enhance the shift to aerobic glycolysis. At the simplest level, a basic alteration in NR behaviour can serve to enhance glycolytic flux thus providing a basis for enhanced survival within the tumour micro-environment. Ameliorating the enhanced NR activity in this context may help to sensitize cancer cells to Warburg targeted therapies and may provide future drug targets.

Keywords

Nuclear Receptors Respond to Environmental Signals

The Nuclear receptor (NR) super-family of transcription factors have wide-ranging actions. NRs sense environmental, systemic and local factors by binding a wide range of lipophilic molecules. They respond by regulating transcriptomes influencing fundamental processes such as proliferation and differentiation. Ligands for NRs are frequently derived from

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dietary derived factors and metabolism, and regulate processes such as glycolysis, oxidative phosphorylation and fatty acid synthesis (reviewed in Refs. 1–3). To achieve these actions NR bind with a variety of co-activators, co-repressors and histone modifying enzymes to form large DNA associated complexes that regulate chromatin structure and gene transcription (reviewed in Ref. 4).

Functionally, the 48 members of the human NR super-family fall into three main groups. Firstly, are those with high-affinity for ligand, such as steroidal receptors (*e.g.* AR and ERα) and seco-steroidal receptors such as VDR and the RARs. The VDR and RARs respond to dietary factors including vitamin D_3 and retinoids and do so at the low nM range, although there is evidence for low affinity binding to other dietary compounds, for example the VDR can bind certain bile acids.[5] The second group including the PPARs, FXRs, and LXRs have low binding affinities, but for a wider range of lipophilic molecules. These NRs respond to μM concentrations of dietary derived factors such as fatty acids and glucose. The classical steroid NRs are predominately in the cytoplasm in the absence of ligand and are shuttled in when activated. By contrast the VDR and RARs, and many other NRs that bind ligand with low affinity are bound to chromatin in the absence and presence of ligand; the addition of ligand re-distributes the receptor and changes the gene regulation function, generally to activation. Thereby regulating gene expression in the presence and absence of ligands allows distinct responses based on the local microenvironment, cellular milieu or other factors.

The final group, the orphan NR, are receptors for which either ligands have not yet been identified or contain no ligand binding domain, examples include NR4A1/NUR77 and ERRs. These orphan receptors frequently utilize co-factors in place of a true ligand, so can be regulated as the other two classes are but through changes in protein bioavailability.[6,7]

It has emerged that this receptor superfamily is centrally placed to regulate many pathways relating to energy metabolism and that analyses of their function has been central to the development of the field of Molecular Endocrinology.[8] These features pivotally position the NR superfamily to mediate cellular response to changes in nutrient availability and systemic and inter-cellular signaling. Coupled with these functions, it is also clear that their activity is frequently altered in cancer, and surprisingly, as a family, their expression is significantly distorted more than predicted by chance.[9] Together, therefore, by physiological and pathophysiological function the NRs appear to be intimately placed within the signaling cascades that are central to the Warburg effect.

The Central Cellular Role of ATP Production and the Warburg Effect

A primer on ATP production

Given that ATP is the fundamental energy unit of the cell, its generation is vital to maintain processes such as transporting molecules against concentration gradients, and protein and nucleic acid synthesis. Additionally the growing cell needs to make a choice over whether to divert glucose away from ATP production either to *de novo* fatty acid synthesis for the generation of cellular structures, or aromatic amino acids to aid in protein synthesis. The synthesis of ATP is therefore a tightly controlled process within the cell and there are many points during the generation of ATP on which signaling cascades converge to bring about

changes to ATP flux. Glucose metabolism provides the most efficient method of generating energy within the cell; other compounds such as proteins and fatty acids may be utilized but give reduced efficiency in the net generation of ATP. Glucose is therefore initially used as a substrate for glycolysis, and its breakdown products are, under normal aerobic conditions, also substrates for the citric acid cycle and oxidative phosphorylation (OXPHOS). For further information the reader is directed to some detailed reviews.[10–12]

Given this role for glucose, there are a host of glucose receptors present on the cell surface and the number and type of transporter vary greatly depending on the tissue and cell type and with disease status. Hexokinase is the first of several regulatory enzymes to process glucose and modifies it through phosphorylation to glucose-6-phosphate (G-6-P), the substrate for the rest of glycolysis and the pentose phosphate shunt (PPS). As G-6-P is not able to bind to glucose transporters, and can be converted to storage molecules such as glycogen, hexokinase has a key regulatory role by depleting the local levels of free glucose in the cell. For every one molecule of glucose, the immediate enzymatic reactions that ensue result in a net increase of two molecules each of ATP and pyruvate. Under normal aerobic conditions pyruvate is imported the mitochondria and is metabolized to Acetyl-CoA, a precursor of citrate, which is central to the citric acid cycle and fatty acid synthesis. Under these conditions maximum chemical potential (about 36 ATPs) is extracted *via* the metabolism of citrate into NADH and $FADH_2$ and finally ATP using the electron transport chain. Under anaerobic conditions, however, such as heavy muscle use, pyruvate entry to the mitochondria is prevented and is rapidly utilized ($\times 100$ faster than under aerobic conditions during OXPHOS) to generate a small amount of ATP (a net increase of just two ATPs) *via* lactate dehydrogenase (LDH) metabolism to lactic acid. This process is extremely inefficient at extracting chemical potential from the glucose; <5% of the total possible ATP is formed.

The Warburg effect–A metabolic shift

Production of ATP *via* "fermentation" as described by Otto Warburg, (now termed aerobic glycolysis) is a key feature of many cancer cells.[13] Tumor initiation and progression requires selection for the most aggressive and resilient cells to power and sustain proliferation and survival. Pathways such as glycolysis, oxidative phosphorylation and fatty acid synthesis are de-regulated to meet the requirements for ATP and precursors for *de novo* biomass.[14] Thus, the strong selection pressures within the tumor micro-environment selects for clones that can generate ATP rapidly at the expense of efficiency whilst also providing the necessary nutrients for rapid cellular division.[13,15,16] The observation that tumours produce massive amounts of the aerobic glycolysis waste product, lactic acid was central to the concept of deregulated metabolism[17,18] and that cancer was even termed "disorder of metabolism."[19] Although cancer is now more accurately defined in terms of genomics, it remains clear that there are substantial changes to metabolic pathways as result of genetic and epigenetic changes. This hallmark of cancer, now known as the Warburg effect, is so widespread and palpable that it has been used to identify primary and metastatic lesions through radio labeled glucose analogues combined with PET scanning for the last 20 years.[20]

Specifically, the Warburg Effect describes what happens in cancer cells when, although oxygen is plentiful, the cell shifts in preference of generating ATP away from the efficient

oxidative phosphorylation and towards the rapid aerobic glycolysis. Although wasteful of glucose, this has significant benefits for the tumour cell. Aerobic glycolysis produces ATP far quicker than the slow route of oxidative phosphorylation and results in the generation of crucial precursors for biomass production such as NADPH which is not produced at such levels *via* oxidative phosphorylation.[16] It is hypothesized that cancer cells utilize the rapid generation of ATP and the increase in *de novo* fatty acid synthesis to grow and divide quickly. The quickest dividing cells are by definition the ones to form the bulk of the tumor, in so long as their growth can be sustained.

Selection for induction of the Warburg shift is therefore likely, but whether this shift is a cause of cancer (due to the accelerated mutation rate in uncontrollably dividing cells) or a consequence downstream of other initiation events has not been experimentally validated. Irrespective of the cellular origins of these adaptations, the advantages to the cell are obvious; this shift not only allows rapid generation of ATP, fatty acids and nucleotides whilst glucose is abundant, but the generation of lactic acid ensures a tumour micro-environment protective against immune attack.[21] Furthermore, glucose flux modeling has indicated that mere presence of glucose elevated above a molecular tipping point turns the cell to be energetically in favour of aerobic glycolysis over oxidative phosphorylation, even in normal cells suggesting a role for cytosolic glucose sensors.[22] Glucose flux and intracellular concentrations in the cancer cell could therefor be the trigger for the Warburg effect to occur.

NR Signaling Impacts on Glucose Metabolism

Increased glucose uptake In cancer

The ultimate gatekeepers for the glucose avarice of tumor cells are the family of transport proteins that regulate the import of glucose. There are three classes of SLC2A/GLUT transport proteins and are grouped based on their sequence homology.[23] In normal biology several GLUTs are expressed in insulin and insulin growth factor (IGF) sensitive tissues and respond to the presence of both Insulin and the IGFs.[24] The class I GLUTs (1–4) appear especially important in cancer progression.[25] GLUT1 expression predicts survival in bladder cancer patients[26] and non-small cell lung tumour,[27] presence of thyroid cancer[28] and marks advanced breast cancer stages and breast cancer cells with high proliferative potential.[29] GLUT1 is also upregulated in colorectal cancers displaying KRAS or BRAF mutations. Intriguingly, however, this stems from glucose deprivation driving mutations in one of the two oncogenes as a way of redressing the glucose levels.[30] When cells with wild-type KRAS were deprived of glucose surviving cells showed a significant mutation rate in the KRAS allele and GLUT1 expression was elevated.

Reflecting the importance of GLUTs, their expression is tightly controlled, for example by repression by wild-type but not mutated p53.[25] Class I GLUT expression and activity is controlled by a range of NRs (Fig. 1). All class 1 GLUTs show tissue specific expression to some extent and are frequently over expressed in a range of tumour types. GLUT-4 expression, for example, is altered in breast cancer[31,32] and is translocated to the plasma membrane in an ER dependent manner.[33] PR as well can act alone and synergistically with ER to elevate GLUT4 expression and increase glycolytic flux.[34]

The TR binds and regulates expression of GLUT1, GLUT3, and GLUT4 in several cell types[35–38] both directly and indirectly through TR-mediated activation of PI3K and stabilization of HIF1α and mTORC1.[39] There is evidence that constitutive over-production of the ligand T_3 is caused by a point mutation in the TSH gene[40] and that this excess T_3 may over stimulate transcription of its downstream targets. Indeed, a range of cancer patients have significantly elevated levels of circulating T_3, T_4 and TSH and that the levels of these factors correlated with development of carcinogenesis.[41] Furthermore, Itoh *et at*. found that TRα1 mutant knock in mice were less able to utilize glucose in the brain,[42,43] but this mechanism in cancer has not been assessed.

Under normal conditions, GLUT4 imports glucose in adipocytes, in a T_3 regulated manner.[44] PPARδ regulates expression of TR directly and also combines with insulin signaling to induce uptake and storage of glucose in adipose tissue.[45] However, PPARδ is unable to upregulate GLUT4 directly, as demonstrated by the observation that GLUT2[46] but not GLUT4[45] is induced in mice treated with the PPARδ agonist GW501516. GLUT4 is, however, directly regulated by PPARγ through a validated PPRE in its promoter, ingestion of the PPARγ agonist pioglitazone by obese Zucker rats led to significant increase in expression of this transporter.[47] The VDR is also able to upregulate GLUT1 and GLUT4 expression in response to calcitriol in normal tissue, this upregulation was significantly more in diabetic models.[48]

Combinatorial NR gene regulation

Often multiple receptors bind at compound response elements. Most frequently there is kinetic competition for the common heterodimer and transactivation partner RXR. Other interactions include competitive binding; TRα can bind the PPRE at the AOX promoter and prevent access for the PPARδ/RXR heterodimer[49] thus antagonizes PPAR induced reporter gene expression.[50] TRα also appears to be a dominant regulator of PPAR-γ genes at some loci.[51] Another type of interaction occurs at the *CYP7A1* promoter where a compound PPARα-LXRα response element exists. Stimulation of either factor leads to gene expression, but stimulation of both prevents expression as the PPAR-LXR dimer binds instead of PPAR-RXR or LXR-RXR[52] This probably occurs throughout the genome; LXR and PPAR bind several degenerate response elements in direct competition with each other and with ChIP-Seq PPAR has been shown to bind to approximately 75% of all LXR sites.[53]

Given that Class I GLUTs are frequently dependent upon IGF signaling, the role for NR regulation in this process is complex. Whilst there appears to be a linear path for activation of GLUT gene transcription by many NRs, they also stabilize IGF activity through the induction IGF binding proteins (IGFBPs).[54–57] Conversely, the transcriptional co-repressors NCOR1 and NCOR2/SMRT are frequently elevated in different tumour types[56,58–60] and prevents expression of many NR targets, including IGF1.[61] However, these co-repressors are themselves under transcriptional control of multiple NRs including the ER[62] and the VDR,[63] allowing tight feed-back regulation to balance the pro-proliferative and anti-glycolytic function of NR co-repressors, as has been described in breast cancer. These observations suggest that tumours selectively target portions of the NR transcriptome to repress or enhance depending upon suitability for advancing tumour growth.

Glucose retention by hexokinase II

Glucose is efficiently retained within the cancer cell through enhanced heoxokinase activity. Hexokinase II (HKII) converts glucose to G-6-P and is a rate-limiting step for of ATP generation. HKII is particularly interesting as, in contrast to the other HK isoenzymes, it is over expressed in many cancers; it has a very high affinity for glucose, both catalytic domains rather than just one are active and it is tethered to the mitochondria allowing access to ATP and avoiding its product-inhibitor G-6-P (reviewed in Ref. 64).

Several NR converge on the regulation of HKII expression (Fig. 1), both directly through PPARγ,[65] CAR,[66] ERR[67,68] and indirectly[69,70] for example, through LXR activation of SREBP1.[71] NRs probably also contribute to its expression through their effects on PI3K activity. Despite HKII responding directly to glucose through elevated gene expression,[72] a characterized glucose cis-element within its promoter has not been identified. LXR is an intriguing candidate for this role. It is a glucose responsive transcription factor[73] and frequently binds to PPAR compound elements[53] (discussed above in Combinatorial NR gene regulation section) of which several have been identified in the HKII promoter. It will be of interest to determine whether LXR shares a compound element with the characterized PPAR response element in the HKII promoter and whether LXR antagonists prevent glucose mediated induction of HKII expression.

Enhancement of glucose metabolism

Free glucose (or G-6-P) can bind LXRs and induce transactivation of LXR targets genes involved in cholesterol, fatty acid and carbohydrate metabolism.[73] LXRs are expressed widely and in both normal and tumorigenic breast[74] and prostate cells.[75,76] Considering the huge intake of glucose in cancer cells, mere is a significant amount of substrate for the LXR to interact with. However, as many NR are regulated by co-repressors and co-activators,[77] the mere presence of ligand may not be sufficient to induce gene expression.

The co-repressors NCOR1 and NCOR2/SMRT limit signaling of NRs including LXRs, PPARs, VDR and RARs.[56,58–60,78–82]. This distortion results in selective skewing of the transcriptome (reviewed in Ref. 4). It remains a tantalizing possibility that LXRα signaling is similarly distorted to sustain the capacity of glucose to signal and facilitate further the Warburg effect. Indeed there is evidence this may occur; LXR has higher basal mRNA levels in prostate cancer cells than non-malignant counterparts and have diminished sensitivity to natural LXR ligands.[60] This is in agreement with data from the SAGE genie anatomical viewer which indicates LXRα shows approximately sevenfold mRNA elevation in tumour compared to non-malignant matched tissue. LXR agonism has significant anti-tumour function through inhibition of Akt activity in a cholesterol-mediated manner,[83] so whether it acts with oncogenic or tumour suppressor behaviour is unclear. Nonetheless epigenetic mechanism mediated *via* distorted co-repressor interactions may be central to the selective distortion of LXRs actions.

Glucose also induces FXR mRNA and protein expression and cooperates with FXR ligands to additively regulate several FXR targets involved in triglyceride and bile acid homeostasis.[84] This is counter to the actions of insulin which inhibit FXR expression and

FXR mRNA is lowered in two rat models of diabetes.[84] Again, there is reasonable evidence in malignancy that the normally well integrated actions of FXR are selectively disrupted and an oncogenic subset of the transcriptome is maintained in a transcriptionally responsive manner.[59,85–87]

These examples highlight the fact that there are several GLUT transporters controlled by NRs that are deregulated in cancer, which lead to increased levels of substrate for the metabolic pathways. A significant association occurs between expression of these GLUT family members and the selective and enhanced functions of key NR such as TR and LXR. In addition to enhancing transport of glucose, NRs can enhance the rate at which conversion to G-6-P by HKII occurs. The mere presence of excessive glucose within the cell appears sufficient for the cell to switch to aerobic glycolysis as a preferential form of energy generation.[22] NR deregulation may therefore aid in the shift to aerobic glycolysis solely because of elevated glycolytic flux. This is an attractive hypothesis as it supports the idea that mitochondrial dysfunction is not necessarily a pre-requisite for the Warburg shift.[88]

Downstream of the initial step of sequestration in glucose metabolism comes the key conversion of pyruvate to lactic acid. This reaction is controlled by the opposing actions of the LDH-A (forward) and LDH-B (reverse) isoforms.[89] Loss of LDH-B is an early event in breast cancer through promoter DNA methylation[90] and LDH-A expression, which drives conversion of pyruvate to lactate, is significantly enhanced in many cancer types. MYC and hypoxia[91] increase transcriptional expression of LDH-A. ChIP assays also revealed that ERRα binds to response elements within the promoters of both LDH-A and LDH-B isoforms in human thyroid cancer tissue and induces LDH gene expression.[92]

The involvement of the nuclear co-activator, PGC-1α, adds a layer of subtlety to the transcriptional relationship between ERRα and LDH. In skeletal cells, under oxidative stress induced by exercise, PGC-1α is able to differentially regulate the two major LDH isoforms. Using ERRα as a direct intermediaory, PGC-1a increases the ratio of LDH-B/LDH-A.[93] Direct stimulation of PPAR-β/δ may also support LDH-B expression in tumours as these NRs are able to induce expression of LDH-B *via* AMPK and MEK2.[94] LDH-B may also be driven indirectly by PPAR-γ through transcriptional activation of MEF2. Conversely, Estradiol (E_2) induces expression of LDH-A in the rat *via* its control over the CREB transcription factor.[95] A contribution to the effects of selective ER modulators (SERMs) is likely to be antagonizing lactate production.

Enhanced glucose metabolism influences the tumor microenvironment

A major corollary of enhanced glucose metabolism is the influence of the epithelial tumour cells over its microenvironment. The excretion of lactic acid causes acidification of the local area. The roles of Carbonic anhydrase XII (CA12) and monocarboxylate transporters (MCT) in this process of acidification are increasingly apparent. CA12 catalyzes conversion of CO_2 to bicarbonate thus acidifying the local region. MCTs are major transporters of lactate and other proton donating moieties. In breast cancer CA12 expression is tightly linked to ERα levels and estradiol stimulates its expression. Using chromatin conformation capture and ChIP assays, Barnett *et al*. established that a distal enhancer becomes bound by ERα and recruits RNA-polymerase and co-activators to the promoter of the CA12 gene.[96] Small

molecules targeting these acidification factors are currently under intensive research (reviewed in Refs. 97 and [98])

Secondary Effects of NRs in the Warburg Effect

The "Warburg kinase" AKT and HIF1a

AKT is a potent oncogenic kinase, and controls the expression and localization of several glucose transporters and hexokinase activity (reviewed in Ref. 70). AKT is amplified in breast and colon cancer[99] and deregulation is common in breast, prostate, pancreatic and gastric cancers.[100–102] AKT activation probably leads to HIF1α stabilization *via* mTORC,[103–106] even in the absence of hypoxia, further enhancing the aerobic glycolysis phenotype. Furthermore AKT deactivation of cell cycle checkpoints leads to rapid proliferation, an increased demand for ATP, and thus depletion of the cellular ATP/AMP ratio. This has the significant effect of deactivating AMPK, the "brake" that can limit the activity of PI3K (the upstream effector of AKT and mTORC).[107] Thus aberrant AKT imposes a positive feedback loop on cell growth by inducing factors that elevate glucose and allow its metabolism to generate ATP whilst repressing factors that control normal cellular checkpoints. PTEN can negatively regulate AKT signaling and is also frequently mutated in several solid cancers.[108–112]

NR regulation of AKT and HIF1a

Crucially, AKT and HIF1a are activated and controlled in multiple ways and the roles of several NRs in their regulation are significant. IGF1 which is stabilized by IGFBPs that in turn are downstream of multiple NRs including VDR,[113] ER [114] and RXR[115,116] can induce AKT activity along with insulin itself. The PV mutation in the TRβ causes hyper-activation of AKT by excessive phosphorylation.[117] T_3 can induce PI3K signaling *via* TR[118–120] and TRIP230, a THR co-factor, interacts with ARNT and HIF1α on the promoters of hypoxia inducible genes.[121] RARβ is downregulated through the PI3K/AKT pathway[122] and all-trans retinoic acid can activate the PI3K/AKT pathway *via* RARs in MEF's and COS-7 cells.[123] FXR is also documented to enhance AKT signaling,[124,125] which can establish positive feedback as AKT can activate PKC, which in turn phosphorylates FXR and cause recruitment of PPARgC1.[126] Interestingly, the co-repressor NCOR1 binds to and represses key members of the AKT/PI3K pathway and is repressed in thyroid cancers, presumably resulting increased AKT signaling.[117]

In addition to being regulated by NRs, activation of the AKT pathway can lead to the deregulation of several NRs. Perhaps surprisingly NUR77[127] which is a potent inducer of HIF1α[128] is inactivated by AKT signaling, although this may be cell type dependent.[129] More predictably however is the AKT mediated inhibition of RARα[130] and RAR mediated cell cycle arrest and differentiation. It is certainly possible therefore that AKT contributes to retinoid therapy resistance.

Under normal conditions, metabolic requirement and hypoxia are major factors governing the rate of metabolism and therefore processes such as glycolytic flux and synthesis of fatty acids. NRs alter these cellular decisions by altering their own transcription targets and influencing the activity of several signaling pathways such as AKT/PI3K. If AKT can cause

the switch to aerobic glycolysis by stabilizing HIF-1, then the switch is in part anticipatory of hypoxia rather than reactive. Switching to the glycolytic pathway increases the amount of lactic acid released by cells thereby causing an acidic environment around them. This selects for cells resistant to an acidic environment in the rapidly dividing tumor, prevents proper immune invasion and is damaging to surrounding normal tissue, thereby giving further mechanisms of selection for aggressive growth of the tumor.[131]

Impact on Cancer Diagnosis and Therapy

Highlighted in this review are nuclear receptors that impinge on multiple aspects of the glycolytic pathway in cancer; some support whilst other inhibit the Warburg effect, and their activity is either enhanced or suppressed to allow the shift to continue. Many NRs respond to dietary derived factors and environmental cues and thus represent a large repertoire of targets against which novel therapies can be directed, and many of which have been attractive targets for differentiation therapy. Stimulation of the NRs PPARd and the PPAR co-factor PGC1a could have a significant impact upon the ability of cancer cells to generate lactate from pyruvate because of their enhancement of the lactacte to pyruvate enzymatic reaction.

Summary

NRs integrate endocrine signals and those from the microenvironment, to control cellular metabolism and growth. Several NRs play key roles in the progression of tumours, either through activation of their oncogenic properties, or through silencing of their tumor suppressor ones. The current review presents evidence that they are acutely involved in the shift from oxidative phosphorylation to aerobic glycolysis, and therefore play a central role in the Warburg effect. The Warburg effect is now understood to be far more than the enhancement of ATP generation, although this is still a major component.

Given their central role in interpreting cellular signals, and the wide-array of transcriptional targets they control, NRs are well placed to allow the tumour to generate ATP and the essential biomass precursors that result from diverting glucose utilization to alternative pathways. Understanding of how glucose transport mechanisms become enhanced in cancer remains incomplete but is partially explained by a combination of oncogene activation[132] and tumour suppressor gene inactivation.[25] There is significant evidence from the studies outlined here that multiple NRs converge on several high capacity/affinity GLUT transporters to bring about gene expression changes. Changes to NR co-factor expression, ligand accessibility and the actual expression of NRs themselves are frequent events in many tumour types and lead to a shift in the activity of their transcriptional targets. NRs therefore provide multiple additional mechanisms through which elevation of GLUT expression to pathological levels is achieved by tumours. In parallel there is a growing appreciation of how NR transcriptomes can be modulated pharmacologically and this therefore represents an exciting area of research to target the distorted glucose metabolism that is prevalent in malignancy.[1,7,133–135]

The integration between NRs, oncogenes, tumour suppressor genes and cellular metabolism underlines the importance of normal and distorted NR functions in tumour progression and their continued suitability for clinical research and drug development.

Acknowledgments

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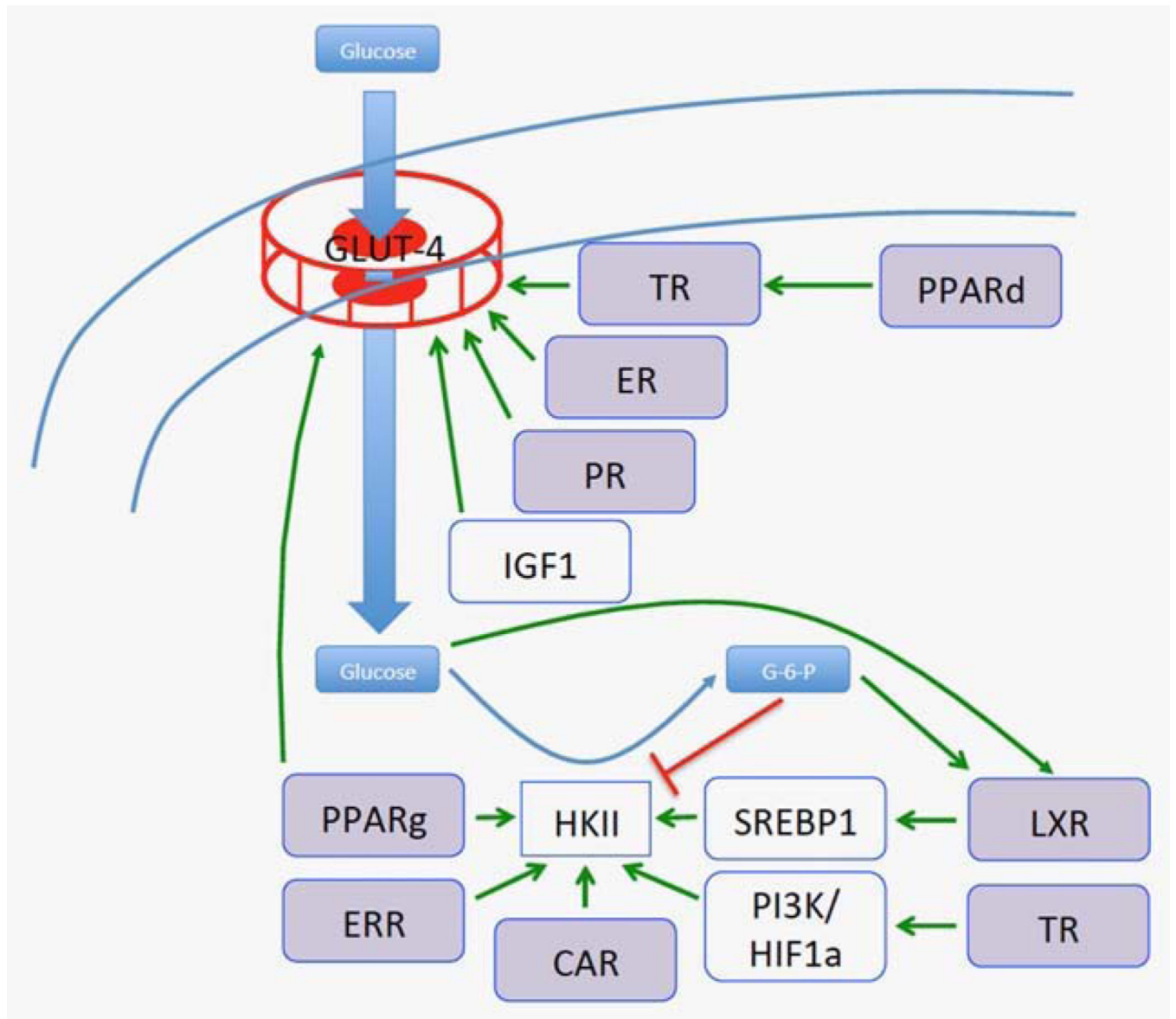
Figure 1.
The interface between nuclear receptor signaling the Warburg effect. Multiple nuclear receptors (TR, ER, PR, PPARs, ERR, LXR, CAR) regulate expression of glucose transporters (such as GLUT4) and the downstream metabolic enzymes that handle its metabolism. Interestingly glucose has been to shown to activate LXR receptors directly.

Table 1

Illustrative examples of NR regulation of key genes that appear to play central roles in the Warburg effect in cancer cells

NR	Target Gene	Direction	Reference
CAR	HKII	Up	65–68
ER	LDH-A	Up	95
	GLUT4	Up	
ERRa	LDHA	Up	92
	LDHB	Up	92
	HKII	Up	66,67
LXR	HKII	Up	71
PGC1a	LDHA	Down	92
	LDHB	Up	92
PPARd	GLUT2	Up	45
	LDHB	Up	93
PPARg	GLUT4	Up	46
	HKII	Up	64
PR	GLUT4	Up	
TR	GLUT1	Up	34–37
	GLUT3	Up	34–37
	GLUT4	Up	43
VDR	GLUT1	Up	47
	GLUT4	Up	48