PROSPECTS
Journal of Cellular Biochemistry 116:1–5 (2015)
Journal of Cellular Biochemistry

AKT as Locus of Cancer Phenotype

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ABSTRACT

Cancer robustness is generated by the positive feedback loops. The positive loops hyperactivate AKT locus forming a cancer phenotype in leukemia, lymphoma, myeloma, plasmocytoma, sarcoma and carcinoma. The positive loops inducing AKT hyperphosphorylation increase activity of the AKT locus and the nodal associated and interconnected signaling genes. Only genes expressed above the threshold in the AKT signaling interactome networks, participate in the formation of the complex cancer phenotype. AKT is the switching locus for the cancer phenotype. The phenotype formation and maintenance is regulated by the AKT locus through an entropy/enthalpy processes. Targeting the AKT by locus chemotherapy, changing redox balance (antioxidant/oxidant), affects phosphorylation and activity of the AKT, inducing conversion of the positive feedback loops and disappearance of the malignant phenotype. J. Cell. Biochem. 116: 1–5, 2015.

KEY WORDS: CANCER PHENOTYPE; AKT LOCUS; POSITIVE FEEDBACK LOOPS; SOLID CANCERS; HEMATOLOGICAL MALIGNANCY

A cancer as a complex and a robust system expresses extreme robustness in relapsed leukemia, myeloma, plasmocytoma, lymphoma, sarcoma, and metastatic carcinoma. A powerful signaling interactome governs the formation of the powerful phenotype through the AKT locus. The phenotype is created by the positive feedback loops, generated in the hypoxic microenvironment [Radisavljevic, 2004a; 2008, 2013a,b,c]. Cancer robustness can fail successfully by targeting AKT locus by the antioxidant/oxidant balance change. AKT locus is the dynamic locus of cancer phenotype. The AKT locus integrates genomic, signaling, and metabolic phenotype of cancer cell [Radisavljevic, 2004a, 2008, 2013a,b,c]. Energy machinery of cancer is the most important for the cancer cell survival. Energy metabolism is regulated through the AKT locus in cancer cell [Kim et al., 2007]. A cancer microenvironment is represented by the hypoxia and lactic acidosis linked to the clinical tumor phenotypes, increased glucose consumption and lactate production [Chen et al., 2008]. The main phenotypic property of the primary and metastatic cancers is upregulation of glycolysis documented by clinical tumor imaging [Gatenby and Gillies, 2004]. When complex cancer system achieves extreme robustness in relapsed leukemia, myeloma, plasmocytoma, lymphoma, sarcoma, or metastatic carcinoma [Radisavljevic, 2013b] cancer phenotype is fully developed.

AKT LOCUS OF CANCER PHENOTYPE

An activating signals from a cancer hypoxic microenvironment hyperphosphorilate the AKT (serine/threonine kinase or protein kinase-B, AKT/PKB) and creating positive feedback loops, induce formation of the system with extreme robustness [Radisavljevic, 2004a, 2008, 2013a,b,c]. Such as system has increased cell proliferation, cell migration, angiogenesis, and extreme cancer robustness [Radisavljevic, 2004a,b, 2008, 2013a,b,c] with the property of the powerful interactome for the cancer multidrug-resistant phenotype [Radisavljevic, 2013c]. The system of the extreme robustness then forms metabolic phenotype and modulates morphological phenotype. That system depends on the number of activated genes that participate in the cancer phenotype formation. Autocrine and paracrine elements from the cancer hypoxic microenvironment generate genomic phenotype, which acting through the signaling phenotype during the formation of the cancer phenotype. A cancer signaling phenotype involves signaling pathways for the cell proliferation such as the NOS/NO/Rb, AKT/Rb pathway [Radisavljevic, 2004b; Imai et al., 2014], the PI3K/AKT/mTOR/RAN and Cdk2/NuMA pathway [Radisavljevic and Gonzalez-Flecha, 2003, 2004], then cell migration and angiogenesis pathway the VEGF/PI3K/AKT/NOS/NO/ICAM-1 [Radisavljevic et al., 2000], and cell apoptosis pathway regulated by the FOXO3A [Radisavljevic, 2003]. All these pathways are integrated in one signaling network where AKT locus is regulatory locus for the formation of the caner phenotype.

A cancer hypoxic microenvironment generates property of the phenotype. Autocrine and paracrine elements from cancer hypoxic microenvironment activate powerful signaling through the AKT locus forming a cancer phenotype. Autostream, downstream, upstream, and rebound activating signals generate positive feedback

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Manuscript Received: 12 August 2014; Manuscript Accepted: 22 August 2014
Accepted manuscript online in Wiley Online Library (wileyonlinelibrary.com): 27 August 2014
DOI 10.1002/jcb.24947 • © 2014 Wiley Periodicals, Inc.

loops that hyperactivate the AKT locus, producing a cancer extreme robustness and forming a cancer phenotype [Radisavljevic, 2013b]. AKT autostream signals generate autostream positive feedback loops which are short positive feedback loops like the autocrine phenomenon. AKT directly interacts with other element and getting back signals which increase its own activity, increasing own phosphorylation. Such signaling loops are autostream positive feedback loops and they are developed by the activated AKT locus [Radisavljevic, 2013b]. Activated AKT locus increases ATP generation through the aerobic glycolysis [Gottlob et al., 2001; Hahn-Windgassen et al., 2005], which hyper phosphorylates and activates back the AKT locus [Wang et al., 2014], closing the positive feedback loop [Radisavljevic, 2013b]. Same phenomenon exists in fatty acid (palmitic acid) stimulation of the AKT, presented by the Pu et al. 2011, where activated AKT by the fatty acids stimulates back fatty acid synthesis [Furuta et al., 2008], closing the positive feedback loop [Radisavljevic, 2013b]. Short and wide positive feedback loops together with autostream positive feedback loops hyperphosphorylate and hyperactivate AKT locus [Radisavljevic, 2013b]. Powerful signals from the positive feedback loops also activate surrounding and in network connected genes in signaling AKT interactome. Those genes, whose expression is above activating threshold, generate a cancer phenotype in leukemia, myeloma, plasmocytoma, lymphoma, sarcoma, and carcinoma. Rest of the genes whose expression is below threshold do not participate in formation of the cancer phenotype and those genes just oscillate in their expression without any impact on the signaling interactome on surrounding and connected genes. If the AKT locus is hyperstimulated, more interconnected genes in signaling interactome are expressed above their activating threshold and they will participate in generation of the cancer phenotype. These genes are incorporated in the signaling interactome through their genomic node and participate in the formation of cancer phenotype by adding their properties into the cancer phenotype. That is the reason of existence of so much diverse cancer phenotypes even in the same type of the malignancy, because each additional activated gene participates in formation of cancer phenotype with its own properties (Fig. 1). Positive feedback loops through the AKT locus create variable signaling, which depends on the number of the genes involved in phenotype formation that generate different cancer phenotypes. The level of AKT hyperstimulation determinates cancer phenotypic properties. The AKT networks of the connected and interactive genes with expression above critical threshold make impact on the caner phenotype.

A cancer microenvironment is represented by the hypoxia and lactic acidosis [Chen et al., 2008]. Lactic acidosis inhibits AKT and glycolysis in cancer cells. That can diminish adaptive shift to anaerobic glycolysis under hypoxia [Graham et al., 2004]. Phenomenon of glycolysis in the presence of oxygen is called aerobic glycolysis or Warburg effect [Gatenby and Gillies, 2004]. Glycolysis generates acetyl-coenzyme A (acetyl-CoA) for the tricarboxylic acid cycle (TCA cycle) or Krebs cycle or citric acid cycle, but reduction of glycolysis in cancer lactic acidosis decreases amount of acetyl-CoA [Chen et al., 2008]. AKT in normal cells suppress beta-oxidation [Elstrom et al., 2004; Buzzai et al., 2005], but lactic acidosis inhibits the AKT, leading to the increase of beta-oxidation of fatty acid that compensates increased demand for acetyl-CoA in cancer [Chen et al., 2008]. Also, fatty acid synthase (FAS) gene is upregulated by hypoxia through the AKT activation [Furuta et al., 2008]. AKT/mTOR signaling has crucial role in development of the sarcoma phenotype [Hernando et al., 2007]. AKT signaling is activated in acute leukemia [Martelli et al., 2006] and chronic leukemia phenotype formation [Longo et al., 2008]. Also, genomic mutation change in chronic lymphocytic leukemia [Wang et al., 2011] and point mutations in myelodysplastic syndromes [Bejar et al., 2011] participate in cancer phenotype formation. All these processes show how cancer cells shift their complex metabolic pathways to adapt to hypoxia and acidosis to be able to maintain ability of cancer progression by the cell proliferation, migration, and angiogenesis through the AKT locus [Radisavljevic et al., 2000; Radisavljevic, 2004a,b, 2008, 2013a,b,c].

A switch from mitochondrial oxidative phosphorylation to the aerobic glycolysis in cancer is an adaptation to intermittent hypoxia [Gatenby and Gillies, 2004]. A cancer phenotype has glycolytic energy production in the presence or absence of oxygen (aerobic glycolysis) [Robey and Hay, 2009]. This metabolic phenotype supports cancer

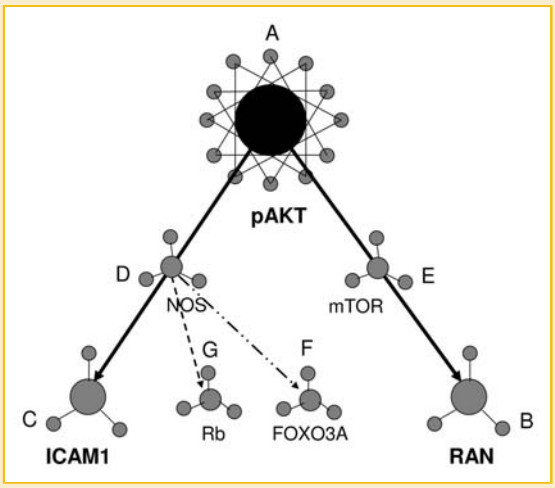

Fig. 1. AKT as locus in interactome networks of cancer phenotype formation. Phosphorylated AKT (pAKT) is the switching locus of a cancer phenotype formation. Signaling pathways from the AKT locus to the signaling nodes ICAM1 and RAN, or RB, FOXO3A through the NOS and mTOR are the main signaling routes for cancer cells proliferation, migration, angiogenesis, and apoptosis. Activity of the AKT locus is supported and maintained by the ATP from glycolysis, lipolysis, or proteolysis. An autocrine and paracrine elements such as: the vascular endothelial growth factor–VEGF, hypoxia–inducible factor–1 alpha–HIF–1 alpha, hepatocyte growth factor–HGF, and molecules nitric oxide and H_2O_2 from cancer hypoxic microenvironment generate positive feedback loops, which hyperphosphorylate and hyperactivate the AKT, a switching locus for aerobic glycolysis, lipolysis and proteolysis, generating ATP, which then activates back AKT by phosporylation, closing autostream positive feedback loop. Downstream, autostream, rebound and upstream signals create short and wide positive feedback loops for hyperactivation of the AKT. If AKT hyperactivation is higher more genes related directly (A) to AKT or indirectly through the signaling nodes ICAM1 or RAN (B, C) or other associated and interconnected genes in networks interactome (D, E, F, G) will be expressed above their thresholds, and they will participate in cancer phenotype formation with their properties.

survival and growth in hypoxic tumor microenvironments [Kim and Dang, 2006]. This cancer biochemical property was used for the ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET scan) to define clinically a stage of metastatic cancers and activity of malignant phenotype [Smith, 2001; Gatenby and Gillies, 2004]. Increased glucose uptake imaged by the ^{18}F-FDG PET/CT scan, depends on the rate of glycolysis in a cancer and is regulated by the upregulated glucose transporters GLUT1, GLUT3, and hexokinases I and II [Burt et al., 2001; Bos et al., 2002; Gatenby and Gillies, 2004].

Oxygen consumption is the basic process in normal and pathologic condition, which is regulated through the cell receptors [Radisavljevic, 1991]. Normal as well cancer cells use oxygen for energy production through mitochondrial oxidative phosphorylation [Hochachka, 1998; Kim et al., 2007]. Oxygen consumption is elevated when AKT is activated [Nogueira et al., 2008]. AKT regulates energy metabolism [Gottlob et al., 2001; Hahn-Windgassen et al., 2005]. AKT activation increases total cellular ATP content through both glycolysis and oxidative phosphorylation [Gottlob et al., 2001; Hahn-Windgassen et al., 2005]. AKT indirectly promotes oxidative phosphorylation via increased glycolysis-derived substrates pyruvate, ADP, and NADH which are essential for the TCA cycle [Gottlob et al., 2001].

A cancer cell becomes highly glycolytic and use aerobic glycolysis (Warburg effect) to produce lactate that will be converted to pyruvate, which enters TCA cycle to generate adenosine triphosphate (ATP) and NADH, a reducing agent that is used for reaction with pyruvate to generate lactate. In cancer cells, pyruvate is converted to lactate 85% during aerobic glycolysis, which is exported from the cell, and then is converted to pyruvate again (reverse process) to enter citric acid cycle for energy generation, an ATP production. Aerobic glycolysis looks like inefficient, loosing ATP, that some authors proposed [Gatenby and Gillies, 2004], but in the reality cancer switch to high energy production. A cancer energy production is crucial in cancer adaptation to aerobic glycolysis to produce lactate, a metabolite that is reversely converted to the pyruvate, which will be oxidatively decarboxylated to form acetyl-CoA to enter TCA cycle, or citric acid cycle (Krebs cycle) to generate much more NADH and ATP. By doing that, a reverse conversion of lactate to pyruvate, a cancer cells instead, that looks like lost 38 molecule of ATP per glucose (36 ATP molecules from pyruvate entering mitochondria plus 2 ATP from glucose-6-phosphate—G6P; also, cells generate 437 ATP molecule from fat), generate many folds higher amount of ATP then normal cells. Two moles of NADH are produced per mole of glucose, and TCA cycle generates 4 molecule of NADH plus one from conversion of pyruvate to acetyl-CoA. For lactate production from pyruvate in aerobic glycolysis NADH is required, where the NADH is oxidized to NAD. Pentose phosphate pathway (hexose monophosphate pathway, or phosphogluconate pathway) (10% of glucose) produces the NADPH in cytosol, a reduced sources for the fatty acid synthesis with acetyl-CoA and malonyl-CoA [McGilvery and Goldstein, 1983; Mathews and Holde, 1989]. Lipid depletion is commonly associated with human cancers, where free fatty acid is mobilized from adipose tissue. When tumor mass is increased to 4% of body weight, basal lipolysis is increased 2–3 times in adipose tissue [Kralovic et al., 1977]. Recently was shown that the enzyme monoacylglycerol lipase (MAGL) regulates liberation and remodeling of stored fats during development of a lipogenic phenotype, and it is highly expressed in aggressive and primary human cancers. MAGL regulates a fatty acid network signaling that promotes tumor growth, migration, and invasion [Nomura et al., 2010]. Palmitic acid (palmitate) stimulates AKT phosphorylation and glucose uptake [Pu et al., 2011]. However, a fatty-acid synthesis is increased in cancer [Mashima et al., 2009]. Fatty acids from lipolysis are used for the ATP production through the acyl-CoA and beta-oxidation generating acetyl-CoA and NADH in liver mitochondria. However, in the peripheral tissue more acetyl-CoA is generated from the ketone bodies where from hydroxybutyrate by the beta-hydroxybutyrate dehydrogenase generates acetoacetate and NADH and then the succinyl-CoA/acetoacetate-CoA transferase activates the transfer of acetoacetate to acetoacetyl CoA and then by the thiolase to the acetyl-CoA [Baynes and Dominiczak, 2007]. Glucose 6-phosphate dehydrogenase regulates the G6P oxidation in the pentose phosphate pathway [McGilvery and Goldstein, 1983; Mathews and Holde, 1989]. An aerobic glycolysis yields considerably more ATP than anaerobic glycolysis. ATP molecules are used for the generation of the NADH, cell migration by cytoskeleton, synthesis of macromolecules, RNA, and DNA. Also, ATP is signaling molecule and it is recognized by the purinergic receptor. ATP is crucial for phosphorylation of the signaling proteins and kinases. ATP-dependent ubiquitination is crucial for protein degradation in proteasome. ATP and NADH are the elements that are highly used for growth and cancer progression. A cancer phenotype formation is the energy dependent, an entropy/enthalpy process. However, phosphorylation of signaling proteins and signal transduction are enthalpy processes [Espinoza-Fonseca et al., 2008].

Pyruvate kinase catalyzes reaction of phosphoenolpyruvate with ADP and phosphorus to generate the ATP. Experimental confirmation is maid by the Liu and colleagues, where metabolic switch from aerobic glycolysis to the mitochondrial oxidative phosphorylation is achieved by the oleanolic acid, suppressing aerobic glycolysis in cancer cells and inducing a switch from pyruvate kinase M2 (PKM2) to the PKM1 [Liu et al., 2014], through the mTOR signaling pathway, which is downstram of the AKT locus [Radisavljevic and Gonzalez-Flecha, 2004; Radisavljevic, 2004a, 2008, 2013a,b,c]. Aerobic glycolysis is activated through the VEGF/AKT/PKM2 in ovary granulosa cancer cell [Schmidt et al., 2008]. It has been found coexpression of pyruvate kinase M2 and pAKT in tumor glycolysis of breast cancer [Benesch et al., 2010]. In human hepatocellular carcinoma is observed upregulation of PKM2 expression in the AKT-dependent manner [Nemazanyy et al., 2013]. Progression of hepatocellular carcinoma was induced via AKT activation and PKM2 pathway [Wang et al., 2012]. Pyruvate kinase M2 (PKM2) is upregulated through the PI3K/AKT/mTOR signaling pathway in aerobic glicolysis during the tumor growth [Sun et al., 2011]. Aerobic glycolysis promotes tumor growth in human glioblastoma multiforme through the AKT and hexokinase 2 (HK2) signaling [Wolf et al., 2011]. In the highly glycolytic cancer phenotype HK2 binds both the ATP and the glucose producing the glucose-6-phosphate [Mathupala et al., 2006]. Cancer cells use AKT locus as an adaptive locus for new aerobic glycolytic condition. The AKT locus is metabolic switch from mitochondrial oxidative phosphorylation to aerobic glycolysis through the AKT, mTOR [Radisavljevic, 2004a, 2008], and pyruvate

kinase M2 signaling pathway [Liu et al., 2014] for the purpose of generating energy-ATP. ATP synthase-β subunit (ATPSβ) over-expression increases intracellular and extracellular ATP content, which increases phosphorylated AKT levels [Wang et al., 2014]. Thus, cancer cell have high glycolysis, and high lipolysis for the high energy demand, because they need to produce high amount of ATP to keep active AKT for cancer cell proliferation, migration, angiogenesis, and cancer progression [Radisavljevic et al., 2000; Radisavljevic, 2004a,b, 2008, 2013a,b,c]. Also, cancer cell needs to produce high amount of the NADH for generation of the fatty acyl-CoA to increase fatty acid synthesis and ATP production.

Autophagy is a catabolic process when cell digests own internal elements to generate energy [Levine, 2005; Yang and Klionsky, 2010; Kimmelman, 2011; Gewirtz, 2014]. Cancer cells using autophagy for survival and progression [Gewirtz, 2014]. Additional ATP production can be made from proteolysis of the cancer patient own proteins which is part of cancer cachexia, a cancer paraneoplastic syndrome [Muscaritoli et al., 2006], where glucogenic amino acids are degraded to pyruvate, and ketogenic amino acids are degraded to acetyl-CoA or acetoacetate [Baynes and Dominiczak, 2007]. A cancer has adaptive phenotype with ability to switch and use all available sources for energy generation including glucose, fatty acids, or proteins if necessary for the ATP production to maintain active AKT as a main locus for cancer progression. Targeting phosphorylated AKT locus by the oxidant/antioxidant balance change [Radisavljevic, 2004a, 2008] induces conversion of the positive feedback loops into negative feedback loops [Radisavljevic, 2013a,b,c] and disappearance of the cancer phenotype.

CONCLUSION

A cancer phenotype is generated from the cancer hypoxic micro-environment by the positive feedback loops. Signaling phenotype is built from such microenvironment creating signaling interactome networks causing hyperphosphrorylation and hyperactivation of the AKT, which activating other genes above their activity threshold, forms genomic phenotype and participates in formation of the morphological, and metabolic cancer phenotype. A cancer has high energy demand for the ATP to keep phosphorylated and active the AKT in formation and maintenance of the malignant phenotype. AKT as a main locus for cancer progression is activated by switching to the aerobic glycolysis, lipolysis, or proteolysis. AKT locus regulates cancer phenotype by the short, wide, and autostream positive feedback loops. Targeting AKT locus by the antioxidant/oxidant balance change leads to the positive feedback loops conversion and disappearance of the malignant phenotype.

ACKNOWLEDGMENT

This work was supported by Yad Chessed Foundation.

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