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Cells Signal Before Driving the Cycle: Metabolic Signaling Regulates Cell Division [Version 1, 2 Approved with Reservations]

Wendy Zimmerman[1]*, Anastassiia Vertii[2]* and Shashi Kant[3]*

[1]Program in Molecular Medicine University of Massachusetts Medical School, USA
[2]Department of Molecular, Cell and Cancer Biology University of Massachusetts Medical School, USA
[3]Division of Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical School, USA

*Corresponding authors: Wendy Zimmerman, Program in Molecular Medicine University of Massachusetts Medical School, Worcester, MA, USA, Email: wendy@wendyzimmerman.com

Anastassiia Vertii, Department of Molecular, Cell and Cancer Biology University of Massachusetts Medical School, Worcester, MA, USA, Email: Anastassiia.Vertii@umassmed.edu

Shashi Kant, Division of Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA, Email: Shashi.Kant@umassmed.edu

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Abstract

Signaling pathways mediate the metabolic status of an organism, more specifically, they regulate cellular adaptation to dietary changes. Perturbation of normal signaling leads to the development of the metabolic syndrome that underlies type 2 diabetes. Deregulation of the same signaling pathways often results in uncontrolled cell cycle progression that promotes tumor formation. Understanding the functional relationship between metabolic signal transduction and cell division is essential for understanding the link between metabolic syndrome and cancer. Nevertheless, the effect of context- and metabolic condition- specific influences of transduction pathways on the cell cycle and cell fate is poorly understood. Today this is an emerging area of research that has potential to uncover new regulatory mechanisms and to prevent metabolic disease-to-cancer transition. In this perspective we discuss recent discoveries that establish the mechanistic and functional connection between metabolic disorder and the cell cycle.

Keywords

Cell Cycle; Signal Transduction; Beta Cells; Cyclin; Type 2 Diabetes; Inflammation; Cancer; Centrosome; Kinetochore

Introduction

Obesity as a result of either hypernutrition or hormonal imbalance in individuals has reached epidemic scale. It is well established that obesity promotes the development of the metabolic syndrome, a condition characterized by several symptoms, including insulin resistance. During insulin resistance insulin sensitive organs like muscle, liver and adipose tissues fail to uptake glucose even in the presence of insulin. Insulin resistance, if left untreated, over time transitions from overproduction of insulin in response to high blood glucose levels to exhaustion, dysfunction and loss of insulin secretion by beta-cells, a hallmark of type 2 diabetes. Recently, metabolic syndrome was characterized by an increase in chronic inflammation markers, namely the pro-inflammatory cytokines tumor necrosis factor alpha (TNFα), interleukin 6 (IL6) and inflammatory marker C-reactive protein (reviewed in [1]). Moreover, obesity and metabolic syndrome-induced inflammation now has been linked to cancer development later in life. More specifically, about 14-20% of all cancers are associated with obesity [2]. The effect of obesity on cancer development is not the same across different cancer types: the most affected organs in which obesity increases the risk of cancer development are intestine, kidney, liver and pancreas [2]. Substantial evidence demonstrates an association between increased body mass index and breast cancer in postmenopausal women [3]. Interestingly, obesity is not only a risk factor that is associated with tumor development, but also a factor that might favor tumor progression. For example, early weight loss after surgically eliminated breast tumors improved relapse-free survival time [4]. There are several theories that attempt to explain how metabolic changes stimulate inflammatory cytokine production, and how the increase in cytokine secretion in serum leads to cancer development, recently reviewed in [5] and [1]. One possible explanation of how metabolic syndrome is linked to cancer is that a metabolically dysfunctional tissue may provide an environment that promotes tumor progression by virtue of its altered hormonal and inflammatory climate [5]. It was recently proposed that obesity promotes cancerogenesis by systemic changes that include insulin resistance, secretion of adipokines by adipose tissue and chronic inflammation that includes polarization of adipose-specific macrophages into a pro-inflammatory M1 population that secretes pro-inflammatory cytokines as well as alteration of other components of the immune response [1]. In addition, tissue-specific factors, like obesity altered microbiota and bacterial lipopolysaccharides have the potential to influence the intestinal environment and promote cancer [1]. Indeed, the risk of cancer is known to increase with age and a recent report demonstrated the connections between age, intestinal permeability, dysbiosis and macrophage dysfunction [6]- all of which are hallmarks of metabolic disorder-related tumor promotion. Macrophages are known for their contribution to obesity [7]. Exposure of macrophages or fibroblasts to free fatty acids (FFA) activates stress MAPK kinase signaling, specifically JNK, which in turn stimulates production of cytokines [8–10]. Cancer is a complicated and tissue-context-dependent disorder with uncontrolled cell division being one of the six common hallmarks [11]. Although, autophagy and ER stress were proposed to be involved in tissue-specific mechanisms that drive cancer development during obesity-induced inflammation [1], the precise mechanisms remain to be elucidated. For example, it is unclear, how adipokines and inflammatory cytokines that are secreted by white fat tissue and macrophages cause defects in cell proliferation in certain tissues.

Here we discuss recent developments in the field of cell metabolism that shed some light on how changes in metabolism affect cell division and cell differentiation.

Metabolic Status Defines Signal Transduction

Dietary supply and the ability of organism to uptake nutrients shape the metabolic landscape of the organism. Nutrients like glucose and saturated fats activate stress-related signaling cascades of mitogen-activated protein kinases. Increase in glucose levels in serum stimulates insulin secretion exclusively by beta-cells. Secreted insulin activates the PI3K/Akt pathway via insulin receptor (IRS1) in many cell types. Its activation is needed for uptake of glucose by cells, a critical step for proliferation. PI3K signaling and its downstream target protein kinase Akt/PKB (protein kinase B) is one of the best-studied nutrient sensitive pathways. Akt is critical for both survival and proliferation, thus connecting the metabolic status of the organism to cell proliferation. There are three isoforms of Akt in humans and mice [12]. The link between proliferation and insulin resistance

came from a study that used a knock-out mouse model that lacks Akt. It was shown that mice deficient for the most abundant Akt isoform in major tissues (or insulin sensitive tissues), Akt2, developed insulin resistance and diabetes [13]. However, uncontrolled activation of Akt is one of the mechanisms that underlie tumor formation, making Akt/PKB one of the best-known oncogenes [12]. Akt activity is regulated by tumor suppressor protein PTEN [14]. PTEN suppresses the PI3K- Akt pathway when mitogen stimuli are not present. PTEN is often mutated in different types of cancers.

However, since the tissue-specific context of insulin-induced PI3K signaling activation and cell division in obese patients is not well understood, it remains an intriguing link between insulin signaling and cell proliferation. More intriguing and even less well known is the effect of PI3K signaling on cell fate. For example, recent reports demonstrate that the differentiation decision that is made by T and B lymphocytes depends on presence and asymmetric inheritance of PI3K. The PI3K/Akt/mTOR pathway not only regulates cell growth and size, but also appears to be critical for differentiation of stem cells [15] and naïve (memory) cells. A recent study demonstrated asymmetry in nutrient-sensitive PI3K/Akt/mTOR signaling during cell division and bifurcation of daughter cells [16]. Asymmetrically distributed during B lymphocyte division, the PI3K/Akt/mTOR cascade suppressed transcription factor Pax5 which is characteristic for plasma cells, and induced plasma cell differentiation transcription factor, IRF4. These changes favor plasma cell differentiation into an antibody-secreting cell, while daughter cells that inherited weaker PI3K/Akt/mTOR signals displayed a plasma cell fate. In the case of T cell differentiation, a stronger PI3K signal silences Tcf1 [16]. Silencing of Tcf1 in CD8+ T cells leads to loss of the self-renewal potential of quiescent memory T cells and determines their fate as effector cells [17,18] . Thus there is a speculative hypothesis that obesity-induced PI3K has a potential to alter cell fate and differentiation potential.

Free fatty acids (FFA) are important components of our diet that when metabolized, give a high yield of ATP energy. Structurally, a fatty acid consists of a caroboxyl group and a chain that can vary in length and number and type of bonds. Based on a presence or absence of double bonds between carbon atoms, there are two major types of FFA, unsaturated and saturated free fatty acids. Unlike unsaturated fatty acids, saturated free fatty acids can lead to insulin resistance [19]. A recent study established that saturated FFAs promote activation of mixed lineage kinase (MLK) and its downstream target JNK MAPK kinase [8, 20]. Interestingly, mice lacking the MLK pathway are protected against high-fat diet-induced insulin resistance. The same MLK-JNK pathway is also critical for the production of inflammatory cytokines *in vitro* and *in vivo* [21]. Importantly the MLK-JNK pathway has been implicated in macrophage polarization, a process that describes a functional switch between pro-inflammatory and anti-inflammatory populations of macrophages. Either MLK3 or JNK1/2 deficiency suppresses the pro-inflammatory M1 polarization in macrophage [9, 22].

An interesting link between metabolic status and cell cycle has been described in the context of beta cells. In adults, new beta cells are derived by replication of existing beta cells [23]. Under normal healthy conditions less than 0.2% percent of beta cells are replicating, while the majority are arrested in G0 stage of the cell cycle. Nuclear expression of cyclin D/Cdk4,6 and cyclin E/Cdk2 is usually associated with cell cycle progression, but in beta cells, cyclin E1/Cdk2 and cyclin D1,3/Cdk4,6 are expressed in the cytoplasm, their activities presumably blocked by the cyclin dependent kinase (Cdk) Ink4 family inhibitors (p15, p16, p18, p19) and CIP/KIP family inhibitors (p21 and p27) which were also expressed in beta-cell cytoplasm [24,25]. Administration of FFAs suppresses proliferation of insulin-secreting beta-cells *in vitro* and in *vivo via* p16 and p18 cell cycle inhibitors [26].

Proliferation of beta-cell can be stimulated by glucose. When subjected to normal mitogenic stimuli the number of proliferative beta-cells increases only to 0.3-0.5% [27]. Much recent work has focused on understanding the G0 arrest and striving to overcome it by stimulating known replicative pathways, increasing the levels or activities of cyclin/Cdk complexes, or reducing expression of cell cycle inhibitors with only limited success, reviewed in [27,28].

Beta-cell function and replication may be mutually exclusive. Klochendler and co-authors used a mouse strain that expresses a cyclin B destruction box fused to GFP to isolate replicative beta-cells by FACS [29]. They found upregulation of hundreds of proliferation dependent genes but downregulation of genes involved in beta-cell specific functions including genes involved in insulin processing, vesicle transport and secretion. Conversely, Szabat and co-authors found that reduced insulin production by cre-lox mediated knockout of the insulin gene promotes cell cycle progression [30]. This suggests that a successful therapeutic approach to beta-cell replacement will need to balance beta-cell function with replication.

Kinetochores and the Centrosome as Mediators of Metabolic Pathways

Growth hormones and growth factors are known to promote cell proliferation. Changes in hormonal profile during obesity is likely one of the reasons for tumor promotion (reviewed in [5]. Nevertheless, in the context of obesity and inflammation, the signal transduction between proliferative hormones and classic mitotic kinases like Aurora kinase A, B and Polo like kinase 1 (Plk1) remain to be poorly understood phenomenon. Aurora kinases and Plk1 initiate mitosis by ensuring spindle pole maturation, chromosome condensation and proper chromosome-microtubule attachments prior to their movement towards the spindle pole. Failure to maintain correct chromosome segregation leads to aneuploidy, a common cause of cancerogenesis, underscoring the role of mitotic kinases in cancer.

Spindle poles develop from non-membranous organelles, the centrosomes. The centrosome, a primary microtubule organizing center in the cell, consists of a pair of microtubule-based centrioles surrounded by pericentriolar material (PCM) [31,32]. Upon Plk1 activation, centrosomes begin to recruit more pericentriolar material that in turn enhances their capacity to nucleate microtubules [33]. Recently we reported an unexpected effect of inflammatory cytokines on centrosome maturation during interphase [34]. Unlike centrosome maturation during mitosis that results from Plk1 activity, cytokine and bacterial lipopolysaccharide exposure lead to activation of the MLK pathway which mediates the recruitment of centrosomal (pericentrin) and trafficking components (marker for recycling endosomes FIP3) to the interphase centrosome. It is unclear, weather such activation would perturb normal cell cycle and proliferation. However, such interphase maturation is specific to inflammation-related response and not to other types of stress [35]. We also reported that the centrosome is critical for the secretions of IL-6 and MCP1, pro-inflammatory cytokines that are known to increase during obesity and metabolic syndrome [34]. It is not clear, however, if these mechanisms operate during obesity and prevent cells from entering the cell cycle. The critical question to address is how the metabolic state of the cell and organism affect cell proliferation and how the proliferation mediates the body's response to changes in metabolic status.

Alterations in metabolism may activate quiescent cells and induce stress-related proliferation. More specifically, beta cells, the only insulin-producing cells in the body are typically well differentiated and consequently, are quiescent cells. Under normal conditions, they respond to increased glucose level in the blood by secretion of insulin. However, with increase in metabolic demands, the cells exit G0 cell cycle stage and re-enter cell cycle [36]. Activation of insulin receptor leads to the FoxM1/PLK1/CENP-A pathway [36]. This is novel mechanism that directly links mitotic components like Plk1 and a centromere-specific histone variant Cenp-A to changes in metabolic status. The transcription of Plk1 and CenpA is critical for mitotic progression and may indicate some metabolism –related chromatin changes [33]. The role of CenpA in mitosis is ensuring kinetochore-microtubule attachment. Recently, an additional role of CenpA in formation of chromosomal passenger complex in Xenopus egg extracts was elucidated [37]. The chromosomal passenger complex is a potential target for anti-proliferative therapy during cancer and regulates cell division by ensuring correct chromosome-microtubule attachment and orientation. One of the major components of this complex is a mitotic kinase Aurora B. Interestingly, centromeres appear to be the sites of active transcription during mitosis. The product of this transcription is long non coding RNA (cen-RNA) that localizes to the chromosomal passenger complex and ensures proper function of Aurora B at the centromeres [37]. Given the conservative nature of centromeres across different species, it is likely that similar mechanisms might be involved in regulation of mitosis in mammalian systems.

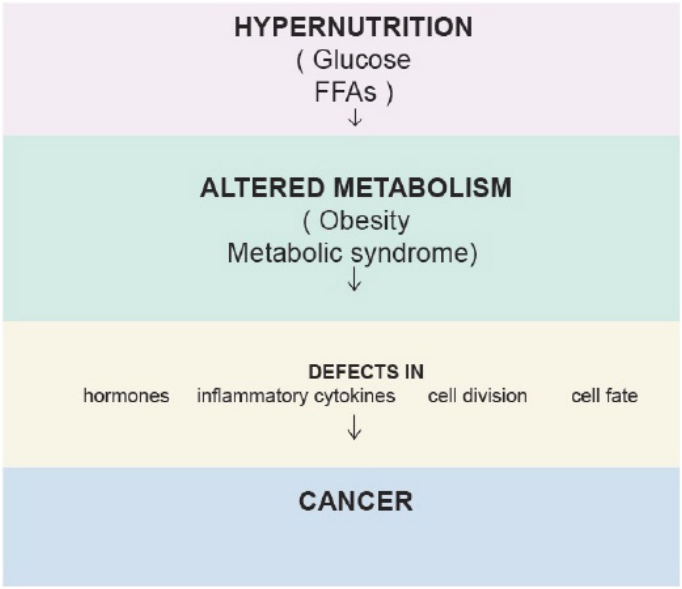

Figure 1: Schematic view of factors that possibly contribute to metabolic syndrome-to-cancer transition.

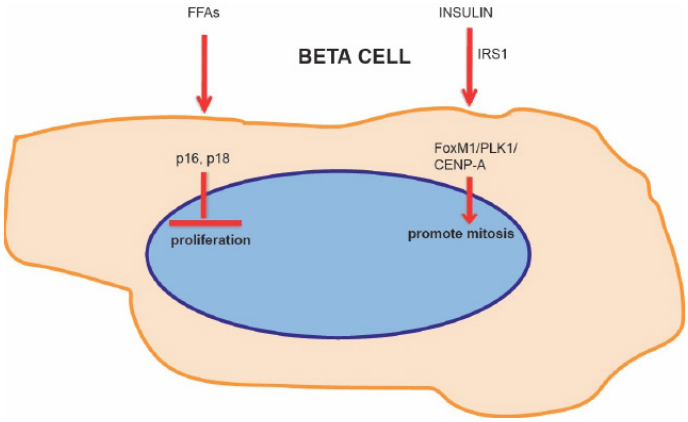

Figure 2: Opposite effects of FFAs and insulin on cell cycle progression of beta cells. Exposure of cells to FFAs blocks cell cycle progression through the cell cycle inhibitor proteins, p16 and p18. In contrast, exposure of cells to insulin stimulates the transcription of two essential for cell division proteins: mitotic kinase Plk1 and kinetochore-specific histone variant CenpA.

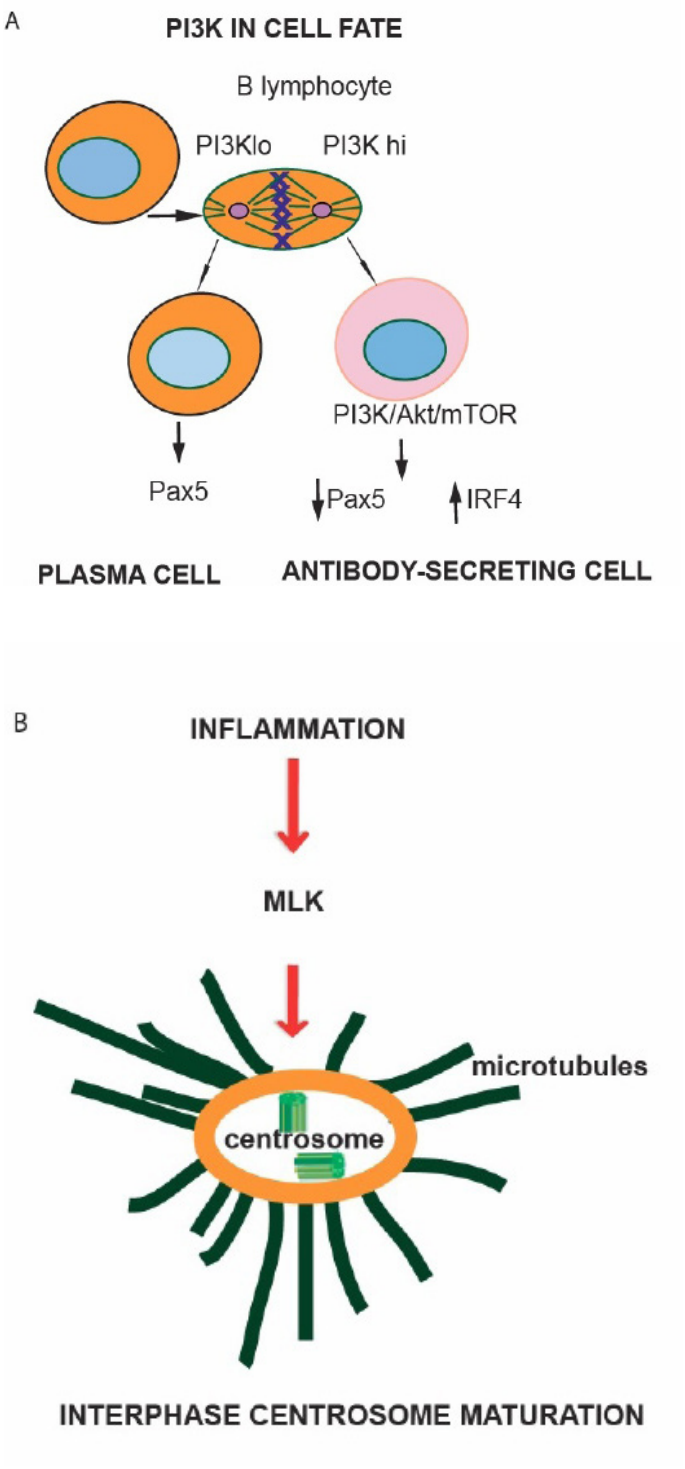

Figure 3: Metabolic pathways mediate cell fate and affect centrosome physiology. A. Asymmetric inheritance of PI3K signaling results in differential induction of transcription factors and leads to a distinct populations of B lymphocytes. B. Inflammatory stimuli activate MLK pathway and induce centrosome maturation in interphase. It is not clear, weather such Plk1-independent centrosome maturation prevents cells from entering mitosis.

Conclusions and Perspectives

It has been established that pro-inflammatory cytokines can favor tumor production. We discuss recent studies that provide a link between inflammation, obesity, cell division and cell fate. In addition to uncontrolled proliferation, later stages of tumor growth require vasculature. Endothelial cells are one of the main cell types that form vasculature. Interestingly, stimuli like hypoxia and less nutrition that typically would negatively impact cell proliferation, cause endothelial cells to proliferate [38]. Intriguingly, endothelial cells from diabetic patients show impaired proliferation [39]. Thus, the effects of an altered metabolic landscape may have different, even opposite effects on different cell types. It seems that FFA treatment and activation of IRS1 have the opposite effect on beta-cells, blocking division. This is particular interesting given that FFAs can induce insulin resistance. Detailed investigation of the interplay of stimuli in cell-type specific context is needed to understand how context helps to shape the signaling make-up that drives the cell fate.

Another intriguing problem is to understand the connections between mitochondrial function, metabolic syndrome, and cell division. Mitochondria provide the energy for secretion as well as cell cycle progression. Mitochondrial dysfunction has been linked to type II diabetes (reviewed by [40]. Cyclin E/Cdk2 activates mitochondria to provide the extra energy needed for S phase [41]. Although most beta cells are not cycling, cyclin dependent kinase 2 (Cdk2) is required for mitochondria to respond to insulin. Kim and co-authors studied beta-cells from Cdk2 deficient mice [42]. When challenged with high glucose, (20 mM), mitochondria in beta cells from knockout mice failed to increase energy production normally, as shown by a reduced increase in the ratio of endogenous NAD(P)H/flavin autoflourescence. This suggests some Cdk2 activity is necessary for beta-cell function, and that despite the presence of Cdk inhibitors, a low level of Cdk2 activity may be present in G0 arrested beta-cells.

Recent advances indicate the role of metabolism-induced signaling pathways, like PI3K and MLK in cell cycle and cell fate decisions, and at the same time, indicated the need for identification of more specific “fine-tuning” components of the pathways that would help to define cell-context dependent effects of metabolic syndrome.

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