Cell

The work of Kumar and Wigge puts down a long-awaited cornerstone upon which to build an understanding of ambient temperature sensing by plants. The signaling networks regulating temperature-mediated physiological responses are likely to be complex and involve modulation by other environmental cues. Molecular dissection of such intricate networks presents a daunting challenge for the future but will be essential for enhancing our understanding of how plants grow and develop in fluctuating natural environments.

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Chewing the Fat on Tumor Cell Metabolism

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DOI 10.1016/j.cell.2009.12.037

Tumor cells undergo a metabolic shift toward specific bioenergetic (glycolysis) and anabolic (protein and lipid synthesis) processes that promote rapid growth. Nomura et al. (2010) now demonstrate that an increase in monoacylglycerol lipase (MAGL) drives tumorigenesis through the lipolytic release and remodeling of free fatty acids.

The re-emergence of the field of tumor cell metabolism has yielded important new insights into the metabolic reprogramming of cells that accompanies their oncogenic transformation (for recent reviews, see Hsu and Sabatini, 2008; Vander Heiden et al., 2009). The fundamental differences in both the catabolic and anabolic properties of a tumor cell relative to its tissue of origin could provide opportunities for new selective therapeutic approaches. How cancer cells sense and use nutrients also impacts our understanding of dietary influences on tumor development and progression. To date, the majority of research on cancer metabolism has focused on the nearly ubiquitous catabolic switch of tumor cells (and other rapidly proliferating cells) from oxidative to glycolytic metabolism even in the presence of oxygen. This is referred to as aerobic glycolysis or, more popularly, the Warburg effect. However,

tumor cells also commandeer anabolic processes resulting in elevated rates of protein, nucleic acid, and lipid biosynthesis. For instance, tumor cells exhibit a pronounced increase in de novo fatty acid synthesis, whereas normal cells are thought to acquire fatty acids primarily from dietary sources (Medes et al., 1953; Menendez and Lupu, 2007). In this issue of Cell, Nomura et al. (2010) demonstrate an unexpected role for lipolytic remodeling of lipid species in promoting the tumorigenic properties of cancer cells.

A functional screen for differences in the activity of serine hydrolases in a small number of human cancer cell lines revealed that the activity of monoacylglycerol lipase (MAGL) was elevated in those lines classified as more aggressive (Nomura et al., 2010). MAGL activity was also elevated in ovarian tumor tissue from patients with more advanced disease. This enzyme hydrolyzes monoacylglycer-

ols (MAGs) to release glycerol and a free fatty acid (FFA), and its best-characterized substrate is 2-arachidonoylglycerol, an endocannabinoid MAG (Long et al., 2009). Interestingly, the more aggressive cancer cell lines and high-grade primary tumors contained elevated FFA levels, which could be substantially reduced by pharmacological and short-hairpin RNA-mediated attenuation of MAGL activity. This surprising finding suggests that MAGL-dependent hydrolysis of MAGs is a major source of intracellular FFAs in aggressive cancer cells.

The MAGL-dependent remodeling of lipids appears to contribute to the transformed properties of tumor cells (Nomura et al., 2010). Using in vitro cell-based assays, the authors found that inhibition of MAGL activity impaired the enhanced migration and invasive capabilities of aggressive cancer cells and diminished their survival upon growth factor with-

drawal. Interestingly, exogenous addition of the saturated FFAs palmitate (C16) or stearate (C18) to MAGL-inhibited cells rescued the migration defects. Reciprocally, overexpression of MAGL or addition of FFAs could enhance these phenotypes in less aggressive cancer cell lines exhibiting low MAGL activity. MAGL knockdown or pharmacological inhibition also blunted xenograft tumor growth in mice, and this was accompanied by a significant decrease in FFA levels within the tumors. Strikingly, these in vivo effects of MAGL inhibition on tumor growth and lipid levels were reversed by feeding the mice a high-fat diet. Collectively, these data demonstrate that MAGL promotes the oncogenic properties of tumor cells by increasing FFA levels.

To determine the mechanism of action of the FFA products of MAGL activity, the investigators took a lipidomics approach to identify lipid species sensitive to increases or decreases in MAGL activity in cancer cells (Nomura et al., 2010). This profile revealed that MAGL activity not only decreases MAGs and increases FFAs, but it also leads to an increase in specific FFA-derived signaling lipids, such as phosphatidic acid (PA), lysophosphatidic acid (LPA), and prostaglandin E2 (PGE_2) (Figure 1). The authors propose that these lipids activate tumor-promoting signaling events, and they demonstrate that LPA and PGE_2 can rescue the migration defects of cancer cells with attenuated MAGL activity. Interestingly, both LPA and PGE_2 stimulate G protein-coupled receptor-mediated signaling events and promote multiple oncogenic properties in tumor cells (Dorsam and Gutkind, 2007). This study suggests that MAGL activity plays a major role in the production of signaling lipids, which then stimulate tumor cells in an autocrine manner.

The relationship between the synthesis, storage, and use of FFAs in tumor cells is poorly understood. Most cancer cells express elevated levels of fatty acid synthase, a multifunctional enzyme that converts malonyl CoA to palmitate, thereby explaining the increase in de novo lipogenesis in these cells (Medes et al., 1953; Menendez and Lupu, 2007). However, the Nomura et al. study makes a compelling case that hydrolysis of acylglycerols, such as MAG, is a major source of FFAs
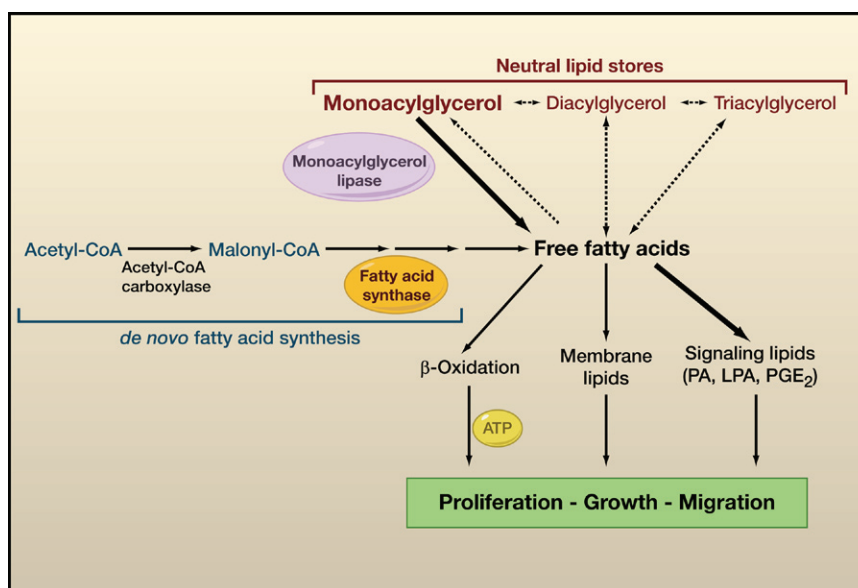

Figure 1. Free Fatty Acids and Tumorigenesis
Tumor cells display elevated rates of de novo free fatty acid (FFA) synthesis due, in large part, to increased expression of fatty acid synthase. Newly synthesized FFAs are believed to be converted to neutral lipid stores, including mono-, di-, or triacylglycerols. The activity of monoacylglycerol lipase (MAGL), which catalyzes the lipolytic release of FFAs from monoacylglycerols (MAGs), is elevated in more aggressive tumor cells (Nomura et al., 2010). MAGL plays a critical role in maintaining the increase in FFAs in such cells and in promoting the production of FFA-derived signaling lipids, such as phosphatidic acid (PA), lysophosphatidic acid (LPA), and prostaglandin E2 (PGE_2). Other potential fates of newly synthesized or released FFAs include conversion to specific lipid species for incorporation into cellular membranes or β-oxidation for the production of ATP. FFA remodeling and utilization contribute to tumor cell proliferation, growth, and migration.

in tumor cells (Figure 1). The authors propose that newly synthesized FFAs are immediately converted into neutral lipid stores and that the use of FFAs is dependent on their lipolytic release, with MAGL being the critical lipase. However, further investigation regarding the fate of newly synthesized FFAs versus those released by hydrolysis of acylglycerols in tumor cells is needed. Through in vitro assays, Nomura et al. focus primarily on the contribution of MAGL-derived lipid mediators to cancer cell migration. However, the tumor-promoting effects of MAGL in the in vivo xenograft mouse model are more likely to depend on increased cell growth and proliferation. The latter are predicted to rely on lipid remodeling for new membrane biosynthesis and, perhaps, β-oxidation for energy production to support accompanying anabolic processes. Although the bioenergetic needs of cancer cells are predominantly met through glycolysis, the oxidation of FFAs offers an alternative route (e.g., Buzzai et al., 2005; Schafer et al., 2009). Again, the question is whether the in vivo fates

of FFAs derived from de novo synthesis versus lipolytic release differ or whether FFAs ultimately enter the same pool for remodeling or catabolic use.

Many exciting new questions arise from the findings reported by Nomura and colleagues regarding the role of both MAGL and exogenous lipids in tumor development and progression. For instance, how are MAGL expression and activity regulated in tumor cells, and how widespread is its activation in cancer? Is MAGL a metastasis factor and can its activity be used as a biomarker to predict the influence of dietary fats and obesity on tumor progression? Although MAGL was found to increase cell migration and invasion in vitro, the effects on tumor metastasis were not examined in the Nomura et al. study. Interestingly, the inhibitory effects of MAGL attenuation on tumor growth were reversed by feeding the mice a high-fat diet, which has been shown to promote metastasis in other xenograft tumor models (e.g., Rose et al., 1991). It will be interesting to determine whether conditions of obesity lead to increased

levels of FFA-derived signaling lipids, such as LPA, within tumors. Finally, the antitumor effects of the MAGL-selective inhibitor used in this study suggest that MAGL is a promising therapeutic target for treating cancer. However, the critical role of MAGL in attenuating endocannabinoid signaling in the brain could lead to behavioral side effects that are unique among cancer drugs (Long et al., 2009). It is clear that we are just beginning to understand the molecular contributions of alterations in lipid metabolism to cancer pathogenesis.

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MicroTUB(B3)ules and Brain Development

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DOI 10.1016/j.cell.2009.12.038

The microtubule network is crucial for the developing nervous system, and mutations in tubulin-encoding genes disrupt neuronal migration. Tischfield et al. (2010) now report that mutations in the tubulin-encoding gene *TUBB3* have a striking impact on microtubule dynamics in neurons, resulting in a diverse set of disease symptoms.

The formation of the nervous system is a complex process that requires functional microtubules during all stages of development. Events such as neurogenesis, neuronal migration, axon pathfinding, and synapse formation are regulated by intrinsic and extrinsic pathways that ultimately impinge on the microtubule network, which carries out the structural changes that underlie each process. However, it is only recently that mutations have been discovered in human genes encoding tubulin, the monomer that polymerizes into microtubules. Mutations in human genes such as *TUB1A1* and *TUBB2B*, which encode α-tubulin and β-tubulin, respectively, or in genes that regulate microtubule function such as *Lis1* and *Doublecortin* (Dcx) (des Portes et al., 1998; Gleeson et al., 1998; Jaglin et al., 2009; Keays et al.,

2007; Poirier et al., 2007) give rise to disorders of brain development. Such disorders are characterized by lissencephaly (lack of brain folds) and polymicrogyria (excessive brain convolutions), which are caused principally by dysfunctional neuronal migration. In this issue of *Cell*, Tischfield et al. (2010) add to this growing literature with their report of new mutations in the human *TUBB3* gene encoding neuronal βIII-tubulin. Using a multidisciplinary approach, they uncover *TUBB3* mutations that produce diverse clinical phenotypes including ocular motility disorder (CFEOM3). Surprisingly, this is due primarily to disrupted axon guidance and not dysfunctional neuronal migration. This study elegantly examines the relationship among *TUBB3* mutations, their impact on microtubule function, and clinical symptoms.

Using a family-based approach, the authors identified eight heterozygous mutations in *TUBB3*. Clinically, the authors discovered that patients with the R262C mutation (the most commonly mutated residue) or the D417N mutation display hypoplasia of the ocular motor nerve and of several other nerve tracts, indicating defects in axon guidance and maintenance. Equally interesting is their observation that patients harboring different mutations in *TUBB3* display a variety of clinical diagnoses. Although most patients suffer from CFEOM3, those with R262H, E410K, or D417H mutations also possess varying degrees of facial paralysis and progressive sensorimotor polyneuropathy. This led the authors to speculate that a genotype-phenotype relationship exists, where a specific mutation is associated with a particular set of