better outcome in cancer treatment. Both targeting of the mitochondrial electron transport chain and the pharmacological scavenging of mitochondrial superoxide prevent metastatic dissemination from primary orthotopic tumors in mice (Porporato et al., 2014). Mitochondrial-generated oxidative stress can also be attenuated with clinically relevant health benefits by increasing the levels of mitochondrial antioxidant enzymes or by ectopically expressing antioxidant enzymes within the mitochondria. For instance, overexpression of mitochondrial-localized catalase in vivo increases lifespan, and transgenic expression of mitochondrial catalase in the MMTV-PyMT mammary cancer model reduces ROS-driven primary tumor invasiveness and markedly suppresses lung metastases (Goh et al., 2011; Schriner et al., 2005). Therefore, strategies that effectively eliminate ROS specifically within the mitochondrial compartment by mitochondrial-specific antioxidant administration might still represent a therapeutic approach for metastatic cancer.

Despite intensive research, current antioxidant strategies are not clinically effective, suggesting that our understanding of this field is limited and the exact nature of the impact of oxidative stress on cancer metastasis requires further investigation. The role of ROS and antioxidants depending on their origin in cancer progression and metastasis needs to be fully characterized in future studies to identify new therapeutic targets.

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Casein Kinase 2—A Kinase that Inhibits Brown Fat Formation

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In adipose tissue, there is a delicate balance between storing and expending energy. In this issue, Shinoda et al. (2015) use phosphoproteomics to identify casein kinase 2 (CK2) as a suppressor of brown adipocyte formation, providing insights into how adipose tissue regulates its composition of white versus brown adipocytes.

On the one hand, it is well known that prolonged exposure to cold will induce "browning," an increase in the number of beige adipocytes (also known as brite; a type of brown adipocyte interspersed among white adipocytes in predominantly white adipose depots), while on the other hand high-fat diet feeding or exposure to thermoneutrality (a temperature of about 28°C–30°C, at which mice do not need to activate brown fat for heat production) will have the opposite effect, with less browning and more of a homogenous white phenotype of adipose depots (Cinti, 2005). Thus, the adipose tissue is a dynamic tissue that responds and adapts to physiological stimuli such as nutritional status and changes in ambient temperature. Using in vivo genetic lineage tracing techniques, Lee et al. (2012) identified a PDGFRα^+, CD34$^+$, and Sca1$^+$ precursor cell with the capacity to proliferate and differentiate into both brown and white adipocytes. Such bipotent precursors developed into brown adipocytes when mice were treated with a β_3-agonist (mimicking cold exposure) and into white adipocytes when mice were high-fat fed. This important finding helps explain the dynamics of

adipose tissue and predicts the existence of a switch that under cold exposure activates a brown fat gene program and, during high-fat feeding, suppresses this program and at the same time activates white adipocyte formation. A key component of this switch is the PRDM16-C/EBP-β transcriptional complex—when these factors are expressed in native fibroblasts they induce a fully functional brown fat program (Kajimura et al., 2009). Further details on how this regulation is executed both in terms of activation and suppression of the different gene programs involved are starting to accumulate, and most factors reported are activators of brown fat formation/function. This complex regulation involves several factors/processes, such as chromatin remodeling mediated by EHMT1 (Ohno et al., 2013), transcriptional activation by Ebf2 and Pparγ (Rajakumari et al., 2013), and the signal-sensing scaffold JMJD1A (Abe et al., 2015). In this issue of *Cell Metabolism*, Shinoda et al. (2015) use a phosphoproteomics approach and find that the caseine kinase CK2 acts as a repressor of brown fat formation.

Shinoda et al. (2015) set out to study how white, beige, and classical brown adipocytes respond to norepinephrine administration, emphasizing activation or suppression of kinases. For this purpose a set of cell lines and primary cells representing the three different types of adipocytes were treated with norepinephrine and subsequently analyzed by LC-MS/MS to compare phosphorylation profiles. This phosphoproteomics approach revealed that five kinases differed between brown and white adipocytes. Further analysis showed that, after norepinephrine administration, one of these kinases, caseine kinase 2 (CK2), was more active in primary white adipocytes compared to both brown and beige adipocytes. Moreover, CK2 activity was induced in the inguinal WAT depot after high-fat feeding. Interestingly, this increase in CK2 activity was selective for WAT since no change in CK2 activity was found in BAT. When CK2 was suppressed in white adipocytes, either by RNAi or a pharmacological approach using the CK2 inhibitor CX-4945, there was a robust induction of *Ucp1* and several other brown selective genes such as *Cidea*, *Cited1*, and *Elov3*. This is an important finding since it reveals that active suppression of brown fat formation in WAT is an integral part of how adipose tissue regulates its cellular composition of brown versus white adipocytes. The authors then demonstrated that phosphorylation of class I HDACs, HDAC1 and HDAC2, was strikingly reduced by CK2 inhibition in white adipocytes, consistent with increased browning, since inhibition of class I HDACs has been linked to increased expression of PGC1α (Galmozzi et al., 2013).

With the addition of CK2 to the family of genes regulating the cellular composition of adipose tissue depots, the field has taken yet another step toward a comprehensive map of the molecular events underlying how this tissue dynamically responds to changes in metabolic status, ambient temperature, and other challenges to metabolic homeostasis. We can now start to dissect, at the molecular level, how the transcriptional machinery including chromatin remodeling responds to such changes. What are the crucial steps in responding to nutritional cues versus defense of normal body temperature during cold exposure? Are these signals transmitted via direct innervation and/or through soluble factors like hormones and cytokines? A lot of attention has been focused on adrenergic PKA-mediated effects on adipose tissue composition, as shown by Shinoda et al. (2015) for the regulation of CK2. How important is this type of regulation in comparison to that of other potent regulators of adipose tissue function such as serotonin (Oh et al., 2015) and adenosine (Gnad et al., 2014)?

These findings that demonstrate a role of CK2 as a repressor of browning in adipose tissue are important not only from a biological science perspective, but also from a therapeutic angle, since they provide a new distinct activity and the possibility of identifying new gene products that take part in regulating CK2 activity that can be targeted and tested for therapeutic purposes. The ultimate aim is to provide a safe and efficient way of activating BAT in humans so that the beneficial effects of having ample amounts of brown fat can be made available to all that suffer from obesity and obesity-linked maladies such as type 2 diabetes.

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