How are peripheral tissue antigens that are Aire independent regulated, given that they are often found in the genome among Aire-dependent genes? Do they employ a similar strategy that includes a role for the DNA-PK complex but instead replace Aire by another master regulator? Lastly, are the genes targeted by Aire in MECs, as compared to those in other cell types (Guerau-de-Arellano et al., 2008), specifically selected to represent the "peripheral self," for example due to a unique complement of modifying factors or chromatin configuration? Regardless of how the answers turn out, Abramson et al. provide us with a persuasive explanation for how Aire, as a single factor, "wakes up" regions of inactive chromatin leading to low-level expression of hundreds of genes in a terminally differentiated cell type devoid of the transcription factors and chromatin configurations that regulate transcription of the respective genes in tissue cells. Remarkably, Aire not only promotes promiscuous gene expression, it also engages in promiscuous partnerships.

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Plant Chromatin Feels the Heat

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DOI 10.1016/j.cell.2009.12.035

Temperature is a key environmental signal regulating plant development, but the mechanisms by which plants sense small changes in ambient temperature have remained elusive. Kumar and Wigge (2010) now reveal that eviction of the histone variant H2A.Z from nucleosomes performs a central role in plant thermosensory perception.

Accurate monitoring of ambient temperature is fundamental to the survival of living organisms. Animals display marked temperature preferences and physically move to optimal thermal surroundings (Hamada et al., 2008). In contrast, plants must adapt their developmental program in response to environmental signals. Temperature can dramatically modify the growth and reproductive strategy of plants, yet little is known of the molecular mechanisms underlying such developmental plasticity. In this issue, Kumar and Wigge (2010) provide a major advance in our understanding of how plants detect changes in ambient temperature.

The majority of research to date has focused on plant adaptation to temperature extremes, such as cold and heat stress (reviewed in Penfield, 2008). In freezing-sensitive species, a prolonged period of cold can initiate signaling cascades and metabolic adaptations that enhance plant survival at subzero temperatures. Exposure to stressful high temperatures can initiate the synthesis of heat-shock proteins (HSPs) that confer some protection against protein denaturation and maintain cellular function. Small fluctuations in ambient growth temperature can, however, also have dramatic effects on plant development. When grown at cooler temperatures, many plants display a compact architecture and delay flowering. In contrast, elevated temperatures result in a graded increase in the elongation of plant axes and acceleration of the transition to reproductive development through the floral integrator FLOWERING TIME (FT) (Balasubramanian et al., 2006).

In an exciting new advance, Kumar and Wigge (2010) reveal that chromatin has a key role in the detection of changes in ambient temperature (Figure 1). The authors exploit the graded thermal response of *HSP70* expression in a forward genetic screen to isolate mutants displaying aberrant thermosensitivity. This elegant strategy results in the isolation of multiple alleles of *arp6*. ARP6

is a subunit of the SWR1 chromatin-remodeling complex, which is required for the deposition of the histone variant H2A.Z in nucleosomes (Li et al., 2005). When grown at cooler temperatures, *apr6* mutants phenocopy wild-type plants grown at higher temperatures. Experiments with isolated chromatin show that temperature directly modifies nucleosome composition and promoter accessibility. The authors additionally demonstrate that temperature-regulated eviction of H2A.Z occurs independently of the direction of the transcriptional response. It can therefore be concluded that temperature-mediated changes in nucleosome composition are not simply a consequence of elevated gene expression.

The authors propose that at cooler temperatures, H2A.Z occupancy represses gene expression by creating a physical block to transcription or by preventing the binding of complexes that activate transcription. Eviction of H2A.Z at higher temperatures would thereby facilitate transcription of these genes. A converse argument is presented for genes displaying downregulation by elevated temperature. In these circumstances, it is suggested that H2A.Z eviction may facilitate the binding of repressors, thereby limiting transcription. In this way, H2A.Z occupancy provides a mechanism to sense graded changes in ambient temperature and modulate gene expression accordingly. The authors also provide evidence for the existence of a parallel mechanism in yeast, suggesting that H2A.Z deposition may be an evolutionarily conserved mechanism for temperature-sensing across eukaryotes.

The temperature sensitivity of H2A.Z deposition provides an important advance in our understanding of how plants sense ambient temperature. It is, however, unlikely that this represents the sole mechanism of plant thermosensory perception. Multiple studies have observed temperature-dependent alterations in the fluidity of plant membranes (Falcone et al., 2004), and more recent work has reported that high temperature leads to an increase in the activity of the basic helix-loop-helix transcription factor PHYTOCHROME INTERACTING FACTOR 4 (PIF4), which is required for plant architectural adaptations to high temperature (Stavang et al., 2009; Koini et al., 2009). An acceleration of flowering is, however, observed in *pif4* plants grown at high temperatures, precluding the involvement of PIF4 in a global mechanism of plant temperature sensing (Koini et al., 2009). It is likely that accurate plant temperature sensing involves the complex integration of chromatin-remodeling events with altered membrane fluidity, in addition to direct effects on protein stability and activity.

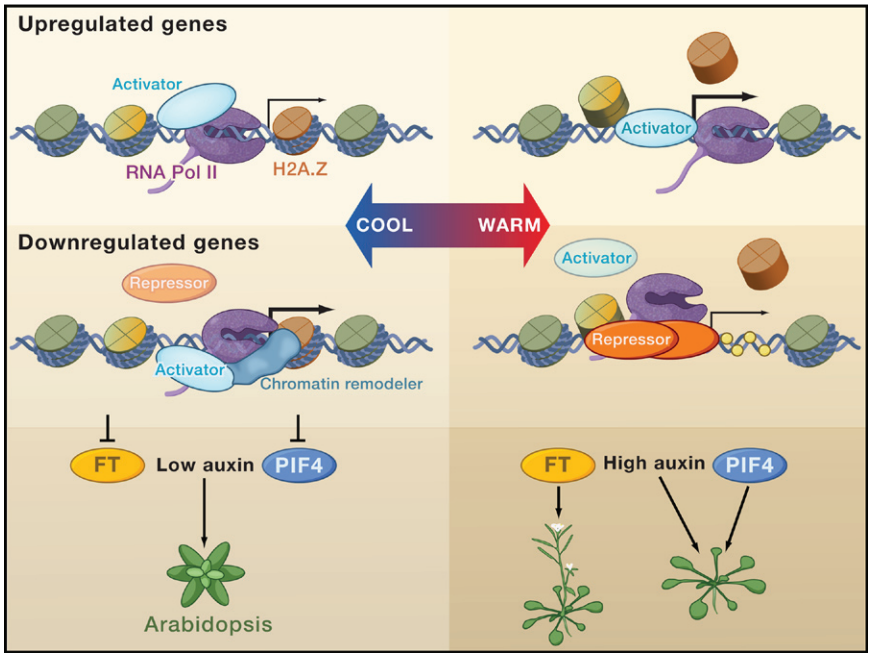

Figure 1. Ambient Temperature Signaling by Plants
When grown at cool temperatures (<22°C), *Arabidopsis* plants contain low levels of the hormone auxin and display reduced expression of the transcriptional regulator PHYTOCHROME INTERACTING FACTOR 4 (PIF4) and the floral integrator FLOWERING TIME (FT). These combined effects result in a compact rosette phenotype and delayed flowering. Temperature elevation leads to changes in the "ambient temperature transcriptome," which are mediated via a temperature-dependent reduction in histone H2A.Z occupancy in nucleosomes. These changes are accompanied by an elevation in auxin levels, increased abundance/activity of PIF4, and enhanced expression of FT. Together, these combined effects result in pronounced elongation of plant axes and the acceleration of flowering.

Epigenetic factors are also known regulate other temperature-mediated responses in plants. The process of vernalization (prolonged exposure to cold) provides winter annual plants with the competence to flower the following spring (reviewed in Kim et al., 2009). Molecular analysis of vernalization in a variety of species has revealed temperature-dependent epigenetic silencing of genes involved in floral repression. In *Arabidopsis*, flowering is prevented through accumulation of the floral repressor FLOWERING LOCUS C (FLC). During cold exposure, *FLC* expression is repressed through a suite of temperature-mediated chromatin modifications, including methylation of histone 3 at lysine residues 9 and 27 (H3K9 and H3K27). The stable repression of *FLC* expression through subsequent mitotic divisions enables the promotion of flowering by floral integrator FLOWERING TIME (FT) in warmer months.

Like all key discoveries, this study by Kumar and Wigge raises many additional questions. Plant growth and development is regulated by the combined activities of multiple hormones. In particular, elongation growth at high temperatures correlates with endogenous auxin content (Gray et al., 1998). It will therefore be of interest to elucidate how changes in the ambient temperature transcriptome link to auxin biosynthesis and the regulation of plant growth. Furthermore, does H2A.Z eviction facilitate binding of PIF4 transcriptional complexes? Is H2A.Z incorporation regulated by other environmental signals controlling elongation growth and flowering?

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 monoacylglycerols (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-