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BRIEFINGS

SUMMARY

Unraveling the internal clockwork that governs seasonality is an exciting challenge. Recent advances include the discovery of special 'timer cells' in the pituitary gland that decode day-length and signal directly to the brain; this pathway is conserved from fish to mammals indicating a 500 million year old ancestry. Now, the focus is on the 'seasonal clock' itself – structural changes in DNA that affect gene expression, and associated cyclical changes in cell growth and rest, are thought to govern the long time frame of innate seasonal rhythms

Looking Inside the Seasonal Clock

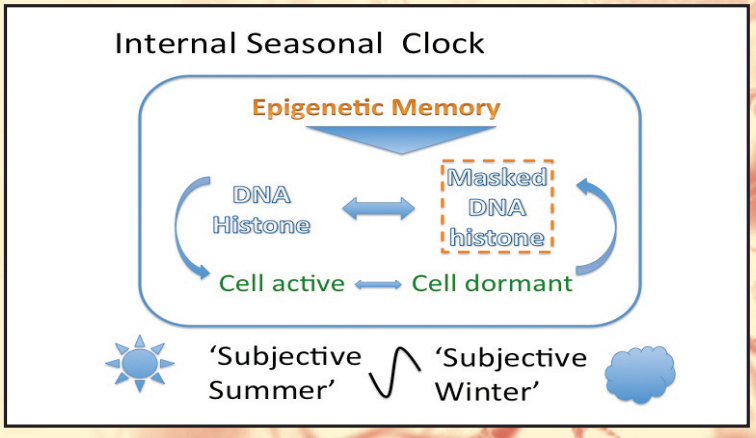
Turning timing upside down

The annual cycle in day-length is the predictable external cue used by most organisms to synchronize their seasonal biology to the seasons. In the last few years, we have made major advances in understanding how day-length is decoded in the body. In mammals, this involves specialized 'timer-cells' in the pituitary gland that transduce the effects of the day-length through melatonin signaling. The molecular mechanisms have been elegantly dissected. Also, there has been the remarkable discovery of the pathway by which these cells control seasonal physiology.

This discovery turns expectations upside-down, since the dogma is that the brain controls the pituitary gland, not *vice versa*. The key hormone is thyroid stimulating hormone (TSH), made by a sub-population of thyrotrope cells sensitive to melatonin, a hormone produced by the brain's pineal gland that is closely involved in the control of daily behavioural cycles.

These TSH cells are located strategically close to the pituitary's attachment to the brain. The target for TSH is the tanycyte cells lining the third-cerebral ventricle; these cells have long projections and make intimate contact with the neurons of the hypothalamus. Here, TSH regulates the metabolism of thyroid hormone (TH) to its biologically active form locally in the brain. This is the critical trigger – local TH levels determine the functional state of the hypothalamus. Exposure to long days activates the TSH-TH-relay, driving the active neuroendocrine state seen in summer, while short days remove the essential TH-dependent chemistry, and shut down the system for winter.

This novel pituitary to brain pathway was first described in quail by scientists in Japan, and later revealed in a wider range of animals. A similar mechanism also exists in bony fishes where the glandular circum-ventricular organ acts as the homologue of the timer system in mammals. This suggests an ancient 500 million year old origin of this seasonal timing



Simplistic model of the internal seasonal clock. Cycle generation across weeks and months occurs due to epigenetic control of structural changes in DNA governing switching between active and inactive states, and corresponding functional changes in cell and tissue activity.

mechanism. The central role of thyroid hormone implies a fundamental link between seasonal timing and the regulation of energy balance.

Search for seasonal clock

In tracking the system that records day-length, there was the prospect of understanding the clockwork mechanisms that generate innate seasonal rhythmicity. Most seasonal organisms (vertebrates, insects, mollusks, algae and flowering plants) continue to express robust, self-sustained seasonal rhythms when kept indoors under constant-controlled day-length. Thus, cycles are not merely induced by environmental cues, but are in essence *genetically* programmed. This explains how changes in physiology and behavior may occur months in advance of environmental events with the effect of optimizing survival and reproductive success. Innate rhythmicity also accounts for the occurrence of seasonal cycles in animals living near the Equator where the external cues are unpredictable, and how many species can migrate across time zones without disrupting their seasonal biology. The simple rule is that having evolved in a periodic world – all organisms are more, or less, cyclical.

"the dogma is that the brain controls the pituitary gland, not vice versa"

We now believe that the innate clockwork can be localized to specific organs, and perhaps even to the level of single cells. The best evidence for this comes from studies in the highly seasonal Soay sheep, where the pituitary gland has been surgically disconnected from the base of the brain. In this experimental animal model, the basic functions of major cell-types in the pituitary gland (corticotropes, thyrotropes and lactotropes) are maintained, supporting key body functions and good health. Remarkably, these experimental sheep continue to express long-term rhythms in prolactin secretion, similar to intact control animals. Under constant long days, the period of the 'free-running' prolactin rhythm is significantly shorter than a year (near 10 months), as is often seen for un-entrained seasonal rhythms. These results have been taken as good evidence that the pituitary gland is an organ that generates self-sustained circannual rhythms, possibly generated within the special 'timer-cells' that read day-length. There is also good reason to believe that other organs and tissues are functionally rhythmic.

Making the super long rhythms

What type of mechanisms might generate the remarkably long time frame of a yearly rhythm in mammals? Currently, the most likely theory is that this will involve fundamental reprogramming of cellular function, with reversibility. A simplistic model is illustrated here. This proposes two levels of control, one involving cyclical reorganization of the state of DNA and the histone proteins that govern whether or not sets of genes are transcribed. The second involves cellular remodeling and tissue regeneration. Together these processes will operate over periods of many months to produce the innate seasonal rhythmicity. The seasonal transformations can be profound representing a reversible metamorphosis that is repeated through the adult life-history.

We do not yet know how DNA/histone re-modeling occurs in seasonal mammals, or the full extent of the predicted regulatory chemistry (e.g. methylation), although this is a well studied feature in embryonic development (i.e. the first phase of the life-history). In plants, however, the seasonal timing mechanisms are much better resolved. The best example is the control of 'vernalization', the phenomenon by which flowering is induced by winter cold over many weeks – a biology familiar to any gardener. Here, cold temperature activates a well-characterized epigenetic memory system that progressively inhibits the flowing-inhibitory gene locus, to trigger flowering. Strikingly, the epigenetic DNA sequences that govern timing in plants, are strongly conserved across plants and animals, and may represent a common point of control for seasonal timing in all organisms.

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