[12], and cold can change RNA editing patterns in ion channel genes [13]. One could imagine a situation where a temperature-dependent post-transcriptional event might alter a clock isoform and/or a downstream effector that interacts with the time-compensated compass in the brain. Another obvious avenue of investigation would be to identify the temperature sensors, and trp channels might be a first place to look [14], but so might the orthologous sensors that convey temperature to the fly brain clock, such as nocte [15]. No doubt the molecular answer to how the compass switches direction will provide a further fascinating glimpse into the mechanisms that drive migration. Finally, these findings expose the vulnerability of the Monarch’s life cycle to temperature change. While the authors have not investigated how brief a period of cold, nor the maximum and minimum temperatures that might be required to effect a south-to-north directional switch, it could be that any prolonged unseasonal cold episodes during the autumn in New England could have quite serious ramifications for those migrants beginning their journey from there. Furthermore, warmer temperatures at the overwintering sites could prevent or significantly modify the return trip north with equally severe costs. Finally, in January 2002, 250 million Monarchs, ~80% of the population in the El Rosario forest sanctuary, were killed because of cold weather, the effects of which were amplified by illegal logging, which allowed the cold air to penetrate more deeply into the forest [16]. Consequently, the work of Guerra and Reppert also highlights the delicate nature of this most spectacular of natural phenomena and its sensitivity not only to human encroachment but also to climate change [17].

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Chromosome Segregation: Disarming the Protector

One of the key features of meiosis is that shugoshin in complex with protein phosphatase 2A (PP2A) protects centromeric cohesin during meiosis I, but not during meiosis II. A new model suggests that a PP2A inhibitor mediates deprotection of centromeric cohesin during meiosis II.

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The cohesin complex mediates cohesion between sister chromatids during both mitosis and meiosis. According to the ‘ring model’, cohesin mediates sister chromatid cohesion by topologically entrapping sister chromatids. At the onset of anaphase, cohesin is cleaved by a protease called...
separase, which opens the cohesin ring. During meiosis, the chromosome number is halved because two rounds of chromosome segregation, called meiosis I and meiosis II, follow a single round of DNA replication. During the first meiotic division, segregation of recombined homologous chromosomes is triggered by separase cleavage of cohesin’s kleisin subunit Rec8 along chromosome arms. A key feature of meiosis I is that centromeric cohesin is protected from separase cleavage by shugoshin/MEI-S332 proteins in complex with PP2A. Shugoshin–PP2A protects centromeric cohesin by opposing phosphorylation of Rec8 [1–3]. Why is it important to protect centromeric cohesion during meiosis I? Cohesin-mediated sister chromatid cohesion is essential for proper attachment of sister kinetochores to microtubules emanating from the opposite poles. Thus, the retention of sister chromatid cohesion at centromeres until the onset of anaphase II is essential for faithful segregation of recombined sister chromatids during the second meiotic division. While it is well established that the shugoshin–PP2A complex mediates protection of centromeric cohesin during meiosis I, it is less understood what renders cohesin at centromeres sensitive to separase cleavage during meiosis II. Previous studies suggested that the mere presence of shugoshin–PP2A at centromeres might not be sufficient to protect centromeric cohesion [4–7]. A new study by Chambon et al. [8] reported in this issue of Current Biology now suggests that inhibitor 2 of PP2A (I2PP2A/SET) mediates deprotection of centromeric cohesin during meiosis II.

Previous cytological observations in mouse oocytes and spermatocytes showed that shugoshin co-localizes with cohesin on metaphase I centromeres, but not in prometaphase II [9,10]. Based on these findings, as well as previous work [11], Suja and Watanabe proposed that during meiosis II, tension across sister kinetochores due to bi-orientation might force the shugoshin–PP2A complex to relocate from cohesin sites at the inner centromere domain towards the inner kinetochore, thus allowing phosphorylation of Rec8 (Figure 1A). Although this model provides an elegant explanation for why the shugoshin–PP2A complex mediates protection of centromeric cohesin specifically during meiosis I but not during meiosis II, other analyses suggested that there might be an additional mechanism that renders centromeric cohesin sensitive to separase cleavage during meiosis II. In several studies, centromeric cohesion was found to prevent segregation of bi-oriented sister chromatids to opposite poles. In Saccharomyces cerevisiae monopolin mutants, for example, sister kinetochores are bi-oriented during meiosis I; nevertheless, cohesin at centromeres remains intact and prevents the segregation of recombined sister chromatids to opposite poles [12]. Similarly, in fission yeast mutants defective in meiotic recombination and chiasma formation, sister kinetochores are frequently bi-oriented in meiosis I, but they only rarely segregate to the opposite poles [13–15]. In addition, ectopic co-expression of Rec8 and Sgo1 in mitotic Schizosaccharomyces pombe cells causes failure of sister chromatid segregation, presumably because of resistance of centromeric cohesin to separase-mediated cleavage [16].
and I2PP2A has also been observed in two other independent studies [18,19]. I2PP2A is a potent inhibitor which can directly bind to PP2A. This raised an interesting possibility that inhibition of PP2A by I2PP2A renders centromeric cohesin sensitive to separase cleavage during meiosis II. Consistent with this model, Chambon et al. found that I2PP2A depletion in mouse oocytes led to a defect in segregation of recombined sister chromatids during meiosis II. However, in mouse oocytes, I2PP2A localized to centromeres during both meiosis I and meiosis II [8]. How is it then possible that I2PP2A inhibits centromeric PP2A specifically during meiosis II? The answer came from a careful cytological analysis of mouse oocytes where Chambon et al. found that I2PP2A co-localized with PP2A and Rec8 in meiosis II cells, but I2PP2A staining was shifted away from PP2A and Rec8 signals in meiosis I cells [8]. Although the mechanism by which I2PP2A is regulated is not well understood, it is interesting that I2PP2A phosphorylation results in enhanced binding to PP2A’s catalytic subunit, thus inhibiting phosphatase activity [20]. This raises an interesting possibility that I2PP2A activity at meiotic centromeres may also be regulated by phosphorylation. This would provide another level of regulation ensuring that centromeric I2PP2A inhibits PP2A activity during meiosis II but not during meiosis I.

The current work of Chambon et al. suggests a new model that explains why the shugoshin–PP2A complex protects centromeric cohesin from separase-dependent cleavage only during meiosis I, but not during meiosis II and provides an elegant alternative to the previous model proposed by Suja and Watanabe (Figure 1). However, these two models are not mutually exclusive and it is possible that both of these mechanisms contribute to step-wise loss of centromeric cohesion during meiosis. The study of Chambon et al. also raises many important questions that remain to be addressed. Does the fact that PP2A co-localizes with I2PP2A mean that PP2A is unable to dephosphorylate cohesin during meiosis II and this allows separase to cleave centromeric cohesin at the onset of anaphase II? Ultimately, it will be necessary to look directly at cohesin and analyze whether centromeric Rec8 is hyperphosphorylated during meiosis II and whether I2PP2A depletion leads to Rec8 hypophosphorylation at meiosis II centromeres. Given the caveats associated with the knock-down approach, it will also be important to analyze meiosis in I2PP2A knockout cells. Moreover, it will be important to show whether the chromosome segregation defect observed in I2PP2A-depleted cells during meiosis II is due to inability to cleave centromeric cohesin. Finally, in the near future, we will hopefully hear more about meiosis in the unconventional model organism Ciona intestinalis (or the related Phallusia mammillata) (Figure 2). This ascidian species provides the advantage of producing large amounts of metaphase I oocytes (10,000 to 100,000 per animal) that are large, transparent and can be induced to undergo synchronous meiosis.

Finally, in the new study, Chambon et al. [8] found that in mouse oocytes PP2A colocalizes with the cohesin subunit Rec8 at the meiosis II centromeres.

If the tension-dependent relocation of shugoshin–PP2A from the centromeric cohesin sites is not the only mechanism responsible for the step-wise loss of sister chromatid cohesion during meiosis, what else can make centromeric cohesin resistant to separase cleavage during meiosis I but not during meiosis II? One possibility is that either shugoshin or PP2A are inactivated during meiosis II. Another possibility is that Rec8 phosphorylation may not be required for separase cleavage during meiosis II [17]. Important insights often come from unexpected corners. Chambon et al. screened a two-hybrid library prepared from oocytes of a marine chordate, Ciona intestinalis (Figure 2), and found that shugoshin Ci-Sgo1 interacts with the PP2A inhibitor Ci-I2PP2A [8]. Physical interaction between human shugoshin SGOL1 and I2PP2A has also been observed in two other independent studies [18,19]. I2PP2A is a potent inhibitor which can directly bind to PP2A. This raised an interesting possibility that inhibition of PP2A by I2PP2A renders centromeric cohesin sensitive to separase cleavage during meiosis II. Consistent with this model, Chambon et al. found that I2PP2A depletion in mouse oocytes led to a defect in segregation of recombined sister chromatids during meiosis II. However, in mouse oocytes, I2PP2A localized to centromeres during both meiosis I and meiosis II [8]. How is it then possible that I2PP2A inhibits centromeric PP2A specifically during meiosis II? The answer came from a careful cytological analysis of mouse oocytes where Chambon et al. found that I2PP2A co-localized with PP2A and Rec8 in meiosis II cells, but I2PP2A staining was shifted away from PP2A and Rec8 signals in meiosis I cells [8]. Although the mechanism by which I2PP2A is regulated is not well understood, it is interesting that I2PP2A phosphorylation results in enhanced binding to PP2A’s catalytic subunit, thus inhibiting phosphatase activity [20]. This raises an interesting possibility that I2PP2A activity at meiotic centromeres may also be regulated by phosphorylation. This would provide another level of regulation ensuring that centromeric I2PP2A inhibits PP2A activity during meiosis II but not during meiosis I.

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Motivational Neuroscience: Instant Desire for Something You Know Is Bad

Avoiding what you know is bad is a major challenge for recovering addicts. New research suggests that powerful desire can develop even for cues that have always been repulsive. Memories about learned cues can promote addiction in certain conditions.

Jonathon D. Crystal

A former addict walks down the street. He sees a bar, or other source of abused substances, and knows what is inside is bad. Will he approach, consume, return to habits so arduously discarded? Can he withstand the potentially intense cravings? Relapse after seemingly successful abstinence is a significant problem in drug abuse [1]. Why do we indulge in drugs that we know are bad? New research by Robinson and Berridge [2] published recently in Current Biology suggests that desires are instantly transformed despite painstakingly learned associations. Desire is based not only on learned information about a substance (or cues associated with it), but also on its current value as indexed by mesocorticolimbic activation. This type of instant transformation of desire is a challenge to traditional learning approaches to motivation and addiction [3, 4].

Traditional learning perspectives predict that past displeasure with a cue predicts future avoidance of the cue, which can only be offset by a gradual experience-based re-computation of cue value. More broadly, this work is consistent with the view that cognitive computations on previous memories plays an important role in drug abuse [5].

The new work shows that a repulsive learned cue for unpleasantness can be instantly transformed into a target of desire. Imagine, then, how much more intense the craving would be for memories of an already pleasant drug experience. In the new research [2], rats received a small squirt of a salty solution directly into the mouth. Salt appetite for this level of saltiness is so repulsive that normal rats show a disgust gape (Figure 1A, and flails or headshakes) when a small squirt was used. This level of saltiness was paired with a distinctive cue (a tone, for example) and the new work shows that a repulsive, intense saltiness (three-times saltier than Dead Sea concentrations of sodium chloride) was used. This level of saltiness is so repulsive that normal rats show a disgust gape (Figure 1A, and flails or headshakes) when a small squirt is infused into its mouth, and rats will not voluntarily drink it under normal conditions. Intensely unpleasant saltiness was paired with a distinctive cue (a tone, for example) and the presentation of a metal lever. A second cue (white noise, for example) was paired with a palatable sucrose solution and a different lever on the opposite side of the rat’s chamber. Of course, rats will voluntarily drink sweet solutions, which evoke positive hedonic reactions (protrusion of the tongue, Figure 1B, and paw licking). After several pairings of the cues, rats readily learned to move away from the intense-salt-associated lever when it was presented with the intense-salt-associated sound.

By contrast, rats learned to approach, nibble, and sniff at the pleasant sucrose-associated lever when the sucrose-associated sound was presented. Hence, approach versus avoidance of the salt-associated lever served as a behavioral measure for the rat’s current motivation toward salt.

After the rats robustly rejected the salt-associated lever, the animals were put into a novel state of salt