mate only once under these conditions. In the other treatments polyandry was encouraged and females were given two, three, or six additional mating bouts. Over the course of the 15 generations the experiment lasted, the number of monandrous populations decreased from 12 to 7, and the cause of these extinctions was the lack of production of functional males. Furthermore, the frequency of X^{SR} in the surviving monandrous populations was significantly higher than that in each of the polyandry treatments (in which the frequencies were not different from one another). The authors conclude that, although all of the offspring of $X^{SR}Y$ males inherit the X^{SR} chromosome, these males produce far fewer offspring than a normal male when females mate multiple times and polyandry allows for sperm competition between males within the reproductive tracts of females. Their results also suggest that local extinction of populations with very high frequencies of the X^{SR} chromosome might be an additional evolutionary force restricting the female-biased sex ratios generated by the meiotic drive.

These findings are novel and important because they illustrate that sexual selection via reproductive competition between males is a strong evolutionary force acting in the opposite direction to and limiting the effects of meiotic drive; together, these opposing forces can establish the polymorphisms seen in nature. Nevertheless, there remains a great deal of additional research to be conducted on this and other meiotic drive systems. It has, for instance, been shown that $X^{SR}X^{SR}$ homozygous females may suffer reduced viability and, in theory, such sexually antagonistic effects of viability selection acting against the spread of the X^{SR} chromosome are sufficient to sustain polymorphism. Such effects may have been present in the experimental cultures of Trevor Price and colleagues, and are even suggested by the periodicity in the frequency of males in the later generations of the polyandrous treatments [6]. In addition, natural populations of this species of fly tend to be considerably more abundant as well as open to migration relative to the closed laboratory populations. Nevertheless, the new study [6] reports a striking set of replicated observations using flies recently derived from nature that not only exhibits frequent, sex-ratio biased caused extinctions, but also a clear rescuing effect of polyandry.

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Transcriptional Memory: Mothers SET the Table for Daughters

Eukaryotic gene transcription within individual cells of a population is often associated with heterogeneous pulses of gene activity. A recent study, however, shows that mothers and their daughters share similar transcriptional frequencies, and inheritance of mother's transcriptional tendencies requires methylation of histone H3 by a Set1 methyltransferase.

Craig L. Peterson

Establishing and maintaining transcriptional states that are heritable to progeny plays a central role during development of multi-cellular organisms. In some cases a transcriptional state is propagated in the absence of the original inducing signal, suggesting some type of transcriptional 'memory'. Perhaps the most widely accepted example of transcriptional memory occurs at homeotic genes where spatial expression patterns are maintained throughout the life of the organism in the absence of the initial segmentation gene products that established the initial transcription states [1]. Likewise, unicellular eukaryotes rapidly adapt to signals from their microenvironment by altering their transcriptional profile, and the ability to pass on a memory of such altered environmental conditions may provide progeny with a selective advantage. Since these heritable changes in gene expression do not involve alterations to an organism's genome, they represent examples of epigenetic regulation.

Over the past ten years, use of the word 'epigenetic' has become synonymous with studies of chromatin structure and function. In particular, patterns of histone post-translational modifications have been suggested to provide a type of code for ON/OFF states of gene expression that might self-propagate during cell division and thus provide heritable marks for gene expression states. Although this view has remained pervasive, histone modifications are generally dynamic, are not self-propagating,

and probably require re-establishment by sequence-specific DNA-binding proteins following each round of DNA replication (for a detailed review see [2]). In one clear example in budding yeast, the memory of an active transcription state does not require particular histone modifications, but rather cytoplasmic inheritance of a signaling molecule [3–5]. Thus, there has been little direct evidence supporting the view that histone modifications function as heritable marks for different gene expression states.

In this issue of *Current Biology*, Chubb and colleagues [6] use single cell analyses of gene expression to demonstrate inheritance of transcriptional patterns from mother to daughter cells in the slime mold *Dictyostelium discoideum*. Remarkably, the inherited transcription states require methylation of histone H3 lysine 4 (H3 K4me) by a SET1 methyltransferase complex. Furthermore, they find that histone H3 K4me is not required for setting the level of transcription *per se*, but this modification only influences inheritance of the mother's particular state, suggesting that H3 K4me may represent one of the first examples of a *bona fide*, epigenetic histone mark.

The study of gene transcription at the single cell level has been revolutionized by pioneering studies from the Singer group, who developed methods to quantify individual transcripts from engineered genes in real time analyses [7]. One particularly powerful approach involves the introduction of multiple copies of a recognition sequence for the bacteriophage MS2 coat protein within the 5′ or 3′ end of the transcribed region of a target gene. Expression of a fluorescent MS2–GFP fusion protein then allows detection and quantification of nascent transcripts within live cells. One surprising theme that has emerged from such studies is that actively transcribed genes are typically expressed in a pulsatory fashion, with RNAs expressed in bursts, followed by periods of gene inactivity. The length and frequency of transcriptional pulses vary among cells in a population, suggesting models in which transcription levels are controlled by stochastic windows of active and inactive gene states [7–10].

In the recent study described by Chubb and colleagues [6], *Dictyostelium* strains were designed that harbored modified *act5* or *scd* genes, which each contained 24 tandem MS2 binding sites within the 5′ end of the respective mRNAs. Constitutive expression of MS2–GFP produces bright GFP foci that mark the location of nascent *act5* or *scd* transcripts, and foci were continuously monitored as cells proceeded through several cell cycles. Similar to previous studies [7–10], the constitutive *act5* and *scd* genes are transcribed in pulses, interspersed with varying periods of gene inactivity. Both genes are most active during S and G2 phases of the cell cycle, with less activity in late G2 and M phases (the ~8 hour *Dictyostelium* cell cycle lacks a measureable G1 phase). To compare the transcriptional behavior of cells within the population, the authors define transcription frequency as the amount of time per hour that the target gene is expressed (i.e., shows a bright GFP focus). Thus, this parameter encompasses both the number of pulses and the duration of each pulse, properties that vary greatly among individual cells. For *act5*, the gene is expressed at an average of 5.5 minutes each hour, but the variability in transcription frequency among random cells is quite large (~3 minutes/hour).

In contrast to the significant variability in transcription frequency among random cells in the population, a quite different view was obtained from analysis of individual mothers and their daughters [6]. In this case, the two daughter cells that derive from division of a mother showed transcriptional frequencies nearly identical to their mother, varying by only ~1 minute per hour for the *scd* target gene. The authors show that this reflects a more similar average burst duration between mothers and daughters, and likely a more similar frequency of transcriptional bursts. Furthermore, even the granddaughter cells show transcriptional frequencies more similar to their parent, indicating that the overall transcriptional behavior of the mother could be inherited through two successive rounds of DNA replication and mitosis. However, the variations in transcriptional frequency were greater in the granddaughter cells, indicating that the memory phenomenon is weakened by successive cell divisions.

How do daughters remember their mother's transcriptional idiosyncrasies? Surprisingly, inheritance of mother's transcriptional frequency requires methylation of histone H3 K4 by a SET1 methyltransferase complex [6]. When either the Set1 or Ash2 subunits of the SET1 complex are inactivated, daughters lose their 'memory' of mother and show highly variable transcriptional frequencies, just like the random population. Likewise, a single H3 K4A amino-acid substitution eliminates memory, directly demonstrating that histone methylation is the key event in this memory phenomenon. In contrast, inactivation of the DNA methyltransferase dmnA or the *Dictyostelium* Set2 homolog, which methylates H3 K36, had no effect on the inheritance of transcriptional frequencies. Thus, H3 K4me may represent a unique mark that provides daughter cells with a memory of their mother's transcriptional program.

Methylation of H3 K4 is generally associated with actively transcribed loci, with the trimethylated form (H3 K4me$_3$) primarily marking a few nucleosomes that flank promoters transcribed by RNA polymerase II (RNAPII) [11]. However, the function of H3 K4 methylation is not yet clear, although methylated H3 K4 is known to interact with a host of transcription factors, including subunits of chromatin remodeling and modification enzymes, components of the RNA processing machinery, and the general transcription factor TFIID [11,12]. In budding yeast, loss of H3 K4 methylation leads to a fairly global defect in RNAPII transcription, but surprisingly the changes in transcription levels are generally quite small (< 2-fold) [13]. Likewise, in *Dictyostelium*, inactivation of the Set1 methyltransferase only significantly alters the expression of 75 genes [14], and there is no significant change in the steady state transcript levels of *act5* or *scd* [6]. Furthermore, inactivation of Set1 does not alter pulse frequency or pulse duration of these genes [6]. Thus, in these cases H3 K4me appears to impact only the inheritance of the mother's transcriptional frequency (either high or low expression) without influencing the actual level of transcription.

How does H3 K4me provide memory of a previous transcription state? Several studies indicate that H3 K4me$_3$ is a co-transcriptional mark that is generated after RNAPII initiation (discussed in [11]). This suggests a simple model in which the 'quality' of the pre-initiation complex (PIC) may determine the subsequent density of H3 K4me$_3$ within promoter nucleosomes. High or low density of K4me$_3$ might then provide a memory of the previous transcriptional frequency, without influencing the actual level of transcription. However, this simple model cannot explain how memory survives DNA replication, as this event will cause a 2-fold dilution of the mother's H3 K4me$_3$ density due to new nucleosome deposition. Furthermore, transcription in the daughter does not appear to re-establish the appropriate mark, as the heterogeneity in transcriptional frequency is larger in the next, granddaughter generation [6]. Thus, memory is more likely to involve a much more complex scenario in which co-transcriptional H3 K4me$_3$ in the mother promotes several downstream events, of which one or more may be stochastic in nature, that together create a heritable 'mark' which can lead to a recapitulation of a similar transcriptional frequency in the subsequent daughter cell.

These results raise another general question: Why would a cell wish to ensure inheritance of a particular transcriptional frequency through one or two cell divisions? *A priori* one would think that relatively minor changes in the frequency or duration of a transcriptional burst would not cause much of a phenotypic consequence. Indeed, it has been suggested that transcriptional bursting will not have much impact on the level of most proteins, as the average protein's half-life is rather long and as such will provide a buffer for bursts in mRNA production (discussed in [10,15]). In contrast, the abundance of proteins with very short half-lives may be significantly altered by changes in transcriptional burst length or frequency. For example, a mother cell that may have acquired a particular transcriptional frequency may as a consequence have altered levels of stress response proteins that confer a growth advantage in certain environmental conditions. Inheritance of this particular transcriptional state would then ensure that daughters reap the benefits of mothers' random 'choice' of transcriptional program.

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Parasitoid Wasps: From Natural History to Genomic Studies

The sequencing of three *Nasonia* genomes provides new insights on the molecular signature associated with parasitoid lifestyle, allows comparison with the social honey bee, and enables the identification of genes underlying between-species and sex-specific differences.

Yannick Wurm and Laurent Keller

> "*I cannot persuade myself that a beneficent and omnipotent God would have designedly created the Ichneumonidae with the express intention of their feeding within the living bodies of caterpillars*."
> Charles Darwin, May 22nd, 1860

With these words to his theist friend, the renowned botanist Asa Gray, Darwin expressed his astonishment at the extremely specialized and selfish lifestyles exhibited by parasitoid wasps. For example, adult females of the jewel wasp *Nasonia vitripennis* locate pupae of filth fly hosts, drill through the pupae's exoskeleton, inject a potent venom and deposit a few dozen eggs. The young feed on the paralyzed host until development is complete. After eclosion, males do not disperse and typically mate with their sisters. This unusual mating system has attracted much attention by naturalists and evolutionary biologists, in particular because it allows quantitative tests of sex ratio evolution and adaptation [1–4]. The sequencing of three *Nasonia* genomes [5] now opens new doors to study many aspects of *Nasonia*'s life history in molecular and genetic terms, as attested by the publication of more than thirty companion papers.