sheep, are sufficient to elicit reproductive responses, and ablating hypothalamic areas abolishes melatonin's effects upon reproduction [16–19]. Thus, many vertebrates have a functional hypothalamic system with which they can potentially interpret day-length changes and regulate seasonal endocrinology and behavior via a more 'classic' pathway than the newly identified *Dio2* pathway. Perhaps *in vivo* manipulations of *Dio2* expression will help to clarify its role in seasonal timing.

Despite these caveats, it seems that these recent studies on *Dio2* regulation via the PT bring us closer to understanding mechanisms of seasonal timing in birds and mammals. Because of the varied nature of the vertebrate photoperiodic response, it will be hard to identify a truly unifying mechanism. Thus, I'll reverse one of Dr. Seuss' sayings and end with: "Sometimes the questions are simple and the answers are complicated."

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Cell Size: A Matter of Life or Death?

Proper growth and development of multicellular organisms require the tight regulation of cell growth, cell division and cell death. A recent study has identified a novel regulatory link between two of these processes: cell growth and cell death.

Cathy Savage-Dunn

Cell size is a fundamental and easily observable aspect of cell phenotype. It is somewhat surprising, then, that the mechanisms regulating cell size remain relatively mysterious. Cell size is dependent on the processes of cell growth, defined as an increase in cell mass, and cell division [1]. While numerous pathways regulating cell division have been identified, much less is known about the pathways regulating cell growth. In a recent issue of *Current Biology*, Chen *et al.* [2] report evidence of a novel cell-growth-regulating mechanism that also functions to antagonize apoptotic cell death. Intriguingly, this growth-promoting activity may also be usurped to promote survival of cancer cells.

Several previous studies suggested a link between the regulation of total protein synthesis and cell-size control. For example, in yeast, genome-wide screens showed that ribosome biogenesis pathways regulate cell size [1]. The rate of ribosome biogenesis is regulated by the target of rapamycin (TOR) kinase, which is responsive to nutrient conditions [3]. Do similar size-regulating mechanisms operate in metazoans as in yeast? The importance of TOR and protein translation in regulating cell size in multicellular organisms has been confirmed by work in *Drosophila* [4]. Furthermore, studies in *Drosophila* have shown that insulin receptor signaling regulates both cell number and cell size, and that disruption of the insulin receptor signaling pathway results in flies with small body size [5]. A similar mechanism regulates size in mammals: knocking-out genes for insulin-like growth factor (IGF) ligands, receptors, or insulin receptor substrate (IRS-1) leads to reduced body size in mouse [6]. A major target of the insulin/IGF pathways in flies and mammals is the TOR kinase. TOR thus serves as a central mediator of

cell-size control responsive to nutritional status and cell signaling pathways.

Studies in the nematode *Caenorhabditis elegans* have also contributed to the understanding of cell-size control. In the worm, cell lineage is nearly invariant, so changes in body size correlate more tightly with changes in cell size. In genetic screens for mutants with small body size, the major pathway identified was the DBL-1 TGFβ-related pathway [7]. DBL-1 is a TGFβ superfamily ligand most closely related to *Drosophila* Dpp and vertebrate BMP2/4 [8]. Mutations of DBL-1 or in its signaling pathway result in small body size. In these mutants, cell number is unchanged, indicating that cell size must be smaller [9]. The molecular mechanisms of cell size control by the DBL-1 pathway remain elusive. One hypothesis has been that the pathway regulates nuclear ploidy [10,11], but this may not be sufficient to account for all of the differences in size seen in mutant animals [9,12]. Ploidy is known to correlate with cell size in many cell types [1].

Now, Chen *et al.* [2] have identified a growth promoting activity in *C. elegans* mediated by *tfg-1*, the worm homolog of the mammalian TRK-fused gene (TFG) proto-oncogene. TFG rearrangements are associated with a variety of human cancers, but the mechanisms whereby they contribute to tumorigenesis are not known [13–15]. *C. elegans tfg-1* is essential for embryonic viability, but the use of RNA interference (RNAi) to inactivate the gene after embryogenesis showed that it has a role in body-size control. Remarkably, these *tfg-1(RNAi)* animals developed into adults with approximately half the body length and 30% of the total body volume of control animals. These reduced-size animals had the same number of somatic nuclei as control animals, indicating no disruption of cell division. Instead, cell volume and nuclear volume were reduced: for example, body wall muscle volume was also about 30% that of controls. In addition to promoting growth, TFG-1 was found to inhibit apoptosis. *tfg-1(RNAi)* embryos contained significantly more apoptotic corpses than controls, while embryos overexpressing *tfg-1* contained significantly fewer apoptotic corpses. TFG-1 thus provides a mechanistic link by which cell growth and cell death can be reciprocally regulated.

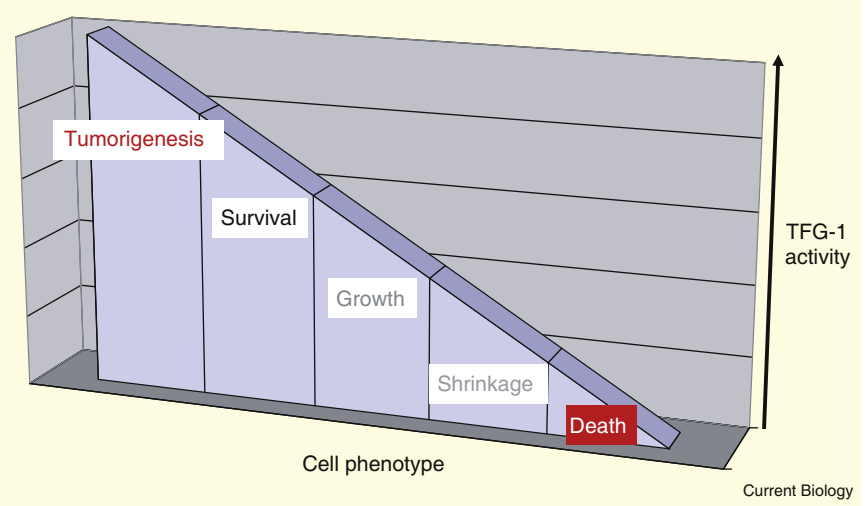

Figure 1. Proto-oncogene *tfg-1* regulates cell size and cell death.

A possible model for the relationship between TFG-1 activity levels and cellular phenotype: TFG-1 promotes cell growth and survival and inhibits apoptotic cell death.

The next question was the nature of the pathway(s) by which TFG-1 regulates cell size and cell death. Chen *et al.* [2] tested for interactions with the DBL-1 TGFβ-related pathway and the *C. elegans* insulin signaling pathway, either of which might mediate TFG-1 regulation of cell size. They found that mutations in the insulin pathway had no effect on cell size. On the other hand, the DBL-1 pathway showed additive effects on growth, indicating that it acts independently of TFG-1. Finally, they found that the reduced cell and nuclear size of *tfg-1(RNAi)* animals are not associated with reduced DNA ploidy. These results suggest that TFG-1 regulates growth through a novel pathway.

Next, cell death regulators were examined for interactions with TFG-1. The core apoptotic machinery in *C. elegans* consists of EGL-1 (BH3-containing), CED-9 (BCL-2), CED-4 (Apaf-1), and CED-3 (caspase) [16]. The increased apoptotic death in *tfg-1(RNAi)* animals was largely dependent on the core apoptotic machinery. In growth regulation, however, mutations in *egl-1, ced-9,* and *ced-3* had no effect on *tfg-1(RNAi)* cell size phenotypes. In contrast, *ced-4* mutations suppressed the cell-size defects associated with *tfg-1(RNAi)*, demonstrating an unexpected function for CED-4/Apaf-1 in cell size regulation. CED-4 may have dual functions in cell-size control, as *ced-4* loss-of-function reduces cell size in a wild-type background but increases cell size in the *tfg-1(RNAi)* background. Chen *et al.* [2] conclude that CED-4 and TFG-1 have antagonistic functions in both cell-size and cell-death regulation.

The existence of an antagonistic link between cell growth and cell death suggests there is a continuum between survival and death in which one finds cell growth and cell shrinkage as intermediate states (Figure 1). These states may be regulated in part by the level of TFG-1 activity. As TFG-1 activity is inhibited, the consequences are first cell shrinkage and ultimately cell death. At the other extreme, inappropriately high TFG-1 activity may lead to tumorigenesis. CED-4 antagonizes these functions of TFG-1, but its relationship with cell size is less linear, since loss of CED-4 function decreases cell size in a wild-type background but increases cell size under *tfg-1(RNAi)* treatment. Because nuclear condensation and cell shrinkage are normally associated with apoptosis [17], reduction in cell size may be considered to be one aspect of the apoptotic cell death program. On the basis of Chen *et al.*'s [2] observations, we can infer that this aspect can be separated from the execution of the remainder of the cell-death program.

The novel observations reported by Chen *et al.* [2] raise many thought-provoking unanswered

questions. First, what are the molecular mechanisms by which TFG-1 regulates cell size and cell death, and does it interact physically or indirectly with CED-4? Second, does a similar regulatory interaction occur in mammals? If so, how do TFG fusion proteins disrupt the regulation of cell growth and cell death? Third, more generally, how does the promotion of growth, but not necessarily cell division, lead to an oncogenic phenotype? Future research into the link between cell size and cell death should illuminate some of these mysteries.

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Animal Sociality: Bat Colonies Are Founded by Relatives

Most bat species breed communally, but how their colonies are founded is a mystery. A recent study suggests that the formation of a new colony starts with related females splitting off from an existing colony.

Gerald Kerth

How social animals form new groups strongly affects the stability of the groups as well as the reproductive success and the social behaviour of the group members [1,2]. For this reason, group formation has been studied intensively, particularly in social insects and primates [1–3]. Bats are highly gregarious mammals and in most species the females form colonies to raise their offspring communally [4]. Exactly how new colonies are formed is mysterious, however, as colony foundation is a rare and elusive event. Until recently, the available evidence was limited to population genetic data, which suggested that bat colonies are founded by groups of females that split off from an existing colony and then settle nearby [5]. Now a paper by Metheny *et al.* [6] on big brown bats (*Eptesicus fuscus*; Figure 1) presents the first detailed field observations of joint movements of individually marked females to a new area, in combination with genetic data on their relatedness. The study reveals that colony formation is initiated by a group of females splitting off from the original colony. The whole colony-fission process occurs over a period of four years. Intriguingly, it also shows that these founding females are closely related to one another, resulting in a higher average relatedness in the new than in the old colony.

As with many other forest-living bats, big brown bat colonies almost daily switch their day roosts (tree cavities) and split into subgroups that later fuse again [6,7]. Such fission–fusion behaviour is widespread among bats and probably allows females to adjust daily group sizes to changing environmental conditions, such as ambient temperature and parasite loads, while maintaining the social relationships among them [4]. Several studies have applied association indices and network analysis to quantify individual associations in bat species with fission–fusion behaviour [7–12]: all of them found non-random roosting associations despite regularly changing subgroup compositions. In Bechstein's bats (*Myotis bechsteinii*) and big brown bats, the only two bat species with fission–fusion behaviour for which genetic data are available, related females do not roost preferentially together [7,8]. This fits well with the observation that kinship in bats is often only of secondary importance for cooperative behaviours, such as information transfer about roosts, which allows colony members to coordinate their roost switching [4,13].

If kinship does not affect daily roosting associations, why then does it matter when females disperse together to start a new colony? The study by Metheny *et al.* [6] does not answer this question, but at least two explanations seem plausible. The first involves cooperation among related colony members, as suggested by Metheny