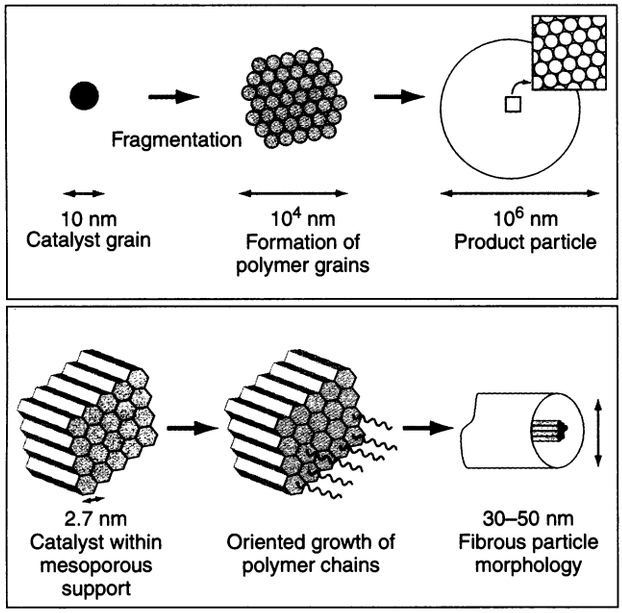


**Directed growth.** The particle growth process in traditional Ziegler-Natta polymerization (**top**) is compared with the concept of oriented nanoreactors of Kageyama *et al.* (*1*) (**bottom**).

best achieved with catalysts that generate a statistical comonomer distribution. For instance, metallocene dichlorides are organometallic complexes with a uniform chemical structure of each active site (*6*, *7*) which ensures high precision of the polymerization reaction, resulting in a narrow molecular weight distribution, an even comonomer distribution, and high stereoregularity of the polyolefin products. Metallocene-based polymer catalysts are now conquering the polyolefin market. Intensive research on homogeneous metallocene catalysts has led to a genuine understanding of the elementary steps of the coordination polymerization mechanism and precise correlations between catalyst symmetry and the resulting polymer microstructure (*6–9*).

The discovery of mesoporous MCM-41 silicas in 1992 (*10*) has opened a route to a completely new generation of polymerization catalysts, which combine the advantages of tunable, molecular, defined metallocene catalysts and extended nanoreactors. In these systems, metal complexes have to be attached to the inner walls of the high–surface area solids. Kageyama *et al.* demonstrate a case in which this challenge has been met with success. Standard, spherical silica gels are already used as support materials for the youngest generation of Ziegler-Natta catalysts, and it may be expected that the new, linear silica nanoreactors will find their way into industrial application. The economic balance between polymer properties and catalyst productivity will be decisive. The ongoing development of coordination catalysts also comprises late transition metal complexes, which will extend the set of conventional and easily available monomers to polar building blocks.

We can envision a highly sophisticated construction kit, in which the proper choice of monomers, catalysts, and nanoreactors will lead to a portfolio of new organic materials with precisely controlled properties. The design of novel polymer architectures from conventional monomers has only just begun.

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PERSPECTIVES: CELL BIOLOGY

# All Creatures Great and Small

**Sally J. Leevers**

Understanding how animals grow (increase in mass) at a certain rate and achieve a specific final size is a challenge that has long fascinated biologists (*1*). The rate of growth and the final size of an organism result from changes in the size and number of cells during development. Early clues to the process of growth regulation were provided by the identification of mutations in yeast that blocked cell division but not cell growth. This simple observation implied that growth can continue in the absence of cell division, and therefore that growth is not simply a matter of increasing cell number. Surprisingly, although these experiments provoked much research into the regulation of cell division, less attention has been paid to the regulation of cell growth (increase in cell size) and of overall growth (increase in mass) in multicellular organisms. However, recent work in the fruit fly *Drosophila* has confirmed that, here too, growth can occur without cell division and that inducing cell division does not necessarily promote growth (*2, 3*). How then is growth regulated?

On page 2126 of this issue, Montagne and colleagues identify a signaling molecule, *Drosophila* S6 kinase (DS6K), which, when mutated, slows growth and reduces cell size and body size (*4*). In mammals, S6 kinases (also called p70 S6 kinases) are targets of insulin signaling that regulate the synthesis of proteins encoded by 5′TOP (terminal oligopyrimidine tract) mRNAs (which are primarily components of the translation machinery). Recently, other molecules on the insulin signaling pathway (*5–8*) and other molecules involved in protein synthesis (*9*) have also been shown to regulate growth rate and/or cell size and body size in *Drosophila*. Taken together, these genetic studies in the fruit fly identify a signaling pathway and a biosynthetic process that contribute directly to the regulation of growth during development.

Montagne and colleagues set out to examine the function of DS6K by identifying *Drosophila* strains with null mutations in the *ds6k* gene. They found that flies without DS6K were developmentally delayed (that is, they grew at a reduced rate) and that their final size was approximately half that of wild-type flies (*4*). Inspection of the wings of these small creatures revealed that they were made up of cells that were reduced in size but similar in number to those of wild-type flies. To find out what was happening earlier in development, the authors examined the larval imaginal discs, sacks of epithelial cells that reorganize during metamorphosis into adult epidermal organs such as the wing. They found that

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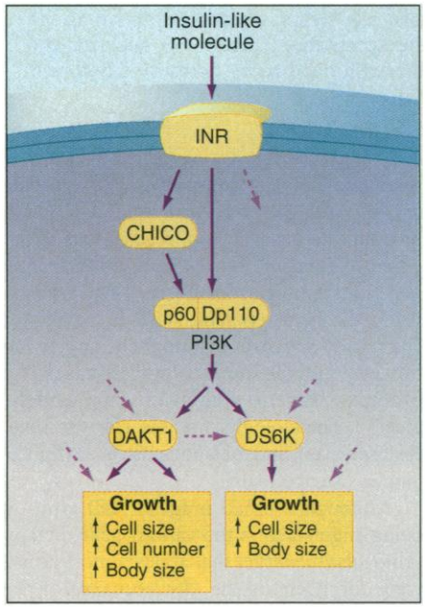
wing imaginal disc cells without DS6K were also small and that they increased in number at a slower rate. Whether the *ds6k* mutant cells increase in number more slowly because they divide less frequently or die more frequently has yet to be determined. So, in the absence of DS6K, development is delayed, cells grow and increase in number more slowly, and ultimately a small but perfectly formed fly containing the normal number of cells is produced.

One way in which mammalian S6 kinases are activated is by the secreted molecule insulin, which regulates glucose metabolism. Insulin signals are transduced via a pathway that includes the insulin receptor (INR), insulin receptor substrate (IRS) molecules, and the lipid kinase, phosphatidylinositol 3-kinase (PI3K) (see the figure). Recent work from several laboratories implies that this pathway is conserved in flies. Flies with mild mutations in the *Drosophila inr* gene and flies that lack the gene encoding the *Drosophila* IRS, appropriately called CHICO (which means small boy in Spanish), are developmentally delayed, contain small cells, and are reduced in size (*5, 6*). Furthermore, mutation or overexpression of *Drosophila* PI3K (*7, 8*) or of DAKT1—the *Drosophila* homolog of the PI3K target Akt/PKB (*10*)—can alter rate of growth, cell size, and body or organ size (*7, 8, 10*). Thus, it seems likely that the insulin signaling pathway regulates growth in *Drosophila*, although further genetic and biochemical analyses are needed to firmly establish the proposed links.

An important difference between DS6K and the other molecules in the insulin signaling pathway is that loss of DS6K in the adult fly ultimately seems only to reduce cell size. Loss of CHICO reduces cell number as well as cell size, whereas loss of INR, PI3K, or DAKT1 is lethal before an adult fly can be produced. It is possible that when *ds6k* is mutated, growth is not severely impaired, and the number of cell divisions necessary to maintain cell number can still occur. In contrast, the amount of growth may not be sufficient to maintain cell number when CHICO is removed, or to produce an adult fly when the other genes are removed. However, mutation of *chico* has a less severe effect than mutation of *ds6k* on other aspects of growth. For example, the development of *chico* mutants is only delayed by 2 to 3 days, compared to 5 days for *ds6k* mutants (*4, 5*). But experiments on growth from different laboratories should be compared cautiously, as differences in nutrition, culture density, and temperature also affect *Drosophila* growth and cell and body size.

Another explanation for the inability of DS6K to influence cell number is provided by knowledge of the links between the molecules in the insulin signaling pathway and the cellular processes that they modulate. S6 kinases lie downstream of the majority of molecules in this pathway and have one specific function: They increase translation of a subset of mRNAs, many of which are involved in protein synthesis (*11*). In contrast, INR, CHICO, PI3K, and DAKT1 have the potential to influence the activity of other molecules as well as DS6K and to regulate additional processes that might influence growth. Perhaps the best example of this is Akt, which can affect mammalian cell survival, division, and metabolism (*12*). It is also noteworthy that biochemical and tissue culture studies with mammalian cells suggest that there is cross-talk among the pathway's signaling components and between those molecules and other signaling molecules. Thus, a signaling network with DS6K on one of its branches is likely to control growth. One interesting question is whether the reduced rate of increase in cell number observed when each of the molecules in the pathway is eliminated arises because of slowed cell division or increased cell death. This issue is difficult to resolve experimentally, as the differences in cell number are small in percentage terms and accumulate over many hours.




**Signaling for growth.** The likely interactions (solid arrows) between molecules that regulate *Drosophila* growth, based on studies of interactions between their mammalian homologs. Broken arrows indicate where branching is possible and where links with other molecules may occur. INR, the *Drosophila* insulin receptor homolog; CHICO, the *Drosophila* homolog of mammalian IRS1-4; Dp110, the *Drosophila* class $I^A$ PI3K; p60, its adaptor protein; and DAKT1, the *Drosophila* homolog of Akt/PKB.

The involvement of protein synthesis in growth control is not that surprising, particularly in *Drosophila* where a class of genes termed *Minutes* have long been known to delay development and to slow cell growth and cell division when mutated. Several *Minute* genes have been cloned and shown to encode components of the ribosomal machinery necessary for global protein synthesis. Furthermore, in a recent genetic screen designed to isolate *Drosophila* genes required for larval growth, Galloni and Edgar identified several genes involved in protein synthesis, including the translation initiation factor Eif4A (*9*). Interestingly, mutation of the growth-defective genes identified by Galloni and Edgar and of many of the *Minute* genes does not alter cell size. Instead, growth and division seem to be slowed in a coordinated manner, allowing normal cell size to be maintained. This suggests that cell growth and cell division are normally coupled, maintaining constant cell size, and that disruption of global protein synthesis does not alter that coupling. In contrast, disruption of signaling via the molecules of the insulin signaling pathway, and of the synthesis of the DS6K target mRNAs, seems to destroy that coupling and hence to alter cell size. The precise mechanism through which cell growth and cell division are coupled has yet to be established, although changes in the pattern of protein synthesis may be involved.

Another important aspect of this work is that, as well as affecting growth at the cellular level, signaling via the molecules of the insulin pathway can also modulate organ and body size. The challenge now is to understand how this signaling network is controlled in response to environmental and developmental cues. We need to understand what switches it on, and (perhaps more important) what switches it off, as this may be the way in which final body size is determined.

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