

## **Genetic control of size in Drosophila**

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# THE ROYAL<br>
SOCIETY<br> **Genetic control of size in** *Drosophila*

# **Sean Oldham, Ruth BÎhni, Hugo Stocker, Walter Brogiolo and Ernst Hafen**\* *Zoological Institute, University of Zurich,Winterthurerstrasse 190, CH- 8057 Zurich, Switzerland*

Zoological Institute, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland<br>During the past ten years, significant progress has been made in understanding the basic mechanisms of<br>the development of mul During the past ten years, significant progress has been made in understanding the basic mechanisms of<br>the development of multicellular organisms. Genetic analysis of the development of *Caenorhabditis elegans*<br>and *Drasob* During the past ten years, significant progress has been made in understanding the basic mechanisms of<br>the development of multicellular organisms. Genetic analysis of the development of *Caenorhabditis elegans*<br>and *Drosop* the development of multicellular organisms. Genetic analysis of the development of *Caenorhabditis elegans* and *Drosophila* has unearthed a fruitful number of genes involved in establishing the basic body plan, patterning patterning of limbs, specification of cell fate and regulation of programmed cell death. The genes involved<br>in these developmental processes have been conserved throughout evolution and homologous genes are patterning of limbs, specification of cell fate and regulation of programmed cell death. The genes involved<br>in these developmental processes have been conserved throughout evolution and homologous genes are<br>involved in the in these developmental processes have been conserved throughout evolution and homologous genes are<br>involved in the patterning of insect and human limbs. Despite these important discoveries, we have<br>learned astonishingly l involved in the patterning of insect and human limbs. Despite these important discoveries, we have<br>learned astonishingly little about one of the most obvious distinctions between animals: their difference in<br>body size. The learned astonishingly little about one of the most obvious distinctions between animals: their difference in body size. The mass of the smallest mammal, the bumble-bee bat, is  $2g$  while that of the largest mammal, the bl body size. The mass of the smallest mammal, the bumble-bee bat, is 2g while that of the largest<br>mammal, the blue whale, is 150 t or 150 million grams. Remarkably, even though they are in the same<br>class, body size can vary mammal, the blue whale, is 150 t or 150 million grams. Remarkably, even though they are in the same<br>class, body size can vary up to 75-million-fold. Furthermore, this body growth can be finite in the case of<br>most vertebrat class, body size can vary up to 75-million-fold. Furthermore, this body growth can be finite in the case of most vertebrates or it can occur continuously throughout life, as for trees, molluscs and large crustaceans. Curre most vertebrates or it can occur continuously throughout life, as for trees, molluscs and large crustaceans.<br>Currently, we know comparatively little about the genetic control of body size. In this article we will<br>review re review recent evidence from vertebrates and particularly from *Drosophila* that implicates insulin/insulin-<br>like growth factor-I and other growth pathways in the control of cell, organ and body size.

**Keywords:** insulin/IGF-I; Chico/IRS; PTEN; growth; nutritional sensor; *Drosophila*

### **1. FACTORS CONTROLLING BODY AND ORGAN SIZE**

**1. FACTORS CONTROLLING BODY AND ORGAN SIZE**<br>Body size is determined genetically. Within species, the<br>genetic constitution of the individual which controls the I. FACTORS CONTROLLING BODT AND ORGAN SIZE<br>Body size is determined genetically. Within species, the<br>genetic constitution of the individual, which controls the<br>processes of growth proliferation and apoptosis dramati-Body size is determined genetically. Within species, the genetic constitution of the individual, which controls the processes of growth, proliferation and apoptosis, dramati-<br>cally controls body size (Conlon  $\&$  Raff 199 genetic constitution of the individual, which controls the<br>processes of growth, proliferation and apoptosis, dramati-<br>cally controls body size (Conlon & Raff 1999). For<br>instance mice that lack growth hormone (GH) insulinprocesses of growth, proliferation and apoptosis, dramatically controls body size (Conlon & Raff 1999). For instance, mice that lack growth hormone (GH), insulin-<br>like growth factor-I (IGF-I) the IGF-I receptor (IGFR) cally controls body size (Conlon & Raff 1999). For<br>instance, mice that lack growth hormone (GH), insulin-<br>like growth factor-I (IGF-I), the IGF-I receptor (IGFR),<br>or insulin receptor substrate (IRS-1) are dramatically instance, mice that lack growth hormone (GH), insulin-<br>like growth factor-I (IGF-I), the IGF-I receptor (IGFR),<br>or insulin receptor substrate (IRS-1) are dramatically<br>reduced in size (Rimoin *et al.* 1966; Araki *et al.* like growth factor-I (IGF-I), the IGF-I receptor (IGFR),<br>or insulin receptor substrate (IRS-1) are dramatically<br>reduced in size (Rimoin *et al.* 1966; Araki *et al.* 1994;<br>Tamemoto *et al.* 1994; Efstratiadis 1998) Some mu or insulin receptor substrate (IRS-1) are dramatically reduced in size (Rimoin *et al.* 1966; Araki *et al.* 1994; Tamemoto *et al.* 1994; Efstratiadis 1998). Some mutations in the gene coding for the insulin receptor caus reduced in size (Rimoin *et al.* 1966; Araki *et al.* 1994; Tamemoto *et al.* 1994; Efstratiadis 1998). Some mutations in the gene coding for the insulin receptor cause a form of Tamemoto *et al.* 1994; Efstratiadis 1998). Some mutations 19<br>in the gene coding for the insulin receptor cause a form of growth retardation in humans known as leprechaunism ju<br>(Taylor 1992). In addition to genetic determ in the gene coding for the insulin receptor cause a form of<br>growth retardation in humans known as leprechaunism<br>(Taylor 1992). In addition to genetic determinants, envir-<br>onmental factors play a critical role in the contro growth retardation in humans known as leprechaunism<br>(Taylor 1992). In addition to genetic determinants, environmental factors play a critical role in the control of body<br>size. Nutrition is paramount in controlling organ an (Taylor 1992). In addition to genetic determinants, envirantly export (Bryant et al. 1993; Bryant 1997). Mutations in onmental factors play a critical role in the control of body discs-large, expanded and lats (also known onmental factors play a critical role in the control of body<br>size. Nutrition is paramount in controlling organ and<br>body size in all species. Limited caloric intake reduces<br>growth in species as diverse as yeast and man size. Nutrition is paramount in controlling o<br>body size in all species. Limited caloric intak<br>growth in species as diverse as yeast and man.<br>Organ growth is regulated at many leve growth in species as diverse as yeast and man.<br>Organ growth is regulated at many levels during

growth in species as diverse as yeast and man.<br>Organ growth is regulated at many levels during<br>development. First, the growth of organs is tightly<br>counled with the final body size (Stern & Emlen (1999) Organ growth is regulated at many levels during<br>development. First, the growth of organs is tightly<br>coupled with the final body size (Stern & Emlen (1999),<br>and references therein), and organ size is also influenced development. First, the growth of organs is tightly<br>coupled with the final body size (Stern & Emlen (1999),<br>and references therein), and organ size is also influenced<br>by the presence or absence of other tissues. For exampl coupled with the final body size (Stern & Emlen (1999), and references therein), and organ size is also influenced by the presence or absence of other tissues. For example, and references therein), and organ size is also influenced<br>by the presence or absence of other tissues. For example,<br>in butterflies, the size of the forewings is influenced by the<br>presence of other competing tissues such a by the presence or absence of other tissues. For example,<br>in butterflies, the size of the forewings is influenced by the<br>presence of other competing tissues such as the posterior<br>wing imaginal discs. If these discs are rem in butterflies, the size of the forewings is influenced by the<br>presence of other competing tissues such as the posterior<br>wing imaginal discs. If these discs are removed surgically<br>during development the forewing becomes la presence of other competing tissues such as the posterior wing imaginal discs. If these discs are removed surgically during development, the forewing becomes larger<br>(Nijhout & Emlen 1998). In mammals, organ size is<br>differentially regulated in different organs. When foetal during development, the forewing becomes larger<br>(Nijhout & Emlen 1998). In mammals, organ size is<br>differentially regulated in different organs. When foetal<br>spleens are transplanted into a mouse embryo each will (Nijhout & Emlen 1998). In mammals, organ size is<br>differentially regulated in different organs. When foetal<br>spleens are transplanted into a mouse embryo each will<br>grow such that the sum of the spleen equals a spleen of differentially regulated in different organs. When foetal<br>spleens are transplanted into a mouse embryo each will<br>grow such that the sum of the spleen equals a spleen of<br>normal size (Metcalf 1964). In contrast, when the sam spleens are transplanted into a mouse embryo each will<br>grow such that the sum of the spleen equals a spleen of<br>normal size (Metcalf 1964). In contrast, when the same normal size (Metcalf 1964). In contrast, when the same<br>\*Author for correspondence (hafen@zool.unizh.ch).

experiment is carried out with thymus, each thymus grows to the size of one thymus (Metcalf 1963). Second, experiment is carried out with thymus, each thymus<br>grows to the size of one thymus (Metcalf 1963). Second,<br>growth is tightly coupled to pattern formation. Patterning<br>processes must be coordinated with growth to orchestrate grows to the size of one thymus (Metcalf 1963). Second,<br>growth is tightly coupled to pattern formation. Patterning<br>processes must be coordinated with growth to orchestrate<br>the final size and shape of the organ (Bryant & Si growth is tightly coupled to pattern formation. Patterning<br>processes must be coordinated with growth to orchestrate<br>the final size and shape of the organ (Bryant & Simpson<br>1984) Induction of ectonic pattern elements like t processes must be coordinated with growth to orchestrate<br>the final size and shape of the organ (Bryant & Simpson<br>1984). Induction of ectopic pattern elements like the the final size and shape of the organ (Bryant & Simpson<br>1984). Induction of ectopic pattern elements like the<br>duplications of chick limbs and *Drosophila* wings by<br>ectonic expression of proteins of the Wingless or 1984). Induction of ectopic pattern elements like the duplications of chick limbs and *Drosophila* wings by ectopic expression of proteins of the Wingless or Hedgebog family is associated with additional growth duplications of chick limbs and *Drosophila* wings by<br>ectopic expression of proteins of the Wingless or<br>Hedgehog family is associated with additional growth<br>(Riddle *et al.* 1993: Basler & Strubl 1994: Zecca *et al.* ectopic expression of proteins of the Wingless or Hedgehog family is associated with additional growth (Riddle *et al.* 1993; Basler & Struhl 1994; Zecca *et al.* 1995) Third alterations in cell-cell contacts can alter Hedgehog family is associated with additional growth (Riddle *et al.* 1993; Basler & Struhl 1994; Zecca *et al.* 1995). Third, alterations in cell-cell contacts can alter growth. Proteins associated with sentate or adheren (Riddle *et al.* 1993; Basler & Struhl 1994; Zecca *et al.* 1995). Third, alterations in cell-cell contacts can alter growth. Proteins associated with septate or adherens 1995). Third, alterations in cell–cell contacts can alter<br>growth. Proteins associated with septate or adherens<br>junctions also determine organ size by suppressing<br>growth (Bryant et al. 1993; Bryant 1997). Mutations in growth. Proteins associated with septate or adherens<br>junctions also determine organ size by suppressing<br>growth (Bryant *et al.* 1993; Bryant 1997). Mutations in<br>*discs-large exhanded* and *lats* (also known as *warts*) res junctions also determine organ size by suppressing<br>growth (Bryant *et al.* 1993; Bryant 1997). Mutations in<br>*discs-large*, *expanded* and *lats* (also known as *warts*) result in<br>tumorous outgrowths of imaginal discs (Wood growth (Bryant et al. 1993; Bryant 1997). Mutations in discs-large, expanded and lats (also known as warts) result in<br>tumorous outgrowths of imaginal discs (Woods & Bryant<br>1991; Boedigheimer & Laughon 1993; Xu *et al.* 1995).<br>Fourth, apoptosis may also play a role in organ gro tumorous outgrowths of imaginal discs (Woods & Bryant 1991; Boedigheimer & Laughon 1993; Xu *et al.* 1995).<br>Fourth, apoptosis may also play a role in organ growth; blocking apoptosis in the compound eye of *Drashbila* 1991; Boedigheimer & Laughon 1993; Xu *et al.* 1995).<br>Fourth, apoptosis may also play a role in organ growth;<br>blocking apoptosis in the compound eye of *Drosophila*<br>results in the generation of additional cells (Hay *et a* Fourth, apoptosis may also play a role in organ growth;<br>blocking apoptosis in the compound eye of *Drosophila*<br>results in the generation of additional cells (Hay *et al.*<br>1994) In the development of the nervous system blocking apoptosis in the compound eye of *Drosophila*<br>results in the generation of additional cells (Hay *et al.*<br>1994). In the development of the nervous system,<br>programmed cell death is an essential factor in deterresults in the generation of additional cells (Hay *et al.* 1994). In the development of the nervous system, programmed cell death is an essential factor in deter-<br>minimum the final number of neurons and support cells 1994). In the development of the nervous system, programmed cell death is an essential factor in determining the final number of neurons and support cells programmed cell death is an essential factor in determining the final number of neurons and support cells (Raff 1996). These few examples illustrate the multitude of extrinsic and intrinsic levels that operate in organ of extrinsic and intrinsic levels that operate in organ (Raff 1996). The:<br>of extrinsic and<br>growth control.

### **2. GROWTH AT THE CELLULAR LEVEL**

Growth is associated with an increase in biomass **EXECUTE AT THE CELLULAR LEVEL**<br>Growth is associated with an increase in biomass<br>through the stimulation of the biosynthesis of cellular<br>components. Growth can occur in the absence of cell Growth is associated with an increase in biomass<br>through the stimulation of the biosynthesis of cellular<br>components. Growth can occur in the absence of cell<br>division by cell enlargement and by the denosition of through the stimulation of the biosynthesis of cellular<br>components. Growth can occur in the absence of cell<br>division by cell enlargement and by the deposition of<br>extracellular matrix (accretion) but the most common components. Growth can occur in the absence of cell<br>division by cell enlargement and by the deposition of<br>extracellular matrix (accretion), but the most common

division (Roush 1996; Neufeld & Edgar 1998; Polymenis type of growth during development is coupled to cell<br>division (Roush 1996; Neufeld & Edgar 1998; Polymenis<br>& Schmidt 1999). When a cell divides, it will normally<br>generate two daughter cells of half the size. These division (Roush 1996; Neufeld & Edgar 1998; Polymenis<br>& Schmidt 1999). When a cell divides, it will normally<br>generate two daughter cells of half the size. These<br>daughter cells then grow until they have reached the & Schmidt 1999). When a cell divides, it will normally generate two daughter cells of half the size. These daughter cells then grow until they have reached the same size as the mother cell before they enter the next generate two daughter cells of half the size. These<br>daughter cells then grow until they have reached the<br>same size as the mother cell before they enter the next<br>round of cell division Therefore growth—increase in daughter cells then grow until they have reached the<br>same size as the mother cell before they enter the next<br>round of cell division. Therefore, growth—increase in<br>hiomass—is tightly counled to cell-cycle progression same size as the mother cell before they enter the next<br>round of cell-division. Therefore, growth—increase in<br>biomass—is tightly coupled to cell-cycle progression.<br>Given the importance of hyperplastic growth for tumour round of cell division. Therefore, growth—increase in<br>biomass—is tightly coupled to cell-cycle progression.<br>Given the importance of hyperplastic growth for tumour<br>development studies of growth control over the past biomass—is tightly coupled to cell-cycle progression.<br>Given the importance of hyperplastic growth for tumour<br>development, studies of growth control over the past<br>vears have primarily focused on the control of cell prolif-Given the importance of hyperplastic growth for tumour<br>development, studies of growth control over the past<br>years have primarily focused on the control of cell prolif-<br>eration. It has been assumed that cell-cycle progressi years have primarily focused on the control of cell proliferation. It has been assumed that cell-cycle progression is an important regulator of growth. However, elegant eration. It has been assumed that cell-cycle progression is<br>an important regulator of growth. However, elegant<br>experiments in *Drosophila* (Weigmann *et al.* 1997; Neufeld<br>et al. 1998) have reminded us recently that the ra an important regulator of growth. However, elegant experiments in *Drosophila* (Weigmann *et al.* 1997; Neufeld *et al.* 1998) have reminded us recently that the rate of property that the rate of property and not the  $\frac{d\mathbf{r}}{d\mathbf{r}}$  *et al.* 1998) have reminded us recently that the rate of growth regulates the rate of proliferation and not the *et al.* 1998) have reminded us recently that the rate of growth regulates the rate of proliferation and not the contrary. Neufeld *et al.* induced genetically marked clones of cells expressing genes whose products promote growth regulates the rate of proliferation and not the<br>contrary. Neufeld *et al.* induced genetically marked clones<br>of cells expressing genes whose products promote (E2F<br>and Dn) or slow down (Rb) cell-cycle progression. Th contrary. Neufeld *et al.* induced genetically marked clones<br>of cells expressing genes whose products promote (E2F<br>and Dp) or slow down (Rb) cell-cycle progression. The<br>overall growth was determined by measuring the area of cells expressing genes whose products promote (E2F<br>and Dp) or slow down (Rb) cell-cycle progression. The<br>overall growth was determined by measuring the area<br>occupied by the cell clone in the imaginal disc after a and Dp) or slow down (Rb) cell-cycle progression. The<br>overall growth was determined by measuring the area<br>occupied by the cell clone in the imaginal disc after a<br>fixed time. Acceleration of the cell cycle by overoverall growth was determined by measuring the area<br>occupied by the cell clone in the imaginal disc after a<br>fixed time. Acceleration of the cell cycle by overexpression of E2F and Dp promoted cell proliferation but fixed time. Acceleration of the cell cycle by over-<br>expression of E2F and Dp promoted cell proliferation but<br>not growth. The clone occupied the same area with more<br>but smaller cells. Conversely slowing down the cell cycle expression of E2F and Dp promoted cell proliferation but<br>not growth. The clone occupied the same area with more<br>but smaller cells. Conversely, slowing down the cell cycle<br>by expression of Rb produced fewer but larger cells not growth. The clone occupied the same area with more<br>but smaller cells. Conversely, slowing down the cell cycle<br>by expression of Rb produced fewer but larger cells<br>without affecting overall growth. These results are cons but smaller cells. Conversely, slowing down the cell cycle<br>by expression of Rb produced fewer but larger cells<br>without affecting overall growth. These results are consis-<br>tent with classical experiments in yeast that demon by expression of Rb produced fewer but larger cells overall body and organ size. One member of this class is<br>without affecting overall growth. These results are consis-<br> $diminutive$  (dm). The dm gene encodes the homologue of the without affecting overall growth. These results are consistent with classical experiments in yeast that demonstrated<br>that growth rates determine the rate of proliferation and<br>not vice versa (Nurse 1975; Johnston *et al*, tent with classical experiments in yeast that demothat growth rates determine the rate of proliferant vice versa (Nurse 1975; Johnston *et al.* 1977).

# **CONTROL**

One area concerns the regulation of cellular size. **CONTROL**<br>
One area concerns the regulation of cellular size.<br>
During normal growth, the size of the cells remains<br>
constant Therefore a cell must be able to determine One area concerns the regulation of cellular size.<br>During normal growth, the size of the cells remains<br>constant. Therefore, a cell must be able to determine<br>when it has reached a certain size to initiate the next During normal growth, the size of the cells remains<br>constant. Therefore, a cell must be able to determine<br>when it has reached a certain size to initiate the next<br>round of cell division. How do cells measure their size constant. Therefore, a cell must be able to determine<br>when it has reached a certain size to initiate the next<br>round of cell division. How do cells measure their size<br>and what determines the critical size for cell-cycle when it has reached a certain size to initiate the next<br>round of cell division. How do cells measure their size<br>and what determines the critical size for cell-cycle<br>progression? How is cell size regulated in response to round of cell division. How do cells measure their size<br>and what determines the critical size for cell-cycle<br>progression? How is cell size regulated in response to<br>extracellular cues? In yeast, the critical size when a cel and what determines the critical size for cell-cycle<br>progression? How is cell size regulated in response to<br>extracellular cues? In yeast, the critical size when a cell<br>undergoes cell division is dependent on the availabili progression? How is cell size regulated in response to<br>extracellular cues? In yeast, the critical size when a cell<br>undergoes cell division is dependent on the availability of<br>nutrients. When yeast cells are placed on poor extracellular cues? In yeast, the critical size when a cell<br>undergoes cell division is dependent on the availability of<br>nutrients. When yeast cells are placed on poor media,<br>they divide at a smaller critical size (Johnsto undergoes cell division is dependent on the availability of nutrients. When yeast cells are placed on poor media, nutrients. When yeast cells are placed on poor media, they divide at a smaller critical size (Johnston *et al.* 1977). Starved *Drosophila* larvae also develop into small flies that contain fewer and smaller cells than fli they divide at a smaller critical size (Johnston *et al.* 1977).<br>Starved *Drosophila* larvae also develop into small flies that<br>contain fewer and smaller cells than flies reared under<br>non-starving conditions (Robertson 195 Starved *Drosophila* larvae also develop into small flies that<br>contain fewer and smaller cells than flies reared under<br>non-starving conditions (Robertson 1959, 1963; Simpson 1979). At the level of the organ growth, how is the final non-starving conditions (Robertson 1959, 1963; Simpson<br>1979). At the level of the organ growth, how is the final<br>size of an organ determined? What are the factors and<br>signalling pathways that coordinate cell intrinsic and 1979). At the level of the organ growth, how is the final<br>size of an organ determined? What are the factors and<br>signalling pathways that coordinate cell intrinsic and<br>extrinsic growth of organs? There is a genetic programm size of an organ determined? What are the factors and<br>signalling pathways that coordinate cell intrinsic and<br>extrinsic growth of organs? There is a genetic programme<br>that determines that a wing of a fly is larger than a signalling pathways that coordinate cell intrinsic and<br>extrinsic growth of organs? There is a genetic programme<br>that determines that a wing of a fly is larger than a extrinsic growth of organs? There is a genetic programme<br>that determines that a wing of a fly is larger than a<br>haltere. Organ size determination appears not to be<br>hased on a cell-counting mechanism since organs of that determines that a wing of a fly is larger than a<br>haltere. Organ size determination appears not to be<br>based on a cell-counting mechanism since organs of<br>normal size can be formed by an increased number of haltere. Organ size determination appears not to be<br>based on a cell-counting mechanism since organs of<br>normal size can be formed by an increased number of<br>genetically altered smaller haploid cells (Santamaria based on a cell-counting mechanism since organs of<br>normal size can be formed by an increased number of<br>genetically altered smaller haploid cells (Santamaria<br>1983) The last area concerns the control of body size normal size can be formed by an increased number of genetically altered smaller haploid cells (Santamaria 1983). The last area concerns the control of body size. What are the evolutionary selective pressures that form genetically altered smaller haploid cells (Santamaria the synthesis of phosphatidylinositol-3,4,5 trisphosphate 1983). The last area concerns the control of body size. (PIP<sub>3</sub>) (Whitman *et al.* 1988). The IRSs probably b 1983). The last area concerns the control of body size. What are the evolutionary selective pressures that form<br>body size? What are the cues that initiate and terminate<br>growth in mammals to specify final body size? Clearly<br>nutrition is a prerequisite, but other factors must dic body size? What are the cues that initiate and terminate<br>growth in mammals to specify final body size? Clearly<br>nutrition is a prerequisite, but other factors must dictate<br>the production of GH for example Genetic dissection nutrition is a prerequisite, but other factors must dictate the production of GH, for example. Genetic dissection of

growth control in genetically amenable organisms such as<br>Drosophila may provide answers to some of these questions *Drosophila* may provide answers to some of these questions.

### **4. MUTATIONS AFFECTING GROWTH IN** *DROSOPHILA*

**3. SOME OF THE BURNING QUESTIONS ON GROWTH**<br> **3. SOME OF THE BURNING QUESTIONS ON G** IN *DROSOPHILA*<br>In *Drosophila*, a number of mutations have been identi-<br>d that affect growth at different levels. They can be In *DrosoFTHER*<br>fied that affect growth at different levels. They can be<br>divided into three different classes. The first class contains In *Drosophila*, a number of mutations have been identi-<br>fied that affect growth at different levels. They can be<br>divided into three different classes. The first class contains<br>mutants that slow down overall growth but do fied that affect growth at different levels. They can be divided into three different classes. The first class contains mutants that slow down overall growth but do not alter divided into three different classes. The first class contains<br>mutants that slow down overall growth but do not alter<br>the final body size. The dominant *Minute* (*M*) mutations<br>belong in this class. They cause a developmen mutants that slow down overall growth but do not alter<br>the final body size. The dominant *Minute*  $(M)$  mutations<br>belong in this class. They cause a developmental delay<br>and result in short slender bristles (Lindslev & Zimm the final body size. The dominant *Minute*  $(M)$  mutations<br>belong in this class. They cause a developmental delay<br>and result in short, slender bristles (Lindsley & Zimm<br>1992) Many *M* genes have been shown to encode ribobelong in this class. They cause a developmental delay<br>and result in short, slender bristles (Lindsley & Zimm<br>1992). Many *M* genes have been shown to encode ribo-<br>somal proteins (Saeboe-Larssen *et al.* 1998). This sugges and result in short, slender bristles (Lindsley & Zimm 1992). Many *M* genes have been shown to encode ribosomal proteins (Saeboe-Larssen *et al.* 1998). This suggests that *M* mutations slow down growth by reducing the 1992). Many  $M$  genes have been shown to encode ribosomal proteins (Saeboe-Larssen *et al.* 1998). This suggests that  $M$  mutations slow down growth by reducing the efficiency of the translational machinery (Morata & that  $M$  mutations slow down growth by reducing the efficiency of the translational machinery (Morata & Ripoll 1975). It is interesting to note that impairing trans-<br>lation by  $M$  mutations affects neither cell size nor b efficiency of the translational machinery (Morata & Ripoll 1975). It is interesting to note that impairing translation by *M* mutations affects neither cell size nor body size. The second class contains mutations that affe Ripoll 1975). It is interesting to note that impairing translation by  $M$  mutations affects neither cell size nor body size. The second class contains mutations that affect the growth of individual organs. All the mutatio lation by  $M$  mutations affects neither cell size nor body<br>size. The second class contains mutations that affect the<br>growth of individual organs. All the mutations known in<br>this class affect organ size indirectly either b size. The second class contains mutations that affect the growth of individual organs. All the mutations known in this class affect organ size indirectly either by altering the organ identity like homeotic mutations, or by growth of individual organs. All the mutations known in this class affect organ size indirectly either by altering the organ identity like homeotic mutations, or by preventing this class affect organ size indirectly either by altering the<br>organ identity like homeotic mutations, or by preventing<br>differentiation and survival of specific cell types within an<br>organ. The third class contains mutation organ identity like homeotic mutations, or by preventing<br>differentiation and survival of specific cell types within an<br>organ. The third class contains mutations that reduce<br>overall body and organ size. One member of this c differentiation and survival of specific cell types within an<br>organ. The third class contains mutations that reduce<br>overall body and organ size. One member of this class is<br> $diminutive (dm)$  The dm gene encodes the homologue of th organ. The third class contains mutations that reduce c-*myc* proto-oncogene and has recently been shown to diminutive (dm). The dm gene encodes the homologue of the c-myc proto-oncogene and has recently been shown to control growth rates and cell size (Gallant *et al.* 1996; Iohnston *et al.* 1999) Another interesting member is c-*myc* proto-oncogene and has recently been shown to control growth rates and cell size (Gallant *et al.* 1996; Johnston *et al.* 1999). Another interesting member is the neurofibromatosis type tumour suppressor protein ( control growth rates and cell size (Gallant *et al.* 1996; Johnston *et al.* 1999). Another interesting member is the neurofibromatosis type tumour suppressor protein (NF1). Mutations in *NFI* result in flies that are red Johnston *et al.* 1999). Another interesting member is the neurofibromatosis type tumour suppressor protein (NF1). Mutations in  $NFI$  result in flies that are reduced in size at all developmental stages (The *et al.* 1997) neurofibromatosis type tumour suppressor protein (NF1).<br>Mutations in *NF1* result in flies that are reduced in size at<br>all developmental stages (The *et al.* 1997). Lastly, the<br>diffusible gas nitric oxide has been implicat Mutations in  $NFI$  result in flies that are reduced in size at all developmental stages (The  $et$   $al$ . 1997). Lastly, the diffusible gas nitric oxide has been implicated in the negaall developmental stages (The *et al.* 1997). Lastly, the diffusible gas nitric oxide has been implicated in the negative control of proliferation (Kuzin *et al.* 1996). It is this third class of mutations that is most rel diffusible gas nitric oxide has been implicated in the negative control of proliferation (Kuzin *et al.* 1996). It is this third class of mutations that is most relevant for the understanding of the coordination of growth tive control of proliferation (Kuzin *et al.* 1996). It is this third class of mutations that is most relevant for the understanding of the coordination of growth in *Drosophila*. In the following sections, we will summari understanding of the coordination of growth in *Drosophila*.<br>In the following sections, we will summarize recent work<br>on the role of the various signalling pathways that control<br>growth without altering cell fate specificat In the following sections, we will summarize recent work<br>on the role of the various signalling pathways that control<br>growth without altering cell fate specification or pattern<br>formation in *Dresebbila* on the role of the various signalling pathways that control<br>growth without altering cell fate specification or pattern<br>formation in *Drosophila*.

### **(a)** *The insulin-signalling pathway*

(a) *The insulin-signalling pathway*<br>(i) *Chico, the* Drosophila *IRS1–4 homologue controls cell size*<br>and survall hody size **(a)** *The*<br>
(i) *Chico, the* Drosop<br> *and overall body size*<br> **In** a search for *n* 

and overall body size<br>In a search for mutations that result in a reduction of body size, we identified mutations in the gene coding for the homologue of the vertebrate IRSs 1^4 (Boehni *et al.* 1999). IRS proteins are multi-adaptor proteins containing the homologue of the vertebrate IRSs  $1-4$  (Boehni *et al.* 1999). IRS proteins are multi-adaptor proteins containing<br>an N-terminally located pleckstrin homology (PH)<br>domain and a phosphotyrosine binding (PTR) domain as 1999). IRS proteins are multi-adaptor proteins containing<br>and N-terminally located pleckstring homology (PH)<br>domain and a phosphotyrosine binding (PTB) domain as<br>well as docking sites for  $S$ H2 domain-containing proteins an N-terminally located pleckstrin homology (PH)<br>domain and a phosphotyrosine binding (PTB) domain as<br>well as docking sites for SH2 domain-containing proteins<br>including  $\text{CRB2/DRK}$ , which activate the  $\text{Ras-mitoren}$ . domain and a phosphotyrosine binding (PTB) domain as<br>well as docking sites for SH2 domain-containing proteins<br>including GRB2/DRK, which activate the Ras-mitogen-<br>activated protein kinase (MAPK) pathway, and p85 well as docking sites for SH2 domain-containing proteins adaptor that binds to the p110 phosphoinositide-3-kinase activated protein kinase (MAPK) pathway, and p85<br>adaptor that binds to the pl10 phosphoinositide-3-kinase<br>(PI3K) (White 1998). The activation of PI3K stimulates<br>the synthesis of phosphatidylinositol-3.4.5 trisphosphate adaptor that binds to the pl10 phosphoinositide-3-kinase<br>(PI3K) (White 1998). The activation of PI3K stimulates<br>the synthesis of phosphatidylinositol-3,4,5 trisphosphate<br>(PIP.) (Whitman *et al*, 1988). The IRSs probably b (PI3K) (White 1998). The activation of PI3K stimulates<br>the synthesis of phosphatidylinositol-3,4,5 trisphosphate<br>(PIP<sub>3</sub>) (Whitman *et al.* 1988). The IRSs probably bind the<br>activated insulin and IGER<sub>s</sub> via their PTB doma  $(PIP<sub>3</sub>)$  (Whitman *et al.* 1988). The IRSs probably bind the (PIP<sub>3</sub>) (Whitman *et al.* 1988). The IRSs probably bind the activated insulin and IGFRs via their PTB domains and to PIP<sub>3</sub> in the plasma membrane via their PH domain (White 1998) activated insuling<br>to  $\text{PIP}_3$  in the (White 1998).<br>Flies homozy PIP<sub>3</sub> in the plasma membrane via their PH domain<br>Vhite 1998).<br>Flies homozygous for *chico* are approximately half the<br>e of wild-type flies (figure 1). The reduction in overall

(White 1998).<br>Flies homozygous for *chico* are approximately half the size of wild-type flies (figure 1). The reduction in overall

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Figure 1. *chico* mutants are dramatically reduced in body size. Figure 1. *chico* mutants are dramatically reduced in body size.<br>*chico* homozygous mutant flies  $(-/-)$  are only about half the<br>size of heterozygous siblings  $(+/-)$ . Note that the reduction Figure 1. *chico* mutants are dramatically reduced in body size.<br>*chico* homozygous mutant flies  $(-/-)$  are only about half the<br>size of heterozygous siblings  $(+/-)$ . Note that the reduction<br>in size is proportional size of heterozygous siblings  $(+/-)$ . Note that the reduction<br>in size is proportional.



Figure 2. Autonomous cell size reduction in eye clones mutant for *chico*. Tangential section of the adult fly eye. Figure 2. Autonomous cell size reduction in eye clones<br>mutant for *chico*. Tangential section of the adult fly eye.<br>Inspection of homozygous mutant tissue, marked by the<br>absence of nigment, reveals that the cells are about mutant for *chico*. Tangential section of the adult fly eye.<br>Inspection of homozygous mutant tissue, marked by the<br>absence of pigment, reveals that the cells are about half the<br>size of pormal cells. The presence of ommatid Inspection of homozygous mutant tissue, marked by the<br>absence of pigment, reveals that the cells are about half the<br>size of normal cells. The presence of ommatidia consisting of<br>heterozygous (arrow) and homozygous mutant ( absence of pigment, reveals that the cells are about half the<br>size of normal cells. The presence of ommatidia consisting of<br>heterozygous (arrow) and homozygous mutant (arrowhead)<br>cells at the border of the clone indicates size of normal cells. The presence of ommatidia consisting of<br>heterozygous (arrow) and homozygous mutant (arrowhead)<br>cells at the border of the clone indicates that *chico* function is<br>autonomously required in each cell  $\rightarrow$  heterozygous (arrow) and homozygous mutant (arrowhead)<br>) cells at the border of the clone indicates that *chico* function is

autonomously required in each cell.<br>body size is due to a reduction in cell size and cell body size is due to a reduction in cell size and cell<br>number. Since cell size and organ size are controlled by<br>intrinsic and extrinsic factors, the loss of *chico* function body size is due to a reduction in cell size and cell<br>number. Since cell size and organ size are controlled by<br>intrinsic and extrinsic factors, the loss of *chico* function<br>may alter the production or secretion of humoral number. Since cell size and organ size are controlled by<br>intrinsic and extrinsic factors, the loss of *chico* function<br>may alter the production or secretion of humoral growth-<br>promoting factors or the response of individua intrinsic and extrinsic factors, the loss of *chico* function<br>may alter the production or secretion of humoral growth-<br>promoting factors or the response of individual cells to<br>these growth-promoting factors. The generation may alter the production or secretion of humoral growthmutant clones in a heterozygous background could distinthese growth-promoting factors. The generation of *chico*<br>mutant clones in a heterozygous background could distinguish between the different sites of action. Loss of *chico*<br>function affects cell size in a cell-autonomous mutant clones in a heterozygous background could distinguish between the different sites of action. Loss of *chico*<br>function affects cell size in a cell-autonomous manner.<br>This is most clearly seen in *chico* mutant clones guish between the different sites of action. Loss of *chico*<br>function affects cell size in a cell-autonomous manner.<br>This is most clearly seen in *chico* mutant clones in the eye, *Phil. Trans. R. Soc. Lond.* B (2000) *Phil. Trans. R. Soc. Lond.* B (2000)



Figure 3. The *Drosophila* insulin/IGFR-signalling pathway. Figure 3. The *Drosophila* insulin/IGFR-signalling pathway.<br>This pathway is conserved in its components and function<br>with the vertebrate insulin/IGFR system Denicted are Figure 3. The *Drosophila* insulin/IGFR-signalling pathway<br>This pathway is conserved in its components and function<br>with the vertebrate insulin/IGFR system. Depicted are<br>components for which there is genetic evidence for g This pathway is conserved in its components and function<br>with the vertebrate insulin/IGFR system. Depicted are<br>components for which there is genetic evidence for growth with the vertebrate insulin/IGFR system. Depicted are<br>components for which there is genetic evidence for growth<br>regulation. Arrows indicate activation, dashed arrows indirect<br>activation and double-headed arrows recruitment components for which there is genetic evidence for growth<br>regulation. Arrows indicate activation, dashed arrows indirect<br>activation and double-headed arrows recruitment to the cell<br>membrane. PTEN negatively regulates the p regulation. Arrows indicate activation, dashed arrows indi-<br>activation and double-headed arrows recruitment to the ce<br>membrane. PTEN negatively regulates the pathway by<br>decreasing PIP, levels. For abbreviations, see the ma activation and doi<br>membrane. PTEN<br>decreasing PIP<sub>3</sub> le activation and double-headed arrows recruitment to the cell<br>membrane. PTEN negatively regulates the pathway by<br>decreasing  $\text{PIP}_3$  levels. For abbreviations, see the main text.

where mutant photoreceptor cells (marked by the absence of pigment) are only half the size of adjacent cells that where mutant photoreceptor cells (marked by the absence<br>of pigment) are only half the size of adjacent cells that<br>are heterozygous for *chico* (figure 2). Additionally, loss of<br>Chico function in the entire eve and head pro of pigment) are only half the size of adjacent cells that<br>are heterozygous for *chico* (figure 2). Additionally, loss of<br>Chico function in the entire eye and head produces flies<br>with tiny heads relative to their normal-siz are heterozygous for *chico* (figure 2). Additionally, loss of Chico function in the entire eye and head produces flies<br>with tiny heads relative to their normal-sized body<br>(ninhead flies) cansule Thus Chico protein is requ Chico function in the entire eye and head produces flies<br>with tiny heads relative to their normal-sized body<br>(pinhead flies) capsule. Thus, Chico protein is required with tiny heads relative to their normal-sized body (pinhead flies) capsule. Thus, Chico protein is required autonomously in cells and organs during development to transmit a growth-promoting signal. autonomously in cells and organs during development to

# (iii) *The insulin- and IGF-I-signalling pathway is conserved*<br>(iii) *The insulin- and IGF-I-signalling pathway is conserved*<br>in Drosophila and is dedicated to arouth control *in* Drosophila *and is dedicated to growth control*

The insulin- and IGF-I-signalling pathway is conserved<br>Drosophila and is dedicated to growth control<br>The homology between Chico and IRS1-4 suggests<br>at other elements in the insulin signalling pathway may in Drosophila and is dedicated to growth control<br>The homology between Chico and IRS1-4 suggests<br>that other elements in the insulin signalling pathway may<br>also control growth in a manner similar to Chico The homology between Chico and IRSI-4 suggests<br>that other elements in the insulin signalling pathway may<br>also control growth in a manner similar to Chico<br>(figure 3) Indeed mutations in the gene coding for the that other elements in the insulin signalling pathway may<br>also control growth in a manner similar to Chico<br>(figure 3). Indeed, mutations in the gene coding for the<br>*Drasobbila* homologue of the insulin/IGE-I receptor (Inr also control growth in a manner similar to Chico<br>(figure 3). Indeed, mutations in the gene coding for the<br>*Drosophila* homologue of the insulin/IGF-I receptor (Inr)<br>affect overall growth (Rosen 1987: Fernandez *et al* 1995 (figure 3). Indeed, mutations in the gene coding for the *Drosophila* homologue of the insulin/IGF-I receptor (Inr) affect overall growth (Rosen 1987; Fernandez *et al.* 1995; Chen *et al.* 1996). C *elegans* possesses on *Drosophila* homologue of the insulin/IGF-I receptor (Inr) affect overall growth (Rosen 1987; Fernandez *et al.* 1995; Chen *et al.* 1996). *C. elegans* possesses only one *Inr* gene in contrast to the two related insulin/ affect overall growth (Rosen 1987; Fernandez *et al.* 1995; Chen *et al.* 1996). *C. elegans* possesses only one *Im* gene in contrast to the two related insulin/IGFRs in vertebrates. The *Dresphila* Inc has almost equival Chen *et al.* 1996). *C. elegans* possesses only one *Inr* gene in contrast to the two related insulin/IGFRs in vertebrates.<br>The *Drosophila* Inr has almost equivalent sequence identity to the insulin/IGFRs in vertebrates contrast to the two related insulin/IGFRs in vertebrates.<br>The *Drosophila* Inr has almost equivalent sequence<br>identity to the insulin/IGFRs in vertebrates and contains<br>properties of both the vertebrate insulin receptor and The *Drosophila* Inr has almost equivalent sequence<br>identity to the insulin/IGFRs in vertebrates and contains<br>properties of both the vertebrate insulin receptor and<br>IGER: growth control as well as metabolic regulation identity to the insulin/IGFRs in vertebrates and contains<br>properties of both the vertebrate insulin receptor and<br>IGFR: growth control as well as metabolic regulation.<br>Although complete loss of Ing function causes embryonic properties of both the vertebrate insulin receptor and IGFR: growth control as well as metabolic regulation.<br>Although complete loss of Inr function causes embryonic<br>lethality partial loss-of-function mutations give rise to IGFR: growth control as well as metabolic regulation.<br>Although complete loss of Inr function causes embryonic<br>lethality, partial loss-of-function mutations give rise to<br>viable small flies with fewer and smaller cells much Although complete loss of Inr function causes embryonic<br>lethality, partial loss-of-function mutations give rise to<br>viable small flies with fewer and smaller cells much like<br>*chico* mutant flies. In contrast to vertebrate i lethality, partial loss-of-function mutations give rise to IGFRs, *Drosophila* Inr contains a C-terminal extension *chico* mutant flies. In contrast to vertebrate insulin/<br>IGFRs, *Drosophila* Inr contains a C-terminal extension<br>with limited homology that can partially substitute for<br>IRS function (Yenush *et al.* 1996) This extension is IGFRs, *Drosophila* Inr contains a C-terminal extension with limited homology that can partially substitute for IRS function (Yenush *et al.* 1996). This extension is also conserved in the *C* elegans homologye of the insu with limited homology that can partially substitute for<br>IRS function (Yenush *et al.* 1996). This extension is also<br>conserved in the *C. elegans* homologue of the insulin<br>receptor (Kimura *et al.* 1997). The difference bet IRS function (Yenush *et al.* 1996). This extension is also conserved in the *C. elegans* homologue of the insulin receptor (Kimura *et al.* 1997). The difference between the lethal and viable phenotype of  $\text{Irr}$  and *c* conserved in the *C. elegans* homologue of the insulin receptor (Kimura *et al.* 1997). The difference between the lethal and viable phenotype of *Inr* and *chico* mutants, respectively may be explained by the partially re receptor (Kimura *et al.* 1997). The difference between the lethal and viable phenotype of *Inr* and *chico* mutants, respectively, may be explained by the partially redundant function of the C-terminal extension of *Dros* lethal and viable phenotype of *Inr* and *chico* mutants, respectively, may be explained by the partially redundant function of the C-terminal extension of *Drosophila* Inr.

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In vertebrates, activation of the insulin/IGFRs triggers<br>a wide variety of intracellular signalling pathways<br>including the Ras–MAPK pathway and the PI3K In vertebrates, activation of the insulin/IGFRs triggers lip<br>a wide variety of intracellular signalling pathways P'<br>including the Ras–MAPK pathway and the PI3K is<br>pathway (Ayruch 1998) In *Drosobbila*, the PI3K pathway including the Ras-MAPK pathway and the PI3K<br>pathway (Avruch 1998). In *Drosophila*, the PI3K pathway<br>is essential for growth regulation. The Chico protein pathway (Avruch 1998). In *Drosophila*, the PI3K pathway<br>is essential for growth regulation. The Chico protein<br>contains two docking sites for the p60 adaptor subunit of<br>Dp110 PI3K and amino-acid substitutions at these site is essential for growth regulation. The Chico protein<br>contains two docking sites for the p60 adaptor subunit of<br>Dp110 PI3K and amino-acid substitutions at these sites<br>inactivate Chico function (S. Oldham and E. Hafen contains two docking sites for the p60 adaptor subunit of<br>Dpl10 PI3K and amino-acid substitutions at these sites<br>inactivate Chico function (S. Oldham and E. Hafen,<br>unpublished data). Mutations in  $b60$  and  $b110$  PI3K inactivate Chico function (S. Oldham and E. Hafen, unpublished data). Mutations in  $p60$  and  $p110$  PI3K reduce the growth rate and cell size in a way similar to *chico* (Leevers *et al.* 1996; Weinkove *et al.* 1999) In unpublished data). Mutations in  $p60$  and  $p110$  PI3K<br>reduce the growth rate and cell size in a way similar to<br>*chico* (Leevers *et al.* 1996; Weinkove *et al.* 1999). In<br>vertebrates increased PIP<sub>e</sub> levels by PI3K trigger reduce the growth rate and cell size in a way similar to *chico* (Leevers *et al.* 1996; Weinkove *et al.* 1999). In vertebrates, increased  $PIP_3$  levels by  $PI3K$  trigger the translocation of protein kinase  $R(PKR)$  to the *chico* (Leevers *et al.* 1996; Weinkove *et al.* 1999). In vertebrates, increased  $PIP_3$  levels by  $PI3K$  trigger the translocation of protein kinase B (PKB) to the membrane by binding of the PH domain of PKB to PIP<sub>s</sub>. I vertebrates, increased  $\text{PIP}_3$  levels by  $\text{PI3K}$  trigger the translocation of protein kinase B ( $\text{PKB}$ ) to the membrane by binding of the PH domain of PKB to  $\text{PIP}_3$ . Indeed, partial loss of PKB function also caus translocation of protein kinase B (PKB) to the membrane<br>by binding of the PH domain of PKB to  $PIP_3$ . Indeed,<br>partial loss of PKB function also causes a reduction in<br>hody and cell size (Verdu *et al.* 1999: Stocker *et al* by binding of the PH domain of PKB to PIP<sub>3</sub>. Indeed, partial loss of PKB function also causes a reduction in body and cell size (Verdu *et al.* 1999; Stocker *et al.* 2000)

# body and cell size (Verdu *et al.* 1999; Stocker *et al.* 2000)<br>
(iii) Drosophila *S6 kinase* (*S6K*): a target of insulin signalling<br>
One of the targets of the PI3K/PKB pathway is

(a) Drosophila *S6 kinase* (*S6K*): a target of insulin signalling<br>One of the targets of the PI3K/PKB pathway is<br>0S6K (Chou & Blenis 1995; Dufner & Thomas 1999) (iii) Drosophila *S6 kinase* (*S6K*): a target of insulin signalling<br>One of the targets of the PI3K/PKB pathway is<br>p70S6K (Chou & Blenis 1995; Dufner & Thomas 1999).<br>In response to PI3K and PKB activation p70S6K phos-One of the targets of the PI3K/PKB pathway is<br>p70S6K (Chou & Blenis 1995; Dufner & Thomas 1999).<br>In response to PI3K and PKB activation, p70S6K phos-<br>phorylates the ribosomal protein S6 (Pullen & Thomas p70S6K (Chou & Blenis 1995; Dufner & Thomas 1999).<br>In response to PI3K and PKB activation, p70S6K phos-<br>phorylates the ribosomal protein S6 (Pullen & Thomas<br>1997) This phosphorylation event permits the preferential In response to PI3K and PKB activation, p70S6K phosphorylates the ribosomal protein S6 (Pullen & Thomas 1997). This phosphorylation event permits the preferential phorylates the ribosomal protein S6 (Pullen & Thomas 1997). This phosphorylation event permits the preferential translation of an mRNA population with a specific 5'-end (5'TOP). (Brown & Schreiber 1996: Ieffries *et al.* 1997). This phosphorylation event permits the preferential translation of an mRNA population with a specific 5'-end (5'TOP) (Brown & Schreiber 1996; Jeffries *et al.* 1997). Most 5'TOP mRNAs code for ribosomal proteins and translation of an mRNA population with a specific 5'-end<br>(5'TOP) (Brown & Schreiber 1996; Jeffries *et al.* 1997).<br>Most 5'TOP mRNAs code for ribosomal proteins and are<br>essential components for ribosome biogenesis and prot (5TOP) (Brown & Schreiber 1996; Jeffries *et al.* 1997). and the expression of the apoptosis inhibitor p35 does not Most 5TOP mRNAs code for ribosomal proteins and are rescue the reduced cell number phenotype (Boehni *et* Most 5<sup>*TOP* mRNAs code for ribosomal proteins and are essential components for ribosome biogenesis and protein synthesis (Meyuhas *et al.* 1996). Mutations in *Drosophila*<br>S6K exhibit a phenotype similar to its putative u</sup> essential components for ribosome biogenesis and protein 19<br>synthesis (Meyuhas *et al.* 1996). Mutations in *Drosophila* a<br>*S6K* exhibit a phenotype similar to its putative upstream (V<br>activators namely delay in developmen synthesis (Meyuhas *et al.* 1996). Mutations in *Drosophila*<br> $S6K$  exhibit a phenotype similar to its putative upstream<br>activators, namely delay in development and a reduction<br>in body size (Montagne *et al.* 1999). In con S6K exhibit a phenotype similar to its putative upstream<br>activators, namely delay in development and a reduction<br>in body size (Montagne *et al.* 1999). In contrast to *chico*<br>mutant flies however the reduction in body size activators, namely delay in development and a reduction<br>in body size (Montagne *et al.* 1999). In contrast to *chico*<br>mutant flies, however, the reduction in body size appears<br>to be exclusively due to a reduction in cell s in body size (Montagne *et al.* 1999). In contrast to *chico* mutant flies, however, the reduction in body size appears to be exclusively due to a reduction in cell size and not cell number. Therefore  $\sqrt{S6K}$  and *chico* mutant flies, however, the reduction in body size appears<br>to be exclusively due to a reduction in cell size and not<br>cell number. Therefore, *dS6K* and *chico* affect cell and<br>organ size to a different degree. Consistent wi to be exclusively due to a reduction in cell size and not<br>cell number. Therefore,  $dS6K$  and *chico* affect cell and<br>organ size to a different degree. Consistent with this<br>notion is the fact that development lasts two day cell number. Therefore,  $dS6K$  and *chico* affect cell and<br>organ size to a different degree. Consistent with this<br>notion is the fact that development lasts two days longer<br>in  $dS6K$  mutants than in *chico* mutants. The li organ size to a different degree. Consistent with this<br>notion is the fact that development lasts two days longer<br>in *dS6K* mutants than in *chico* mutants. The link between<br>dS6K and PI3K is likely to involve the *Drosobbil* notion is the fact that development lasts two days longer<br>in *dS6K* mutants than in *chico* mutants. The link between<br>dS6K and PI3K is likely to involve the *Drosophila* TOR<br>(target of ranamycin) homologue In mammalian cel in  $dS6K$  mutants than in *chico* mutants. The link between  $dS6K$  and  $P13K$  is likely to involve the *Drosophila* TOR (target of rapamycin) homologue. In mammalian cells, activation of  $dS6K$  requires  $P13K$  and TOR act dS6K and PI3K is likely to involve the *Drosophila* TOR (target of rapamycin) homologue. In mammalian cells, activition of dS6K requires PI3K and TOR activity, while in veast the TORs have been shown to control (target of rapamycin) homologue. In mammalian cells, activation of dS6K requires PI3K and TOR activity, while in yeast the TORs have been shown to control activation of dS6K requires PI3K and TOR activity,<br>while in yeast the TORs have been shown to control<br>cytoskeletal organization (TOR2), ribosome biogenesis,<br>and nutrient-dependent changes in amino-acid permewhile in yeast the TORs have been shown to control<br>cytoskeletal organization (TOR2), ribosome biogenesis,<br>and nutrient-dependent changes in amino-acid perme-<br>ability (Thomas & Hall 1997: Lawrence & Abraham cytoskeletal organization (TOR2), ribosome biogenesis, in<br>and nutrient-dependent changes in amino-acid perme-<br>ability (Thomas & Hall 1997; Lawrence & Abraham<br>1997: Heitman et al. 1991: Schmidt et al. 1998: Powers & and nutrient-dependent changes in amino-acid perme-<br>
1997; Hawrence & Abraham During embryogenesis, there is little cell growth and cell<br>
1997; Heitman *et al.* 1991; Schmidt *et al.* 1998; Powers & division occurs without ability (Thomas & Hall 1997; Lawrence & Abraham<br>1997; Heitman *et al.* 1991; Schmidt *et al.* 1998; Powers &<br>Walter 1999). Indeed, mutations in *dTOR* have growth<br>defects similar to those of other components like *dPDK1* 1997; Heitman *et al.* 1991; Schmidt *et al.* 1998; Powers & Walter 1999). Indeed, mutations in *dTOR* have growth defects similar to those of other components like *dPDK1* and *dPKR* in the Inr pathway (F. Rintelen, S. Ol Walter 1999). Indeed, mutations in *dTOR* have growth defects similar to those of other components like *dPDK1* and *dPKB* in the Inr pathway (F. Rintelen, S. Oldham, H. Stocker and E. Hafen, unpublished data) defects similar to those of other components like *dPDK1* and *dPKB* in the Inr pathway (F. Rintelen, S. Oldham, H. Stocker and E. Hafen, unpublished data).

### (iv) *PTEN: an important negative regulator of growth*

The Inr/PI3K pathway is an essential positive regulator<br>The Inr/PI3K pathway is an essential positive regulator<br>growth in Drosobbila and must be under stringent (iv) *PTEN: an important negative regulator of growth*<br>The Inr/PI3K pathway is an essential positive regulator<br>of growth in *Drosophila* and must be under stringent<br>control to ensure that appropriate growth happens at the The Inr/PI3K pathway is an essential positive regulator<br>of growth in *Drosophila* and must be under stringent<br>control to ensure that appropriate growth happens at the<br>correct place and time Various levels for negative regu of growth in *Drosophila* and must be under stringent<br>control to ensure that appropriate growth happens at the<br>correct place and time. Various levels for negative regula-<br>tion of the vertebrate insulin and IGERs have been control to ensure that appropriate growth happens at the correct place and time. Various levels for negative regulation of the vertebrate insulin and IGFRs have been shown:<br>the tyrosine phosphatases PTPIB and IAR can inhib correct place and time. Various levels for negative regulation of the vertebrate insulin and IGFRs have been shown:<br>the tyrosine phosphatases PTPIB and LAR can inhibit<br>insulin receptor function (Goldstein *et al.* 1998) an tion of the vertebrate insulin and IGFRs have been shown:<br>the tyrosine phosphatases PTPIB and LAR can inhibit<br>insulin receptor function (Goldstein *et al.* 1998) and the<br>insulin and IGERs undergo ligand-induced internaliza the tyrosine phosphatases PTPIB and LAR can inhibit any apparent effect on the apoptotic rate. Flies mutant for<br>insulin receptor function (Goldstein *et al.* 1998) and the partial loss-of-function mutations in  $dMyc$  are d insulin receptor function (Goldstein *et al.* 1998) and the<br>insulin and IGFRs undergo ligand-induced internalization<br>and downregulation (Lammers *et al.* 1989). IRS has<br>multiple sering residues whose phosphorylation has be insulin and IGFRs undergo ligand-induced internalization<br>and downregulation (Lammers *et al.* 1989). IRS has<br>multiple serine residues whose phosphorylation has been<br>suggested to mediate damnening of the insulin signal (Su and downregulation (Lammers *et al.* 1989). IRS has<br>multiple serine residues whose phosphorylation has been<br>suggested to mediate dampening of the insulin signal (Sun<br>et al. 1992: Hotamisligil et al. 1996: Peraldi et al. 1 multiple serine residues whose phosphorylation has been<br>suggested to mediate dampening of the insulin signal (Sun<br>*et al.* 1992; Hotamisligil *et al.* 1996; Peraldi *et al.* 1996). The

pathway (Avruch 1998). In *Drosophila*, the PI3K pathway (Huang *et al.* 1999; Machama & Dixon 1999). Loss of<br>is essential for growth regulation. The Chico protein PTEN (phosphate and tensin homologue at chromosome<br>contain Dp110 PI3K and amino-acid substitutions at these sites generation of bigger cells and increased proliferation inactivate Chico function (S. Oldham and E. Hafen, (Goberdhan *et al.* 1999; Huang *et al.* 1999). Loss of PTEN lipid product of PI3K can be subject to regulation as well. PTEN is a lipid phosphatase with specificity for  $\text{PIP}_3$  and is a negative regulator of Inr signalling in *Drosophila* PTEN is a lipid phosphatase with specificity for PIP<sub>3</sub> and<br>is a negative regulator of Inr signalling in *Drosophila*<br>(Huang *et al.* 1999; Maehama & Dixon 1999). Loss of<br>PTEN (phosphate and tensin homologue at chromosome is a negative regulator of Inr signalling in *Drosophila*<br>(Huang *et al.* 1999; Maehama & Dixon 1999). Loss of<br>PTEN (phosphate and tensin homologue at chromosome<br>10) function in marked clones in *Drosophila* results in th (Huang *et al.* 1999; Maehama & Dixon 1999). Loss of PTEN (phosphate and tensin homologue at chromosome 10) function in marked clones in *Drosophila* results in the generation of bigger cells and increased proliferation PTEN (phosphate and tensin homologue at chromosome 10) function in marked clones in *Drosophila* results in the generation of bigger cells and increased proliferation (Goberdhan *et al* 1999: Huang *et al* 1999) Loss of P 10) function in marked clones in *Drosophila* results in the<br>generation of bigger cells and increased proliferation<br>(Goberdhan *et al.* 1999; Huang *et al.* 1999). Loss of PTEN<br>in the entire head of *Drosophila* creates fl generation of bigger cells and increased proliferation (Goberdhan *et al.* 1999; Huang *et al.* 1999). Loss of PTEN in the entire head of *Drosophila* creates flies with giant heads relative to their normal bodies which de heads relative to their normal bodies, which demonstrates in the entire head of *Drosophila* creates flies with giant<br>heads relative to their normal bodies, which demonstrates<br>that PTEN normally regulates organ size in a negative<br>fashion (S. Oldham and E. Hafen unpublished data) heads relative to their normal bodies, which demonstrathat PTEN normally regulates organ size in a negalashion (S. Oldham and E. Hafen, unpublished data).

### fashion (S. Oldham and E. Hafen, unpublished data).<br>(v) *Insulin signalling is required for growth but not survival during*<br>imaginal disc development *imaginal disc development* imaginal disc development<br>The IGF-I growth factor is a potent survival factor in

imaginal disc development<br>The IGF-I growth factor is a potent survival factor in<br>tissue culture cells. IGF-I promotes survival of some<br>neuronal cell types through the activation of PI3K and The IGF-I growth factor is a potent survival factor in<br>tissue culture cells. IGF-I promotes survival of some<br>neuronal cell types through the activation of PI3K and<br>PKR and subsequent inactivation of Bad (Yang et al. 1995; tissue culture cells. IGF-I promotes survival of some<br>neuronal cell types through the activation of PI3K and<br>PKB and subsequent inactivation of Bad (Yang *et al.* 1995;<br>Datta *et al.* 1997) Is the slower growth and the red neuronal cell types through the activation of PI3K and<br>PKB and subsequent inactivation of Bad (Yang *et al.* 1995;<br>Datta *et al.* 1997). Is the slower growth and the reduction<br>in cell number of *chico* mutant flies caused PKB and subsequent inactivation of Bad (Yang *et al.* 1995;<br>Datta *et al.* 1997). Is the slower growth and the reduction<br>in cell number of *chico* mutant flies caused by increased<br>apoptosis of imaginal disc cells during de Datta *et al.* 1997). Is the slower growth and the reduction<br>in cell number of *chico* mutant flies caused by increased<br>apoptosis of imaginal disc cells during development? This<br>does not seem to be the case since no evide in cell number of *chico* mutant flies caused by increased apoptosis of imaginal disc cells during development? This does not seem to be the case, since no evidence for apoptosis of imaginal disc cells during development? This does not seem to be the case, since no evidence for increased cell death is observed in *chico* mutant tissues and the expression of the apoptosis inhibitor p<sup>35</sup> d does not seem to be the case, since no evidence for<br>increased cell death is observed in *chico* mutant tissues<br>and the expression of the apoptosis inhibitor p35 does not<br>rescue the reduced cell number phenotype (Boehni *et* increased cell death is observed in *chico* mutant tissues<br>and the expression of the apoptosis inhibitor p35 does not<br>rescue the reduced cell number phenotype (Boehni *et al.*<br>1999) Similarly cells lacking PI3K function do and the expression of the apoptosis inhibitor p35 does not a detectable increase in programmed cell death 1999). Similarly, cells lacking PI3K function do not show<br>a detectable increase in programmed cell death<br>(Weinkove *et al.* 1999). Thus, in imaginal discs cell<br>survival does not require Chico/PI3K signalling but is a detectable increase in programmed cell death<br>(Weinkove *et al.* 1999). Thus, in imaginal discs cell<br>survival does not require Chico/PI3K signalling but is<br>probably promoted by other factors. Possible survival survival does not require Chico/PI3K signalling but is probably promoted by other factors. Possible survival survival does not require Chico/PI3K signalling but is<br>probably promoted by other factors. Possible survival<br>signals may come from the epidermal growth factor<br>receptor (EGER) pathway or the extracellular matrix probably promoted by other factors. Possible survival<br>signals may come from the epidermal growth factor<br>receptor (EGFR) pathway or the extracellular matrix<br>(Bergmann *et al.* 1998: Ilic *et al.* 1998: Kurada & White signals may come from the epidermal growth factor<br>receptor (EGFR) pathway or the extracellular matrix<br>(Bergmann *et al.* 1998; Ilic *et al.* 1998; Kurada & White<br>1998) 1998). (Bergmann *et al.* 1998; Ilic *et al.* 1998; Kurada & White 1998).<br>Although complete loss of PKB, PI3K, and insulin/<br>IGFR function does not absolutely block growth in

Although complete loss of PKB, PI3K, and insulin/ Although complete loss of PKB, PI3K, and insulin/<br>IGFR function does not absolutely block growth in<br>mutant clones of cells, loss of function mutations in *PKB*<br>(in germ line clones) and *Int* cause embryonic lethality IGFR function does not absolutely block growth in<br>mutant clones of cells, loss of function mutations in *PKB*<br>(in germ line clones) and *Inr* cause embryonic lethality<br>and an increase in cell death has been reported in *PK* mutant clones of cells, loss of function mutations in *PKB*<br>(in germ line clones) and *Inr* cause embryonic lethality<br>and an increase in cell death has been reported in *PKB*<br>mutant embryos (Staveley *et al.* 1998). The r (in germ line clones) and *Inr* cause embryonic lethality<br>and an increase in cell death has been reported in *PKB*<br>mutant embryos (Staveley *et al.* 1998). The role of the and an increase in cell death has been reported in  $PKB$ <br>mutant embryos (Staveley *et al.* 1998). The role of the<br>insulin-signalling pathway during embryogenesis appears<br>to be different from its role in a growing enitheliu mutant embryos (Staveley *et al.* 1998). The role of the insulin-signalling pathway during embryogenesis appears to be different from its role in a growing epithelium.<br>During embryogenesis there is little cell growth and insulin-signalling pathway during embryogenesis appears<br>to be different from its role in a growing epithelium.<br>During embryogenesis, there is little cell growth and cell<br>division occurs without cell enlargement. Consequent to be different from its role in a growing epithelium.<br>During embryogenesis, there is little cell growth and cell<br>division occurs without cell enlargement. Consequently,<br>cells become progressively smaller Whether the incre During embryogenesis, there is little cell growth and cell<br>division occurs without cell enlargement. Consequently,<br>cells become progressively smaller. Whether the increased<br>apoptosis observed in PKB mutant embryos is a dir division occurs without cell enlargement. Consequently,<br>cells become progressively smaller. Whether the increased<br>apoptosis observed in PKB mutant embryos is a direct<br>consequence of the loss of PKB survival signalling or a cells become progressively smaller. Whether the increased apoptosis observed in PKB mutant embryos is a direct consequence of the loss of PKB survival signalling or a apoptosis observed in PKB mutant embryos is a direct<br>consequence of the loss of PKB survival signalling or a<br>more indirect effect of abnormal specification or prolifera-<br>tion remains to be tested consequence of the loss of<br>more indirect effect of abno<br>tion remains to be tested. **(b)** *Coordination of growth control pathways*

## *in* **Drosophila**

(i) Drosophila *Myc controls growth in* **Drosophila**<br>
(i) Drosophila *Myc controls growth*<br>
Recent genetic analysis of the *Drosophila* homologue of<br>
c-*myc* demonstrated that it also controls growth without<br>
any apparent effect on the apoptotic rate. Flies Recent genetic analysis of the *Drosophila* homologue of<br>c-*myc* demonstrated that it also controls growth without<br>any apparent effect on the apoptotic rate. Flies mutant for<br>partial loss-of-function mutations in *dMyc* a e-myc demonstrated that it also controls growth without<br>any apparent effect on the apoptotic rate. Flies mutant for<br>partial loss-of-function mutations in  $dMyc$  are delayed in<br>development reduced in size and possess small s any apparent effect on the apoptotic rate. Flies mutant for partial loss-of-function mutations in *dMyc* are delayed in development, reduced in size and possess small, slender bristles (Gallant *et al.* 1996; Johnston *et al.* 1999). The reduction in body size is caused by a reduct development, reduced in size and possess small, slender bristles (Gallant *et al.* 1996; Johnston *et al.* 1999). The reduction in body size is caused by a reduction in the number and the size of individual cells. Although the  $dMvc$  phenotynes are similar to those of *chico*, *d* reduction in body size is caused by a reduction in the number and the size of individual cells. Although the *dMyc* phenotypes are similar to those of *chico*, there are a

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few notable differences. Loss of  $dMyc$  function disproportionately reduces bristle size, a phenotype characteristic few notable differences. Loss of *dMyc* function disproportionately reduces bristle size, a phenotype characteristic of the *Minute* mutations that affect ribosome biogenesis. Indeed one of the conserved target genes of dM tionately reduces bristle size, a phenotype characteristic<br>of the *Minute* mutations that affect ribosome biogenesis.<br>Indeed one of the conserved target genes of dMyc in<br>*Drosobhila* is called *hitchoune* and encodes an RN *Drosophila* is called *pitchoune* and encodes an RNA helicase Indeed one of the conserved target genes of dMyc in<br>*Drosophila* is called *pitchoune* and encodes an RNA helicase<br>that may be involved in some aspects of ribosome<br>function (Zaffran *et al* 1998) Overexpression of dMyc in *Drosophila* is called *pitchoune* and encodes an RNA helicase<br>that may be involved in some aspects of ribosome<br>function (Zaffran *et al.* 1998). Overexpression of dMyc in<br>the posterior wing compartment increases cell size that may be involved in some aspects of ribosome<br>function (Zaffran *et al.* 1998). Overexpression of dMyc in<br>the posterior wing compartment increases cell size but<br>does not alter organ size. Overexpression of pl10 PI3K function (Zaffran *et al.* 1998). Overexpression of dMyc in the posterior wing compartment increases cell size but does not alter organ size. Overexpression of p110 PI3K, the posterior wing compartment increases cell size but<br>does not alter organ size. Overexpression of pl10 PI3K,<br>however, increases cell size and the size of the same<br>compartment in the wing (Weinkove *et al.* 1999) dMvc does not alter organ size. Overexpression of pl10 PI3K,<br>however, increases cell size and the size of the same<br>compartment in the wing (Weinkove *et al.* 1999). dMyc<br>expression is tightly regulated during development and compartment in the wing (Weinkove *et al.* 1999). dMyc expression is tightly regulated during development and compartment in the wing (Weinkove *et al.* 1999). dMyc<br>expression is tightly regulated during development and<br>responds to patterning signals such as Wingless (Johnston<br> $et al. 1999$ ). Myc may therefore, be a critical compone expression is tightly regulated during development and<br>responds to patterning signals such as Wingless (Johnston<br>*et al.* 1999). Myc may, therefore, be a critical component<br>in integrating patterning and growth information. responds to patterning signals such as Wingless (Johnston *et al.* 1999). Myc may, therefore, be a critical component in integrating patterning and growth information. The insulin-signalling pathway on the other hand may *et al.* 1999). Myc may, therefore, be a critical component<br>in integrating patterning and growth information. The<br>insulin-signalling pathway, on the other hand, may<br>regulate growth in response to environmental factors such in integrating patterning and growth information. The<br>insulin-signalling pathway, on the other hand, may<br>regulate growth in response to environmental factors such<br>as the availability of nutrients. Thus, it appears that insulin-signalling pathway, on the other hand, may<br>regulate growth in response to environmental factors such<br>as the availability of nutrients. Thus, it appears that<br>dMvc and the insulin-signalling pathway control overlanregulate growth in response to environmental factors such<br>as the availability of nutrients. Thus, it appears that<br>dMyc and the insulin-signalling pathway control overlap-<br>ning subsets of growth functions ○ as the availability of nutrients. Thus, it appears that △ dMyc and the insulin-signalling pathway control overlapping subsets of growth functions.

### (ii) *The Ras pathway controls growth in* Drosophila

In addition to its better understood roles in cell fate (ii)  $The Ras pathway controls growth in Drosophila$  tions, see the main text.<br>In addition to its better understood roles in cell fate<br>specification and survival, the EGFR-Ras-MAPK it appears that IGF-I In addition to its better understood roles in cell fate<br>specification and survival, the EGFR–Ras–MAPK<br>pathway also is involved in growth control (Diaz-<br>Beniumea & Garcia-Bellido 1990: Diaz-Beniumea & specification and survival, the EGFR–Ras–MAPK it<br>pathway also is involved in growth control (Diaz-<br>Benjumea & Garcia-Bellido 1990; Diaz-Benjumea & fir<br>Hafen 1994: Karim & Rubin 1998) Loss-of-function de pathway also is involved in growth control (Diaz-<br>Benjumea & Garcia-Bellido 1990; Diaz-Benjumea &<br>Hafen 1994; Karim & Rubin 1998). Loss-of-function<br>clones of surviving cells are reduced in size in the adult Benjumea & Garcia-Bellido 1990; Diaz-Benjumea &<br>Hafen 1994; Karim & Rubin 1998). Loss-of-function<br>clones of surviving cells are reduced in size in the adult<br>wing Whether this level of control occurs during prolif-Hafen 1994; Karim & Rubin 1998). Loss-of-function<br>clones of surviving cells are reduced in size in the adult<br>wing. Whether this level of control occurs during prolif-<br>eration or during differentiation needs to be examined wing. Whether this level of control occurs during proliferation or during differentiation, needs to be examined.

# eration or during differentiation, needs to be examined.<br>
(c) *The insulin-signalling pathway: an evolutionarily***<br>
conserved nutritional sensing pathway?** *c* insulin-signalling pathway: an evolutiona<br>conserved nutritional sensing pathway?<br>similarity between flies reared under limiting The insulin-signalling pathway: an evolutionarily<br>conserved nutritional sensing pathway?<br>The similarity between flies reared under limiting food<br>nditions and flies carrying viable mutations in compo-

conserved nutritional sensing pathway?<br>The similarity between flies reared under limiting food<br>conditions and flies carrying viable mutations in compo-<br>nents of the insulin-signalling pathway is striking. In each The similarity between flies reared under limiting food<br>conditions and flies carrying viable mutations in compo-<br>nents of the insulin-signalling pathway is striking. In each<br>case, development is delayed and body size is re nents of the insulin-signalling pathway is striking. In each and 1999). They are secreted by the fat body into the haemo-<br>case, development is delayed and body size is reduced lymph and can stimulate proliferation in imagi nents of the insulin-signalling pathway is striking. In each<br>case, development is delayed and body size is reduced<br>owing to fewer and smaller cells. In yeast, poor nutrition<br>also reduces the critical cell size when cells u case, development is delayed and body size is reduced<br>owing to fewer and smaller cells. In yeast, poor nutrition<br>also reduces the critical cell size when cells undergo cell<br>division. In these cells TOR controls growth in r owing to fewer and smaller cells. In yeast, poor nutrition<br>also reduces the critical cell size when cells undergo cell<br>division. In these cells, TOR controls growth in response<br>to changing nutrient conditions (Beck & Hall also reduces the critical cell size when cells undergo cell<br>division. In these cells, TOR controls growth in response<br>to changing nutrient conditions (Beck & Hall 1999; division. In these cells, TOR controls growth in response<br>to changing nutrient conditions (Beck & Hall 1999;<br>Cardenas *et al.* 1999; Hardwick *et al.* 1999). In *C. elegans*,<br>the insulin-signalling and transforming growth to changing nutrient conditions (Beck & Hall 1999;<br>Cardenas *et al.* 1999; Hardwick *et al.* 1999). In *C. elegans*,<br>the insulin-signalling and transforming growth factor- $\beta$ <br>(TGE-R)-signalling pathways coordinately cont Cardenas *et al.* 1999; Hardwick *et al.* 1999). In *C. elegans*, the insulin-signalling and transforming growth factor- $\beta$  (TGF- $\beta$ )-signalling pathways coordinately control alternative developmental programmes in resp the insulin-signalling and transforming growth factor- $\beta$ <br>(TGF- $\beta$ )-signalling pathways coordinately control alternative developmental programmes in response to nutrient<br>conditions (Estevez et al. 1993; Kenyon et al. 19 (TGF-β)-signalling pathways coordinately control alternative developmental programmes in response to nutrient conditions (Estevez *et al.* 1993; Kenyon *et al.* 1993; Gottlieb & Ruykun 1994: Ren *et al*. 1996). In this imm native developmental programmes in response to nutrient<br>conditions (Estevez *et al.* 1993; Kenyon *et al.* 1993;<br>Gottlieb & Ruvkun 1994; Ren *et al.* 1996). In this immaconditions (Estevez *et al.* 1993; Kenyon *et al.* 1993;<br>
Gottlieb & Ruvkun 1994; Ren *et al.* 1996). In this imma-<br>
In summary, the similarity of the phenotypes caused<br>
ture dauer stage, nematodes can endure periods of l Gottlieb & Ruvkun 1994; Ren *et al.* 1996). In this imma-<br>ture dauer stage, nematodes can endure periods of low<br>food availability largely due to the accumulation of fat<br>(Riddle 1988: Kimura *et al.* 1997). A similar incre ture dauer stage, nematodes can endure periods of low<br>food availability largely due to the accumulation of fat<br>(Riddle 1988; Kimura *et al.* 1997). A similar increase in<br>linid stores has been described in *chico* mutant fl food availability largely due to the accumulation of fat<br>(Riddle 1988; Kimura *et al.* 1997). A similar increase in<br>lipid stores has been described in *chico* mutant flies and<br>IRS-2 knock-out mice (Boehni *et al.* 1999: D. (Riddle 1988; Kimura *et al.* 1997). A similar increase in a conserved role of this pathway in the control of overall lipid stores has been described in *chico* mutant flies and growth during development. The intricate coo lipid stores has been described in *chico* mutant flies and S-2 knock-out mice (Boehni *et al.* 1999; D. Burks and<br>Mitte, unpublished data).<br>Although most members of the TGF- $\beta$  family in<br>most members of the TGF- $\beta$  family in

*M.* White, unpublished data).<br> *Although most members of the TGF-β family in<br>
<i>Drosophila* are involved in pattern formation during devel-<br>
compert mutations in *haboar the Drosophila* bomologue of Although most members of the  $TGF-\beta$  family in<br>*Drosophila* are involved in pattern formation during devel-<br>opment, mutations in *baboon*, the *Drosophila* homologue of<br>the type I activin receptor cause a reduction of size *Drosophila* are involved in pattern formation during development, mutations in *baboon*, the *Drosophila* homologue of the type I activin receptor, cause a reduction of size without any overt patterning defects (Brummel opment, mutations in *baboon*, the *Drosophila* homologue of the type I activin receptor, cause a reduction of size without any overt patterning defects (Brummel *et al.* 1999). It is interesting to note that mutations in the type I activin receptor, cause a reduction of size without any overt patterning defects (Brummel *et al.* 1999). It is interesting to note that mutations in TGF- $\beta$  pathway homologues in *C. elegans* result in reduced body size, similar, to mutations in the insulin-simul 1999). It is interesting to note that mutations in TGF- $\beta$ <br>pathway homologues in *C. elegans* result in reduced body<br>size similar to mutations in the insulin-signalling<br>pathway in *Dresobbila* (Krishna et al. 1999: Morit pathway homologues in *C. elegans* result in reduced body<br>size similar to mutations in the insulin-signalling<br>pathway in *Drosophila* (Krishna *et al.* 1999; Morita *et al.*<br>1999: Suzuki *et al.* 1999) From this correlativ size similar to mutations in the insulin-signalling<br>pathway in *Drosophila* (Krishna et al. 1999; Morita et al.<br>1999; Suzuki et al. 1999). From this correlative evidence,



Figure 4. Schematic representation of multiple pathways affecting growth. Nutritional and patterning cues must be Figure 4. Schematic representation of multiple pathways<br>affecting growth. Nutritional and patterning cues must be<br>coordinated to regulate growth and cell cycle. For abbrevia-<br>tions, see the main text affecting growth. Nutritic<br>coordinated to regulate g<br>tions, see the main text.

it appears that IGF-I/insulin and TGF- $\beta$  signalling may it appears that IGF-I/insulin and TGF- $\beta$  signalling may<br>act as a general nutritional sensing system to regulate<br>final body size. Confirmation of this hypothesis will it appears that IGF-I/insulin and TGF- $\beta$  signalling may<br>act as a general nutritional sensing system to regulate<br>final body size. Confirmation of this hypothesis will<br>depend on the genetic characterization of the insulin act as a general nutritional sensing system to regulate<br>final body size. Confirmation of this hypothesis will<br>depend on the genetic characterization of the insulin-like<br>and TGE-8 ligands whose expression levels may change final body size. Confirmation of this hypothesis will depend on the genetic characterization of the insulin-like and  $TGF-\beta$  ligands whose expression levels may change depend on the genetic characterization of the insulin-like<br>and TGF- $\beta$  ligands whose expression levels may change<br>in response to different nutrient conditions. Although in<br> $C$  elegans and in Drasobbila there, are multipl and TGF-β ligands whose expression levels may change<br>in response to different nutrient conditions. Although in<br>*C. elegans* and in *Drosophila* there are multiple genes<br>coding for insulin-like and TGF-β pentides no mutati in response to different nutrient conditions. Although in *C. elegans* and in *Drosophila* there are multiple genes coding for insulin-like and TGF- $\beta$  peptides, no mutations have yet been identified in these genes in *D*  $C. elegans$  and in *Drosophila* there are multiple genes coding for insulin-like and TGF- $\beta$  peptides, no mutations have yet been identified in these genes in *Drosophila* (Kutty *et al.* 1998: W. Brogiolo and E. Hafen unpubcoding for insulin-like and TGF- $\beta$  peptides, no mutations<br>have yet been identified in these genes in *Drosophila*<br>(Kutty *et al.* 1998; W. Brogiolo and E. Hafen, unpub-<br>lished data). Another class of growth-promoting fac have yet been identified in these genes in *Drosophila* (Kutty et al. 1998; W. Brogiolo and E. Hafen, unpub-<br>lished data). Another class of growth-promoting factors are the imaginal disc growth factors (Kawamura *et al.* lished data). Another class of growth-promoting factors<br>are the imaginal disc growth factors (Kawamura *et al.*<br>1999). They are secreted by the fat body into the haemo-<br>lymph and can stimulate proliferation in imaginal dis are the imaginal disc growth factors (Kawamura *et al.* 1999). They are secreted by the fat body into the haemo-lymph and can stimulate proliferation in imaginal discs. They are potentially a link between nutritional sensi 1999). They are secreted by the fat body into the haemo-<br>lymph and can stimulate proliferation in imaginal discs.<br>They are potentially a link between nutritional sensing<br>of amino acids in the fat body and growth of imagina lymph and can stimulate proliferation in imaginal discs.<br>They are potentially a link between nutritional sensing<br>of amino acids in the fat body and growth of imaginal<br>discs (Zinke et al. 1999: Britton & Edgar 1998) Their They are potentially a link between nutritional sensing<br>of amino acids in the fat body and growth of imaginal<br>discs (Zinke *et al.* 1999; Britton & Edgar 1998). Their<br>synergy with insulin to promote imaginal disc growth of amino acids in the fat body and growth of imaginal discs (Zinke *et al.* 1999; Britton & Edgar 1998). Their synergy with insulin to promote imaginal disc growth supports the idea that multiple signalling pathways are discs (Zinke *et al.* 1999; Britton & Edgar 1998). Their synergy with insulin to promote imaginal disc growth supports the idea that multiple signalling pathways are required for coordinated growth.

### **5. SUMMARY**

5. SUMMARY<br>In summary, the similarity of the phenotypes caused<br>the loss of components in the insulin/IGE-I-signalling **by the similarity of the phenotypes caused**<br>by the loss of components in the insulin/IGF-I-signalling<br>nathway in invertebrates and vertebrates strongly suggests pathway in invertebrates and vertebrates strongly suggests by the loss of components in the insulin/IGF-I-signalling<br>pathway in invertebrates and vertebrates strongly suggests<br>a conserved role of this pathway in the control of overall<br>growth during development. The intricate coord pathway in invertebrates and vertebrates strongly suggests<br>a conserved role of this pathway in the control of overall<br>growth during development. The intricate coordination of<br>the various growth- and pattern-formation pathw a conserved role of this pathway in the control of overall<br>growth-during development. The intricate coordination of<br>the various growth- and pattern-formation pathways<br>requires a complex and probably partially redundant growth during development. The intricate coordination of the various growth- and pattern-formation pathways<br>requires a complex and probably partially redundant<br>interplay of multiple signalling systems (figure 4). This is<br>evident from the fact that cells lacking any one of the requires a complex and probably partially redundant<br>interplay of multiple signalling systems (figure 4). This is<br>evident from the fact that cells lacking any one of the<br>components in the insulin pathway are still able to g interplay of multiple signalling systems (figure 4). This is<br>evident from the fact that cells lacking any one of the<br>components in the insulin pathway are still able to grow<br>and differentiate albeit at a severely reduced r evident from the fact that cells lacking any one of the components in the insulin pathway are still able to grow and differentiate albeit at a severely reduced rate. Determining how the signals from these pathways are components in the insulin pathway are still able to grow<br>and differentiate albeit at a severely reduced rate.<br>Determining how the signals from these pathways are<br>integrated is a major challenge for the future and differentiate albeit at a severely red<br>Determining how the signals from these paintegrated is a major challenge for the future.

megrated is a major chancinge for the future.<br>We thank Peter Gallant, Barbara Froesch, Knud Nairz,<br>Sebastian Breuer and the rest of the laboratory for their We thank Peter Gallant, Barbara Froesch, Knud Nairz,<br>Sebastian Breuer and the rest of the laboratory for their<br>excellent finishing touches S.O. thanks Keana Ruby and We thank Peter Gallant, Barbara Froesch, Knud Nairz, Sebastian Breuer and the rest of the laboratory for their excellent finishing touches. S.O. thanks Keana Ruby and

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