development, whereas absent (or greatly reduced) expression in s^w/s^w animals gives rise to animals that are almost completely white because their melanocytes die early in development. Melanocytes are also required for normal function of the inner ear, which helps to explain why some s^w/s^w dogs are deaf[9].

Boxers and balancing selection

Complete resequencing of *S* and s^w in boxers revealed a surprising number, 46, of polymorphisms that distinguish the two alleles, so the precise molecular cause of the s^w mutation is not so clear. In this regard, efforts of dog breeders have created both an opportunity and a potential frustration for molecular geneticists. Bruce Cattanach, well known for his studies on X-chromosome inactivation and gametic imprinting in mice, is also a well-known breeder of boxers, and he wrote in *Boxerama* (No. 5, Christmas 1974):

> Current fashion dictates that the British Boxer must have near-maximum permissible amounts of white coat markings, strategically placed, in order to be successful in the show ring. Such 'flashy' specimens are considered more eye-catching than their 'plainer' brethren and, in some circles, it is even held that the indefinable character, quality, is only found in animals with relatively large amounts of white.

But the same breed standard does not permit the breeding of white (s^w/s^w) boxers. A tendency to pick heterozygotes (S/s^w) for breeding is a perfect recipe for balancing selection, causing progressive accumulation of sequence variants that distinguish the *S* and s^w alleles.

Setting aside the issue of spotting and balancing selection, prospects for identifying additional genetic traits in dogs are outstanding given that most morphologic and behavioral diversity is thought to arise not from mutation but from selection on standing genetic variation present in the ancestral dog population[10]. Indeed, a little more than 60 years after the aforementioned grant to the Jackson Laboratory, the potential of dog genetics and the prescience of dog geneticists (Clarence Cook Little in particular) have not changed, but the technology has: recent advances in genomics have created the opportunity that lies before us. The principal challenge now is with phenotypes: how are we to measure and classify behaviors such as herding, pointing and that "indefinable character" so treasured by breeders of boxers?

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Aging and cancer: killing two birds with one worm

Anne Brunet

Two new studies explore the genetic mechanisms connecting aging and tumor growth in *Caenorhabditis elegans*. This work should provide a basis to consider ways to prevent and treat age-dependent cancers.

Age is a major risk factor for cancer. But is this age dependency of cancer risk just due to the inevitable accumulation of damage to cells as an organism ages, or are there specific genetic or epigenetic mechanisms that coordinately regulate aging and cancer? Two recent studies by Julie Pinkston-Gosse, Cynthia Kenyon and colleagues, one of which is on page 1403 of this issue, address this question by exploring the genetic mechanisms connecting aging and cancer in *C. elegans*[1,2].

Defining the model

C. elegans offers a powerful genetic system to study organismal aging. Although worms live only 2–3 weeks, the genetic mechanisms that regulate their longevity are remarkably conserved in long-lived mammals. For example, the pathway that connects the insulin/insulin-like growth factor 1 (IGF-1) receptor to FOXO transcription factors is a central regulator of longevity in organisms ranging from worms to mammals[3]. Thus, *C. elegans* might be a compelling model to identify potential common mechanisms of longevity and tumor suppression. However, unlike humans, worms do not normally get cancer as they age, most likely because the majority of cells that constitute an adult worm—except for the germ cells—can never divide again. Nevertheless, a worm model of cancer can be created by forcing the germ cells of the worm to divide. This is achieved by abolishing the function of the gene *gld-1* (ref. 4). In this worm model of cancer, the germ cells re-enter the cell cycle and proliferate uncontrollably, eventually killing the animal before its time.

In a previous study[1], Pinkston *et al.* found that mutating the insulin receptor gene not only extends normal worm lifespan but also prevents the premature organismal death induced by tumors in *gld-1* mutant worms. Reducing insulin signaling shrinks the tumor by inducing apoptotic cell death specifically in tumor cells. The specific apoptosis of the tumor cells may be linked to the fact that lowering insulin elicits in the tumor a physiological state similar to that induced by genotoxic stress[1]. Reducing insulin signaling also impairs the cell division of tumor cells, thus preventing the massive amount of cell growth that normally occurs in germline tumors[1]. These findings revealed that slowing aging could also prevent tumor progression in tumor-prone worms.

Following FOXO

Can *C. elegans* be used to identify novel genes that counter both aging and cancer? In their study in this issue[2], Pinkston-Gosse and Kenyon focus on target genes of the FOXO transcription factor DAF-16, which is activated by mutations in the insulin receptor, and test whether these target genes affect lifespan and tumor size in this worm cancer model (**Fig. 1**). They identified 29 FOXO/DAF-16 target genes that negatively or positively influence the growth of tumors and lifespan. Half of these genes also affect aging in normal worms, underscoring the link between aging and cancer. Remarkably, a number of these genes have mammalian orthologs whose protein products are known to be involved in mammalian cancer (for example, nucleoporins, Mxi1 and bNIP3).

These results are particularly exciting in light of recent findings that the FOXO family of transcription factors acts as a tissue-specific tumor

Anne Brunet is in the Department of Genetics, Stanford University, Stanford, California 94305, USA.
e-mail: anne.brunet@stanford.edu

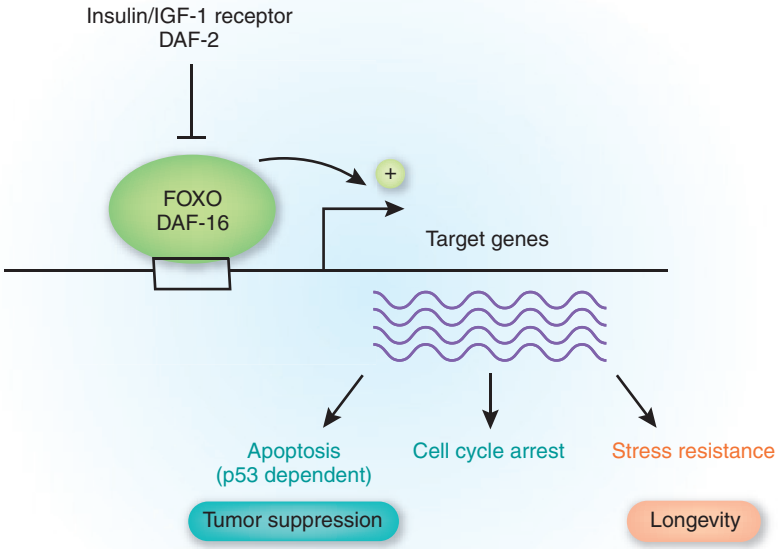

Figure 1 FOXO/DAF-16 regulates a coordinated program of genes that regulate tumor growth in *C. elegans*. FOXO/DAF-16 transcription factor is activated by lowering insulin/IGF-1 signaling. Active FOXO/DAF-16 is known to transactivate a program of genes that promote longevity by eliciting stress resistance in *C. elegans*[15]. Pinkston and Kenyon[2] show that FOXO/DAF-16 also transactivates a series of target genes that promote tumor cell apoptosis and prevent tumor cell growth in *C. elegans*. In mammals, the FOXO family acts as a tumor suppressor[5], suggesting that the ability of FOXO to coordinate longevity and tumor suppression is conserved.

suppressor in mice[5] and that, in humans, individuals with tumors with inactive FOXO have a worse prognosis than those with active FOXO[6]. Thus, the genes identified in this new study by Pinkston-Gosse and Kenyon[2] may be effectors of FOXO-dependent tumor suppression, at least in some tissues in mice and humans. As FOXO-dependent gene expression programs in mammals differ depending on the tissue in which the FOXO family is inactivated[5], it will be essential to understand which types of cancers are modeled by the worm germline tumors. In this regard, the fact that mice mutant for PTEN—a tumor suppressor that activates FOXO transcription factors—develop germ-cell tumors raises the possibility that the worm tumor model might resemble germ- cell tumors in mammals[7]. More generally, the genes identified in this study may be pivotal to regulating tumor growth in cancers in which the insulin/IGF-1 pathway is aberrantly activated or in which PTEN is inactivated, such as breast cancer, prostate cancer and glioblastoma.

The study by Pinkston-Gosse and Kenyon[2] further explores the functional interaction between two tumor suppressors: FOXO transcription factors and *cep-1*, the worm ortholog of the gene encoding the well-known tumor suppressor p53. The authors suggest that FOXO acts upstream of p53 to induce apoptosis (**Fig. 1**). In mammalian systems, the interaction between these two transcription factors is complex: p53 and FOXO can physically bind in response to stress and share a number of target genes. FOXO has been shown to prevent p53-dependent repression of specific target genes[8], and p53 can inhibit FOXO activity[9], suggesting that several positive and negative feedback loops of regulation may be at play between these two key tumor suppressors. As many human cancers involve mutations affecting both the proteins of the PTEN-FOXO pathway and p53, exploring the reciprocal interactions between the two will be important for understanding how tumor suppression and longevity are orchestrated.

The best of both worlds?

Do the genes identified in this screen provide clues to the cellular mechanisms that underlie tumor suppression and longevity? Pinkston-Gosse and Kenyon find that some FOXO/DAF-16 target genes promote apoptosis whereas others prevent cell proliferation in these germline tumors in worms (**Fig. 1**). Notably, FOXO/DAF-16 specifically acts in tumor cells and not in normal cells to promote apoptosis. It will be interesting to understand the molecular basis of this selectivity, as distinguishing tumor cells from normal cells is a key goal in the development of cancer therapies. Whether the cell has a normal or a mutated p53 gene may be critical in the ability of FOXO to selectively promote cell death of tumor cells. Other types of cellular responses might also have pivotal roles in shrinking tumors in this worm model, including cellular senescence (a permanent cell cycle arrest) and autophagy (the self digestion of cells). Indeed, cellular senescence is a very efficient barrier *in vivo* against tumor initiation in mammals[10]. The role of autophagy in cancer is still being evaluated, but mounting evidence indicates that autophagy is necessary for tumor suppression[11]. It will be interesting to test whether these other cellular responses have a role in this worm model of cancer.

Remarkably, FOXO target genes that prevent cancer can also slow down aging in normal worms. Mechanisms that normally prevent tumor formation may also extend lifespan, even in a cancer-free organism[12]. Indeed, recent evidence indicates that ectopically expressing tumor-suppressor genes in mice diminishes aging-associated damage[13]. These findings offer a view that differs from the 'antagonistic pleiotropy' model, whereby tumor suppression is achieved at the expense of longevity. One way in which tumor suppressors may prevent cancer at the expense of longevity is by eliciting cellular senescence. Indeed, although senescent cells form a great barrier against cancer, they can also be damaging for aging tissues by secreting toxic cytokines[14]. In addition, although cellular senescence in cancer cells is beneficial to prevent cancer, senescence in normal adult tissue-specific stem cells may impair the renewal of tissue. It will be important to test whether the genes identified in the study by Pinkston-Gosse and Kenyon prevent cancer and extend longevity in mammals. More generally, understanding which genetic mechanisms lead to antagonistic pleiotropy and which lead to concerted action against both cancer and aging should help identify ways to prevent and treat age-dependent cancers.

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