Could cancer drugs provide ammunition against ageing?

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Recent advances in our understanding of the molecular and cellular signalling pathways that drive ageing have revealed several genetic and environmental manipulations that can increase lifespan across different species. Research on the underlying biology of ageing has not only revealed it to be a biologically malleable process but has also paved the way for the development of pharmacological interventions that could increase lifespan and delay the onset and/or progression of age-related disease.

An emerging theme from recent studies is that manipulating the activity of cancer-promoting pathways, by increasing the activity of tumour suppressor proteins or inhibiting the function of oncogenes, can extend lifespan. For example, increasing the gene dosage of the tumour suppressor *Pten* or genetic inhibition of its direct target, the Class 1 phosphatidylinositol 3-kinase (PI3K), equivalent to PTEN activation, extends lifespan in mice[1, 2]. Moreover, an extra genomic copy of the *Ink4/Arf* locus, resulting in elevated expression of its encoded tumour suppressor proteins, extends lifespan[3], while mice haploinsufficient for the *Myc* oncogene live longer than their wild-type littermates[4]. Interestingly, while cancer incidence was reduced in several of these models, lifespan extension was also observed in cancer-free individuals, suggesting that cancer protection and delayed ageing are separable effects of the genetic manipulations imposed.

We have now added inhibition of oncogenic Ras-Erk-ETS signalling to this anti-ageing mix[5]. Hyperactivation of the Ras oncogene is believed to be responsible for around 30% of all human tumours. The Ras proteins function as small GTPases, cycling between inactive GDP-bound and active GTP-bound states to transmit signals from receptor tyrosine kinases (RTKs). Activation of Ras therefore leads to the induction of several RTK signalling pathways including the extracellular signal-regulated kinase (Erk)/mitogen activated protein kinase (Mapk) signalling cascade.

Using the fruit fly, *Drosophila melanogaster,* we selectively mutated the insulin receptor substrate, *chico*, to disrupt either of the two key outputs of insulin/IGF-like signalling (IIS) in flies, Ras-Erk-ETS or PI3K-AKT-Foxo signalling[5]. We found that selective inhibition of signalling through either of these pathways increased longevity. Moreover, direct genetic inhibition of Ras or Erk extended lifespan through activation of the E-twenty six (ETS) transcription factor, Anterior Open (AOP). We showed that lifespan extension by Erk or PI3K inhibition was not additive, suggesting that the two pathways converge on a common set of genes to regulate lifespan. Indeed, the two down-stream effectors of the two branches, the transcription factors Foxo and AOP, can be found occupying the same genomic sites. Importantly, we demonstrated that exposure of adult flies to trametinib, a small molecule inhibitor of Erk activation, currently in clinical use as a cancer therapy, extended their lifespan. While

the exact targets and/or processes affected remain unknown, it would seem that, as with other cancer prevention pathways, the anti-ageing effects of Ras inhibition are separable from its anti-cancer activity because trametinib exposure at doses conducive to lifespan extension did not alter the cancer-like pathology of extensive proliferation of the adult intestinal stem cells.

So if cancer prevention is not responsible for lifespan extension in these animals then what is? One potential mechanism by which these animals live longer could be through the promotion of beneficial metabolic changes. For example, *Myc*$^{+/-}$ mice have a higher metabolic rate and show a more youthful metabolic transcriptome at older ages[4]. Mice with overexpression of PTEN have increased energy expenditure and are protected from obesity and metabolic syndrome[1] while long-term inactivation of PI3K results in age-related reductions in insulin insensitivity, glucose intolerance and fat accumulation[2]. It remains to be determined whether inhibiting Ras-Erk-ETS signalling can extend mammalian lifespan but, intriguingly, inhibition of Erk activation in mice using trametinib can improve several deleterious metabolic outcomes associated with obesity as a result of high-fat feeding or genetic intervention[6]. Thus, targeting the activity of these cancer prevention pathways may confer longevity effects by offering protection from metabolic pathologies during ageing, independently of effects on cancer (Figure 1). It is worth noting that the beneficial metabolic effects of trametinib in mice were observed at much lower doses than those used in xenograft tumour models[6] suggesting that the therapeutic window of these compounds for anti-ageing effects may be much safer than for cancer treatment and with fewer side-effects.

The connections between cancer prevention and longevity are obviously complex. For example, cellular senescence, an important mechanism for tumour suppression, is often described as a contributing factor in age-related pathologies[7]. Nevertheless, the anti-ageing effects of reducing cancer-promoting pathways opens up the intriguing possibility that repurposing the available goldmine of cancer drug therapies could offer new treatments for other age-related diseases and possibly even key aspects of ageing itself.

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Figure 1.