Aging and Cancer relationship: a Caenorhabditis elegans point of view.
Cancer incidence increases with age and represents the second cause of death after cardiovascular diseases in the general population of industrialized countries. Why old people are at more risk for cancer? What are the physiological changes that take place during aging which favor cancer development? Can we define common mechanisms and molecular pathways that affect both aging and cancer?

In order to answer those questions we are exploring the relationship between genes involved in cancer and in the control of lifespan using the genetic model system Caenorhabditis elegans. This little worm has been instrumental in dissecting molecular pathways involved in lifespan control. Among others, the attenuation of the insulin/IGF1 pathway and dietary restriction are both responsible for lifespan lengthening from C.elegans to mammals.

We have shown that the human tumor suppressor gene PTEN, which is one of the most frequently mutated gene in human tumors, controls longevity in worms (1). Indeed, it can lengthen the lifespan of short-lived mutants. Furthermore, the same regulatory modules in the PTEN protein are required for both the control of lifespan and of tumorigenesis. Research on aging in model organisms has shown that different tissues age in a coordinated fashion. Notably, inactivation of the insulin/IGF1 pathway in the nervous system only is sufficient to increase overall fitness/lifespan. We discovered that although PTEN is well known for its role in antagonizing the insulin/IGF1 pathway, it also modulates lifespan by acting in several tissues (2), beyond the insulin/IGF1 pathway (3), and thus appears as an significant actor of age regulation.

Further investigation revealed that PTEN is also required for lifespan extension in response to dietary restriction (DR). By looking for new genetic partner of PTEN, we identified a novel regulator of lifespan, called SLCF-1. Mutants for the slcf-1 gene mimic lifespan extension by (DR) in worms fed ad libitum. Characterization of the genetic and metabolic interplay between PTEN and SLCF-1 revealed that slcf-1 inactivation induces a moderate stress (as a result of higher reactive oxygen species production by the mitochondria) and that PTEN mediates an adaptative response to this stress that makes worms stronger and more resistance to endogenous and exogenous stressors and thus long-lived (figure). Interestingly, SLCF-1 functions in one tissue: the intestine and it is also expressed in this tissue in mammals. One can tentatively suggest that inactivation of
SLCF-1 by drugs may protect against cancer by increasing PTEN activity, and by recapitulating the beneficial effect of DR with no need to eat less.

**Conclusion**

More than 300 theories of aging have been proposed and this high number probably reflects the complexity and the many different ways aging can be modulated. The most popular, « the free radical theory of aging », postulates that oxidative damage of different components of cells and tissues (due to reactive oxygen species accumulation as normal byproduct of mitochondrial metabolism), leads to the alteration of organs function and eventually to death. Nonetheless, some recent studies tend to show that antioxidant therapy have no effect and can even increase mortality. Those observations may be explained by our results showing that a moderate stress is better than no stress (4), as an illustration of Nietzsche’s most memorable quotes: “what doesn’t kill you, make you stronger”.

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