Contraception protects females against germline tumours… in worms

Genetic females of the nematode worm *C. elegans* initially produce 30-40 oocytes that accumulate in two U-shaped gonad arms, after which oocyte production ceases until a male is encountered. Oocyte accumulation is perceived as a signal that sperm is lacking and it triggers a feedback that blocks germline stem cell proliferation and the production of new oocytes. Only following male encounter and mating do germline stem cell proliferation and oocyte production resume. Interestingly, females that inherit a predisposition to growing germline tumours and have accumulated oocytes, are largely protected from developing these tumours due to the feedback signal, for as long as they do not mate with a male.

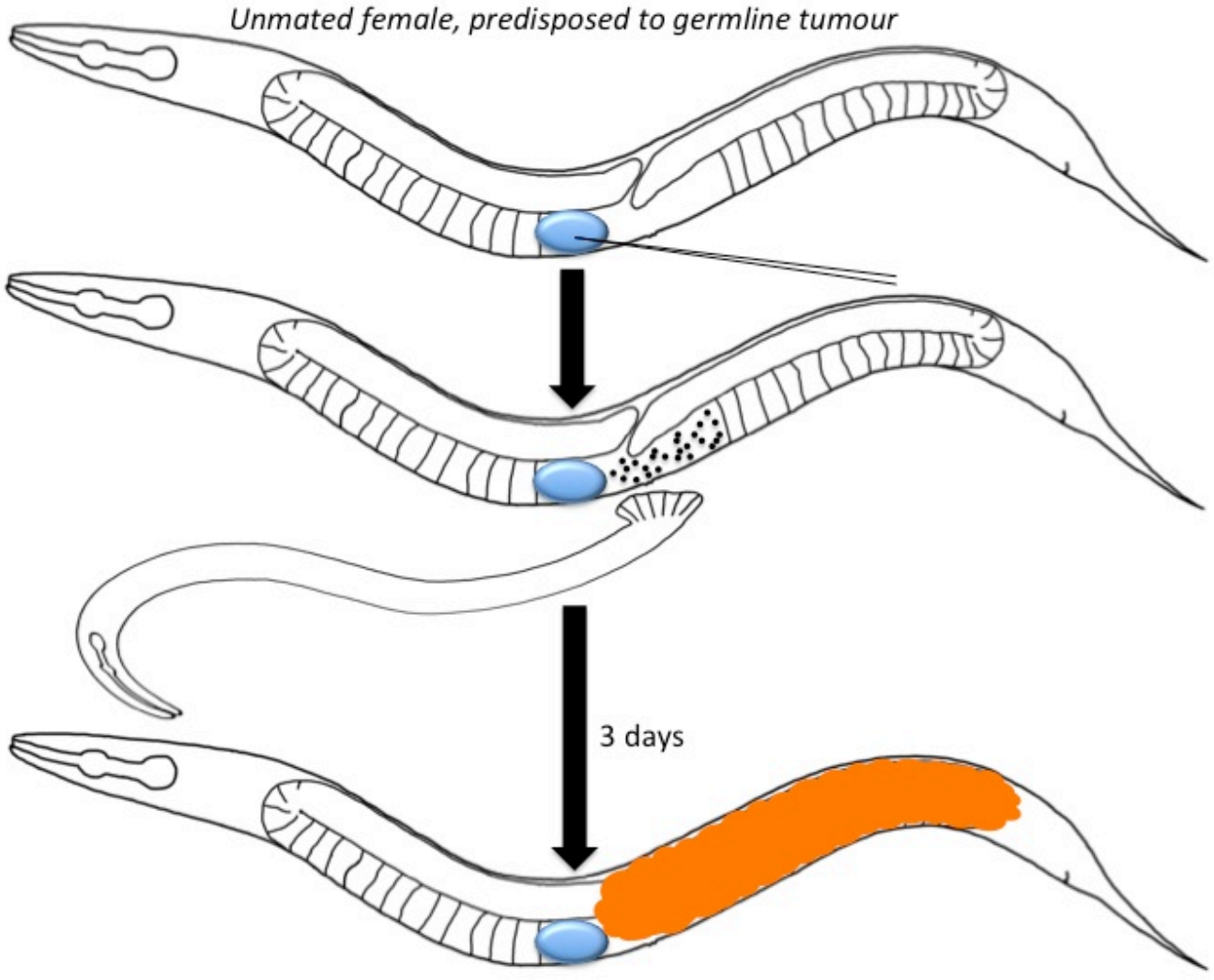

Fig. 1. Young unmated genetic females of the nematode C. elegans accumulate unfertilized oocytes (rectangles) in each of two gonad arms. Oocyte accumulation is perceived as a signal that

sperm (black dots) is absent and it feeds back to block germline stem cell proliferation and differentiation, thereby preventing the production of new oocytes. This oocyte accumulation feedback efficiently blocks the growth of germline tumours in predisposed animals. As soon as such a tumour-predisposed young female mates with a male though, oocyte accumulation will be relieved, the feedback inactivated, leaving the germline tumour free to grow. If an oil diaphragm (blue) is micro-injected in one of the two gonad arms, this prevents sperm from accessing the oocytes in that gonad arm upon mating, thereby specifically relieving oocyte accumulation in the unprotected arm. Under these conditions, only the unprotected gonad arm develops a germline tumour (orange), meaning that the feedback does not spread to the other gonad arm, and that germline stem cell proliferation is locally controlled in these nematode worms.

On the other hand, germline stem cell proliferation and oocyte production are at all times dependent on insulin signaling, which is activated by food intake. That is, food intake systemically activates insulin signaling throughout the animal's body, which in turn, promotes cell growth and proliferation by stimulating cellular absorption of nutrients throughout animals. Accordingly, similar to females having accumulated oocytes, insulin resistant mutants are protected against germline tumours.

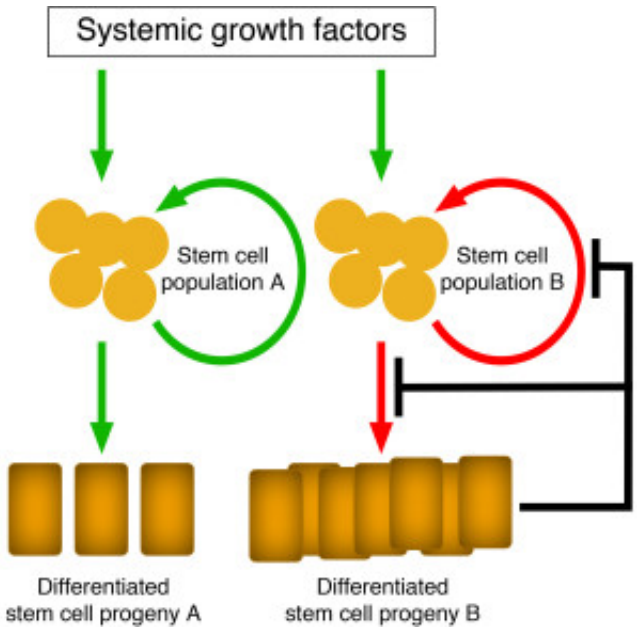

Fig. 2. In vivo mechanisms monitor for the over-accumulation of differentiated stem cell progeny and feedback to locally block the proliferation-stimulatory effects of systemically-distributed growth factors specifically on their source stem cells.

A key question that this situation poses is what happens if oocyte accumulation was to occur in only one of the two gonad arms: would the feedback signal block germline stem cell proliferation only in that arm, or in the other arm as well? In other words, can oocyte accumulation locally counteract the proliferation-stimulatory insulin signal? Nematode contraception was invented to answer this question, in the form of a tiny oil droplet that is micro-injected in the spermatheca of one of the two gonad arms prior to allowing treated females to mate with a male (Fig. 1). The oil droplet acts like a diaphragm and prevents the sperm to access the accumulated oocytes only in the injected gonad arm. Interestingly, this keeps the oocyte accumulation feedback activated specifically in the contraception-protected gonad arm, still locally blocking germline tumour growth, while germline stem cell proliferation resumes and a germline tumour develops in the unprotected gonad arm (Fig. 1). Thus, oocyte accumulation does not affect the response to insulin signals throughout animals, and instead acts locally in the stem cell population from which the accumulated oocytes originated.

This concept is important because it shows that stem cell populations, as well as tumorous growth, can be locally regulated *in vivo*. Indeed, despite the fact that some growth factors that dramatically influence stem cell activities are regulated at the systemic level, their final effect on stem cells is not the same throughout every stem cell population as it is refined locally by the need for production of differentiated stem cell progeny (Fig. 2). If we were able to hijack these local feedback mechanisms, we may be able to specifically target tissues of parts of tissues by growth-suppressing drugs to locally suppress tumour growth, thereby alleviating most side effects of current systemic anti-cancer treatments.

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