

Therapy with antitumor lipids: Worming the way

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Antitumor lipids (ATL) form a family of synthetic compounds capable of selectively inducing cell death in tumor cells. The prototype molecule of this family is edelfosine and in contrast to other antitumoral drugs, it acts on cell membranes rather than on DNA. The apparent selectivity on tumor cells seems to be related to a preferential accumulation of the drug in cancer cells involving cholesterol-rich lipid raft. However, in spite of these properties, so far the clinical applications of ATLs in cancer therapy have been very limited. A broader clinical application of these compounds would require the search of more clinically active compounds, and a much better understanding of the mechanisms by which some tumors are more sensitive than others to ATLs. To answer these questions using tumor tissue culture cell lines or murine models can be technically challenging. Sánchez-Blanco and colleagues have used the nematode *Caenorhabditis elegans* as a starting point to cope with these limitations. *C. elegans* has been a model organism in biology for more than 40 years and can now be found in laboratories worldwide. Furthermore, it has become widely used as a model for human diseases, because it provides a cheap and fast alternative to traditional more expensive and time-consuming models such as mouse and rat. Sánchez-Blanco et al. have found that edelfosine has a selective lethal effect to the *C. elegans* embryo without affecting the overall physiological status of adult worms. The embryo is composed of proliferating cells while the adult soma is composed of quiescent cells and therefore this result demonstrates that in *C. elegans* ATLs seem to maintain the selective killing ability that is the basis for their clinical application. Moreover, previous research in cultured mammalian cells suggested that a main factor for this selectivity was related to the high cholesterol content of cancer cells. As Sánchez-Blanco et al. have noted, one of the reasons for the selective effect of edelfosine in embryos was related to the high cholesterol content found in the embryo. Moreover, thanks to the fact that *C. elegans* cannot synthesize cholesterol *de novo*, and it has to be provided on culture medium, Sánchez-Blanco et al., using conditions that modified the cholesterol concentration in the worm growth medium, were able to demonstrate that the effect of ATLs in worms was directly related with the cholesterol concentration. The use of *C. elegans* in drug discovery offers several advantages and Sánchez-Blanco and colleagues show many of them in this report. Firstly, they demonstrated that *C. elegans* could be used to screen *in vivo* for additional more active ATLs. As a proof of principle they have compared the efficiency of different ATLs and they have found that the worm model mimicked the differential sensitivity to ATLs observed in various tumor cell lines, opening the door to the use of worms for the design of more active drugs. Secondly, they have taken advantage of the well-established role of *C. elegans* as workhorse of hard-core geneticists, who have developed elaborate genetic tools. Using an educated choice of mutants, Sánchez-Blanco et al. have found that mutants in the insulin/IGF-like signaling pathway displayed a marked resistance to edelfosine. Strikingly, they were able to translate this finding to mammalian cells and they showed that inhibition of Akt1, one of the components of this pathway, in a human tumor cell line also renders the treated cells less sensitive to edelfosine. Again, this finding opens the way to understand the molecular basis of ATL sensitivity and resistance in tumor cells. In summary, Sánchez-Blanco and colleagues showed in this elegant piece of work that the mechanisms driving embryonic lethality in *C. elegans* upon ATL treatment can be extrapolated to human models. This work further supports the use of *C. elegans* in facilitating the identification of new targets and strategies in the fight against cancer processes.

It also reinforces the need for genetic screens and studies of model organisms to discover novel signaling pathways that reveal possible therapeutic targets.