A New Anticancer Agent Derived from Sea Sponges

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Researchers at Harvard University have succeeded in synthesizing halichondrin B, a very complex molecule which is produced naturally by sea sponges and which possesses an exceptional anticancer activity.

A large number of the medications which are currently in use are derived, in one way or another, from nature. One need only think of aspirin, derived from the bark of the willow, which has become the most commonly purchased medication in history since it was commercialized in 1899. Another is artemisin, also isolated from tree bark (qinghao tree) which has become an effective treatment against malaria. This situation is also true concerning cancer, where more than 60% of the clinical chemotherapy treatments currently in use are directly derived from plant sources (taxol, vincristine, vinblastine) or else plant products were used to chemically derive even more powerful products (etoposide, irinotecan, docetaxel). All these medications reflect the great diversity of therapeutic molecules present in nature, produced by plant enzymes, along with the ingenuity of humans in identifying these molecules and using them to fight the diseases which afflict us.

ANTICANCEROUS SEA PRODUCTS

Several observations made over the past few years have suggested that ancient sea animals are another potential source of medications. This is notably the case for sea sponges, the common ancestor of all animals currently living on the planet[1]. Although they are quite primitive (sponges are simple colonies of cells which live together, without differentiated organs and with a very simple nervous system), these animals have developed, over the course of evolution, an impressive arsenal of molecules (over 6500 known to date, many of them unknown in the terrestrial world) to protect themselves against the viruses, fungi and predators present in their environment.

In 1986, a group of Japanese scientists reported the identification of 8 anticancerous compounds isolated from *Halichondria okadai*, a sponge that is widespread along the Pacific coast of Japan[2]. Named halichondrins, these molecules exhibited very strong anticancer activity when they were tested in animal models, an activity produced by their ability to inhibit the formation of microtubules, a structure essential for the division of cells. While other anticancer agents also target microtubules (paclitaxel and vinblastine, amongst others), it has been shown that halichondrins (halichondrin B) were even more effective and could thus prove to be a very interesting tool for the treatment of cancer.

LARGE-SCALE PRODUCTION

Despite its enormous potential, we do not yet know the clinical potential of halichondrin B in patients due to the difficulty in purifying or of synthesizing the quantities of these molecules necessary for conducting clinical tests.

Halichondrin B is an extremely complex molecule containing 31 chiral centres, i.e. points where the orientation of the atoms in space is asymmetric, and thus could theoretically produce 4 billion distinct forms of the molecule during laboratory synthesis. Up until now, the only successful synthesis of this molecule required a hundred chemical reactions and produced only a few milligrams, a quantity which is clearly insufficient for testing its activity.

Thanks to new reagents which have allowed an improvement in the efficiency of the chemical reactions involved in the synthesis of complex molecules, a team of chemists from Harvard University were able to report the synthesis of over 10 grams of halichondrin B[3]. With a purity of 99.8% and a synthesis which respects the good manufacturing practices developed for the pharmaceutical industry, the molecule can thus now be tested in humans and a Phase I clinical test is already underway in Japan. Thirty years later, we will thus finally know if our oldest ancestors, the sea sponges, can contribute to our battle against cancer.

(1) Feuda R. Improved modeling of compositional heterogeneity supports sponges as sister to all other animals. Curr Biol. 2017; 27: 3864-3870.

(2) Hirata Y and Uemura D. Halichondrins—antitumor polyether macrolides from a marine sponge. Pure & Appl. Chem. 1986; 58: 701-710.

(3) Kawano S et al. A landmark in drug discovery based on complex natural product synthesis. Sci Rep. 2019; 9: 8656.

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