A la Pêche aux Moules

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Abstract In a recent manuscript, Goff and collaborators (Metzger et al. 2016) reported data arguing for the spread of contagious cancer cells among different species of shellfish. Although horizontal transmission of cancer cells has been observed in a few cases in higher organisms, it appears to be rather frequent among molluscs. Recent evidence supports the concept of inter-species horizontal infectious transmission of cancer cells both in molluscs but also in mammals, including humans.

Keywords Cancer · Infectious disease · Horizontal transmission · Pathogens · Leukemia · Immunodepression · Bivalve · Parasite · Molluscs

Several converging studies lead to the conclusion that transmissible cancer, once thought to be restricted to a few *genera* occurs in a wide panel of species, including dogs (*Canis lupus familiaris*) (Murgia et al. 2006), marsupial Tasmanian devil (*Sarcophilus harrisii*) (Pearse and Swift 2006), and soft shell clams (*Mya arenaria*) (Metzger et al. 2015). An experimental case of transmissible tumor in hamster was also reported (Copper et al. 1964).

Title of a French rhyme for children, which is about « fishing for mussels » which says « Fishing for mussels, I no longer want to go, Mommy, Fishing for mussels, I no longer want to go. » see <https://www.youtube.com/watch?v=MXOzi6dMsSg>

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In marine bivalves,¹ many malignant neoplasias have been described among which two predominant types, the gonadal and Disseminated Neoplasia (DN) have raised industrial concerns (reviewed by Carballal et al. 2015).

Gonadal neoplasia (GN) results from abnormal proliferation of undifferentiated germ cells, whereas DN resembles higher eucaryote leukemia as it consists of abnormal cells proliferating in the circulatory system of molluscs of commercial importance (Peters 1988). Although gonadal neoplasm has been reported in Hard Shell Clams (*Mercenaria mercenaria*) from the Indian River, Florida (Hesselman et al. 1988), DN is prevalent in several bivalve species (Barber 2004; Díaz et al. 2013; Martín-Gómez et al. 2013; Carballal et al. 2015).

After Mollusc proliferative neoplastic disease was first reported in oysters (*Crassostera virginica et gigas*) (Farley 1969), other marine bivalves species from 4 continents and all oceans except the Arctic were found to be carriers of proliferative diseases (reviewed by Carballal et al. 2015).

In the continuation of their studies (Metzger et al. 2015) on the horizontal transmission of leukemia by soft-shell clam clonal cancer cells, Metzger et al. (2016) have investigated DN in Mussels of four different species of molluscs among which the mussels (*Mytilus trossulus*), cockles (*Cerastoderma edule*), and the golden carpet clams (*Polititapes aureus*).

¹ In the mollusca phylum (molluscs, AKA mollusks) bivalves have a shell which is made of two two hinged sections. Mussels, Scallops, Clams, Oysters are marine bivalves. In botany, bivalve refers to seed cases opening in two halves.

The salient features of the DN from 2 out of 28 mussels, *M. trossulus*, growing in the Pacific Northwest Coast, can be summarized as follows:

- i) Both of them contained high levels of haemocytic neoplastic cells identified on the basis of their rounded shape, and non-adherent morphology.
- ii) The genotype of neoplastic cells from the 2 carriers did not match that of normal solid tissue and haemocytes, whereas the genotype samples from all healthy animals matched the normal one.
- iii) Comparison of both single nucleotide polymorphism (SNP) and EF1alpha gene sequence in normal and tumor cells indicated that the cancer cells did not originate from the hosts. Furthermore, the SNP profile of the neoplastic cells from the two carrier individuals were identical, therefore strongly suggesting that they arose from a single clonal origin.

In order to determine whether the transmissible neoplastic cell line identified in the mussels from Pacific Northwest Coast was widespread in the *M. Trossulus* population, the authors ran a similar set of studies on a series of 250 mussels from Vancouver Island. The results clearly indicated that a transmissible cancer lineage exists in the wild population.

Previous studies had established a high prevalence of DN in cockles and golden carpet shell clams from the Galician Coast (reviewed by Díaz et al. 2016; Carballal et al. 2013).

Genotyping of solid tissues and haemocytes from 12 cockles of which 6 were showing signs of DN, indicated that the neoplastic genotypes did not group with those of normal tissues, confirming the existence of a potential transmissible cancer.

The genotypes of the neoplastic cells clustered in two distinct branches, therefore suggesting the existence of at least two independent lineages.

The authors also performed a sequencing analysis of genes encoding mtCOI,² EF1alpha,³ and rDNA ITS,⁴ in 31 golden carpet shell clams (*P. aureus*). The results obtained and further molecular studies established that the genotype from the cancer cells were very dissimilar and did not match the sequence of normal cells but showed an almost perfect match with the genotype of the « pullet carpet shell » (*Venerupis corrugata*). The highest levels of *V. corrugata* sequences were detected in hemocytes, suggesting that cancer cells infiltrated the carpet shell clams via the circulation in which they propagated.

These results highlighted an interspecies transmission that was quite different from the situation that had been observed with other transmissible neoplastic cells molluscs.

Although transmissible cancers have been described in several species in nature, they generally occur within the same species. For example, the canine transmissible venereal tumor (CTVT) is a disease whose infectious agent has been identified as the cancerous cells themselves. The pattern of microsatellite variation in the genome of tumors calls for a purely asexual mode of transmission (Rebbeck et al. 2009).

While the dog tumor does not appear to be necessarily lethal, the spreading of *Tasmanian devil* tumors has dramatic consequences, as it is driving the *Tasmanian devil* population towards extinction (see reviews by Belov 2012 and Ostrander et al. 2016).

In these cases, the clonal populations of tumor cells that have adapted to the infected host behave as intra-species parasites (Murgia et al. 2006; Weiss and Fassati 2015).

The cases of Mollusc parasitic tumor cells described above illustrate the same type of situation, even though they are transmitted through sea water.

Much more disturbing and puzzling are the documented cases of cross-species transmission of cancer cells. The unique example provided by the study of Metzger et al. (2016) is not an isolated one. The results reported recently by Muehlenbachs et al. (2015) establish that the « invasion of human tissue by abnormal, proliferating, genetically altered tapeworm cells is a novel disease mechanism that links infection and cancer. The case behind this conclusion refers to the malignant transformation of the dwarf tapeworm *hymenolepis nana* in a human host. Tapeworm infections are very frequent in the human population. It has been estimated that up to 75 million individuals are silent carriers (Crompton 1999). It is predicted⁵ that by 2150, the 11, 543 millions population of human individuals living on earth will be constituted of 17.7 % children. At the same time, it is estimated that the 2, 886 million *Ascaris* infections will then result in a morbidity of 664 million people. *H. nana* is the causative agent of hymenolepiasis. Adults measure between 15 to 40 mm in length. The complete life cycle of *H.nana* takes place in the small intestine of infected individuals, and autoinfection can persist for years. It is among the most common cestode infecting humans. However, infections are usually not detected because they are asymptomatic.

This high load of parasites resulting from this permanent infection can become of significance in a context of immunodepression. For example, extra-intestinal *H nana* cysticercoidiasis⁶ was identified in asthmatic Egyptian patients (Gamal-Eddin et al. 1986), a situation where immunosuppression is known to occur (Oehling et al. 1997).

² Mitochondrially Encoded Cytochrome C Oxidase I

³ Elongation factor 1-alpha 1

⁴ Ribosomal internal transcribed spacer (ITS)

⁵ Long-range world population projections from United Nations (1992)

⁶ Cysticercosis is a parasitic tissue infection caused by larval cysts

In a similar context stool of a patient diagnosed with HIV were found to contain *H. nana* eggs and *Blastocystis hominis*⁷ cysts. As established by lymph node and lung biopsies, the patient developed a cancer with atypical cell features. Their small size suggested a non human origin and polymerase chain reaction performed on cancer cells identified DNA of *Hymenolepiasis*. As extra-intestinal infections by *Hymenolepiasis* are rare, the presence of tapeworm DNA in the cancer cells of the patient raised questions. As a matter of fact, the parasite DNA sequences were found to carry several mutations characteristic of cancer cells.

As stated by the authors, « human disease caused by parasite-derived cancer cells is a novel finding ». In this case, it is highly probable that the immunosuppressed status of the HIV-infected patient, permitted the multiplication of mutated infectious cells that acquired the properties of cancer cells.

Once thought to be a « medium-proof » unique species on earth, *Homo sapiens* has already shown its responsiveness to the outside world, through its sensitivity to epigenetic factors. The host-parasite interactions, and the transmission of tumor cells such as those that are reported above may lead to uncover a human permeability that is much greater than was ever expected. Intimate relationships with other species can represent a critical aspect in the complex array of elements that govern the evolution of all living species including human.

Interspecies transmission of diseases might be one aspect of horizontal interspecies exchange of genetic material and should not stop those who enjoy eating mussels to keep doing so...

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