

## CANCER

# Transmissible tumours under the sea

**In some species, cancer cells can be directly transmitted between individuals. An analysis in shellfish now shows that some transmissible cancers can even cross the species barrier.**

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In a paper online in *Nature*, Metzger *et al.*<sup>1</sup> report the discovery that transmissible cancers are widespread in one group of marine shellfish, known as bivalves, and that such cancers can even jump between species. These findings suggest that cancer cells are common infectious agents in marine environments, and challenge our understanding of the nature of cancer and its interaction with its hosts.

Cancer occurs when a single cell in the body acquires genetic changes that drive inappropriate cell proliferation. Once initiated, cancer evolves by natural selection, often producing cell lineages that spread through the host by a process called metastasis. However, cancer does not normally spread beyond the host's body. Until now, such transmissible cancers — cancer-cell lineages with the potential to metastasize through an animal population — were considered to be exceedingly rare. Only four examples were known in nature: two affecting Tasmanian devils, one in dogs and another in soft-shell clams<sup>2–4</sup>. Metzger and co-workers now report four previously unidentified transmissible cancers: one that affects mussels (*Mytilus trossulus*) found in British

Columbia, one that affects golden carpet shell clams (*Polititapes aureus*) on the Iberian coast and two transmissible cancers of probably independent origin in common cockles (*Cerastoderma edule*).

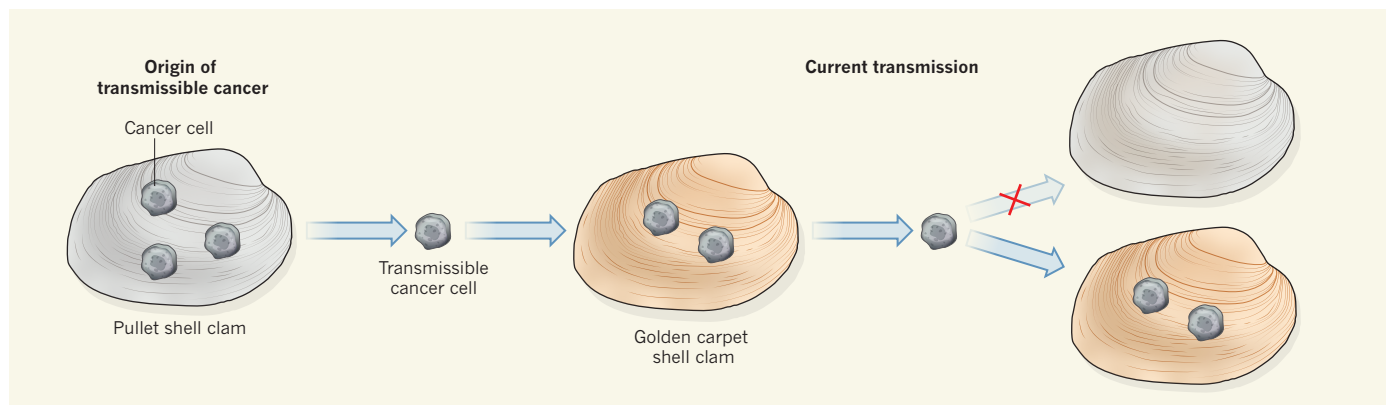
These cancers all cause a leukaemia-like disease in affected individuals called disseminated neoplasia, which had previously been observed, and which manifests as an excess of large, abnormal cells in the circulatory system. Diseased animals have thick, opaque circulatory fluid, and their tissues become clogged with invasive cancer cells<sup>5,6</sup>. The tendency for many bivalve species to develop disseminated neoplasia has been known<sup>7</sup> since the 1960s, but the underlying cause of the condition was not understood.

Metzger and colleagues performed a genetic analysis of cancer and host tissues from several individual mussels, cockles and golden carpet shell clams. They found that, in many cases, the cancer cells bore no genetic similarity to their hosts, but instead were highly similar to cancerous tissues derived from other individuals of the same bivalve species. These findings confirmed that many cases of disseminated neoplasia in bivalve species are due to horizontal transfer of living cancer cells between hosts.

A particularly unexpected finding of Metzger and colleagues' work was that DNA extracted from cancer cells in golden carpet shell clams showed no genetic match with normal DNA from this species, but instead indicated that the cancer cells originated in a different species — the pullet shell clam (*Venerupis corrugata*). Surprisingly, however, pullet shell clams — which share a habitat with golden carpet shell clams — are not known to have a high prevalence of disseminated neoplasia. Perhaps the pullet shell clam has adapted to resist infection by the transmissible cancer that first arose in a member of its own species; despite this, the cancer has survived by engrafting to a new host species (Fig. 1).

Altogether, these findings seem to paint a picture of shellfish beds around the world that are awash with microscopic cancer cells metastasizing both within and between species. Although the mechanisms of cancer transmission remain unclear, the immobile nature of these filter-feeding invertebrates suggests that the cancer cells may float through the marine environment and enter their hosts by breaching the digestive or respiratory tracts. The mode by which cancer cells exit their diseased hosts is another puzzle. Perhaps this is a passive process enabled by trauma or predation, or maybe cancer cells actively migrate out of the body by co-opting host signalling pathways. Investigating the density and viability of free-living bivalve neoplastic — and non-neoplastic — cells in the external marine environment will be an interesting area for future study.

Although disseminated neoplasia has been reported in many bivalve species, the current work and previous studies<sup>5,6</sup> reveal that its prevalence varies greatly both within and between species. Variable prevalence of bivalve transmissible cancers, particularly within localized populations, hints at a fierce,



**Figure 1 | Cancer cells can be transmitted between shellfish species.** A study by Metzger *et al.*<sup>1</sup> has found that a transmissible cancer occurring in golden carpet shell clams (*Polititapes aureus*) originated in a different species — the pullet shell clam (*Venerupis corrugata*). Although the two clam species share a habitat, the cancer is currently detected only in golden carpet shell clams, suggesting that pullet shell clams may have acquired resistance to infection by this cancer.

ongoing pathogen–host evolutionary arms race beneath the sea. Although any mechanisms of host immunity to the cancers are unknown, their elucidation will provide insight into the diversity of cancer immunological and immune-evasion processes across species. Furthermore, it is not known how frequently new disseminated neoplasias arise in bivalves; identifying the genetic changes that distinguish cancers that remain in one host from those that become transmissible may provide valuable information about the mechanisms of transmissibility.

Determining the timescales and geographical distances that underpin the evolutionary histories of transmissible cancers in bivalves will provide a greater understanding of these diseases. It is possible that, like the canine transmissible cancer<sup>8</sup>, these cancers are ancient cell lineages that have co-evolved with their hosts through the millennia; or perhaps their emergence is a relatively recent occurrence, possibly stimulated by infectious agents, environmental changes, aquaculture or other anthropogenic activities.

The potential for cancer cells to become free-living infectious agents raises questions about the implications for cancer transmission in humans. Although person-to-person transmission and survival of cancer cells has been reported during organ transplantation, pregnancy, experimental treatments and surgical accidents, such exchanges are rare and never spread beyond transfer between two individuals<sup>8</sup>. Interestingly, however, the recent discovery of tapeworm neoplastic cells that spread within their severely immunocompromised human host<sup>9</sup> consolidates Metzger and co-workers' finding that cancers can invade new host species.

The risk of cancer is inherent in multicellular organisms, and the basic evolutionary drive of this disease does not respect individual or even species barriers. Bivalve transmissible cancers provide a new model system in which to explore cancer transmission and host response. An understanding of the aetiology of disseminated neoplasias in these animals is also a boon for the aquaculture industry, providing new opportunities for

disease biomonitoring and control. The discovery of widespread transmissible cancers under the sea is an exciting conceptual advance, and opens up further avenues for cancer research. ■

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