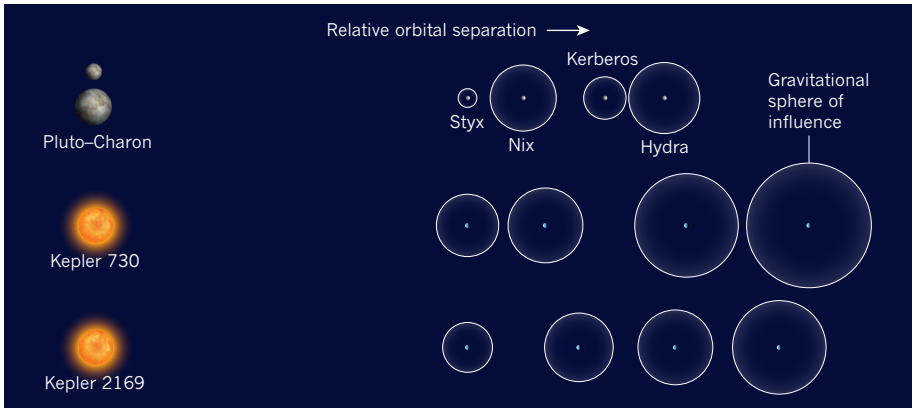

Figure 2 | Orbital architecture. The satellite system of Pluto–Charon resembles some of the exoplanet systems discovered by the Kepler space observatory. Pluto's small moons orbit the system's centre of mass clockwise; the exoplanets orbit their respective stars (Kepler 730 and Kepler 2169). For each system, the scale is set relative to the orbit of the innermost moon or planet (the relative scales vary across systems; the gap between Pluto and Charon is not on the same scale as the orbits of the moons). The dots indicate the relative positions of the moons or planets; the circles show their respective gravitational spheres of influence. Similarly to the exoplanets, the spheres of influence of Pluto's moons leave little space for other potential (as yet undiscovered) objects in intermediate orbits.

satellite formation[5,7]. Large fragments that survived the giant impact, thought to have led to the creation of the system, might have irregular shapes; satellites grown from much smaller particles might be more rounded. The authors find that the ellipsoidal shapes of the two larger moons, Hydra and Nix, seem more consistent with grown satellites than with impact fragments. Their optical reflectivity, at 40%, is similar to Charon's (36–39%), but lower than Pluto's (50–65%, which is comparable to the reflectivity of sea ice). With a reflectivity of only 4–6%, Kerberos is as dark as coal and seems out of place with such bright companions. Perhaps it is a dark fragment that was ejected during the giant impact.

It is hoped that NASA's New Horizons[8] spacecraft, due to fly by Pluto in July, will throw yet more light on these questions. Close-up images taken by the spacecraft will further constrain the sizes, shapes and reflectivities of Nix, Kerberos and Hydra, but not of Styx — it is too small to be resolved in the images. The mission's spectroscopic measurements of the relative abundances of various ices will probably yield a reflectivity for Styx, and allow comparison of the compositions of the satellites. If new satellites or rings of small particles are found, and their bulk properties established, this will provide additional information on the extent of the system. These much-anticipated observations will lead to improved theories of the formation and evolution of planets and their satellites. Linking all these results to ongoing observations of the growing population of known exoplanets will extend tiny Pluto's reach far beyond the Solar System. ■

Scott J. Kenyon *is in the Department of Solar, Stellar and Planetary Physics, Smithsonian Astrophysical Observatory, Cambridge, Massachusetts 02138, USA.*
e-mail: skenyon@cfa.harvard.edu

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CANCER

Opening LOX to metastasis

New findings implicate the enzyme lysyl oxidase (LOX), secreted by oxygen-deprived breast cancer cells, in inducing bone lesions that precede and facilitate the spread of the cancer cells to the bone. SEE LETTER P.106

NETA EREZ

Despite extensive research, breast cancer remains one of the leading causes of cancer-related deaths in women, and mortality from breast cancer is almost exclusively a result of the tumour spreading to distant organs. Bones are the most common site of metastasis associated with breast cancer, affecting up to 80% of women with metastatic disease. Bone metastases are typically incurable and encompass severe disease features, including pain, bone destruction, hypercalcaemia and debilitating skeletal-related events[1]. In this issue, Cox *et al.*[2] (page 106) establish a mechanistic link between bone metastasis of breast tumours and expression of the enzyme lysyl oxidase (LOX) by breast cancer cells.

Metastases in bones and other organs are typically diagnosed months or years after the initial diagnosis and removal of the primary tumour. This temporal lag is, at least in part, due to the fact that although disseminated tumour cells have cell-intrinsic survival and proliferative programs, they must be able to manipulate tissue cells in the new and hostile microenvironment of the metastatic organ to support their growth[3,4]. The early molecular changes at the metastatic niche are the rate-limiting step of metastasis, and understanding the mechanisms that facilitate the formation of a hospitable niche is a central challenge in cancer research.

Hypoxia (lack of an adequate oxygen supply) in the primary tumour is generally associated with increased metastases[5]. However, when Cox and colleagues performed retrospective analyses of hypoxic breast tumours from humans, they found that hypoxia was correlated with increased bone metastases only in a subtype of breast tumour that does not express the receptor for oestrogen (ER^- tumours). In an attempt to identify the factors underlying this specificity, Cox *et al.* analysed the proteins secreted by those breast cancer cells that were attracted to the bone and found that high levels of LOX were associated with bone metastases in ER^- breast tumours. LOX belongs to a family of secreted proteins that crosslink collagen fibres in the extracellular matrix (ECM), which determines the strength and structural integrity of tissues[6]. LOX has been shown to contribute to metastasis of breast cancer to lungs by modifying the ECM at the metastatic niche[6,7], but it had not previously been implicated in regulating bone homeostasis.

Using a transplantable mouse model of breast cancer that spontaneously metastasizes to bone, the authors demonstrate that LOX is secreted by hypoxic breast cancer cells and that it disrupts the balance between bone formation and destruction such that there is greater overall bone loss (resorption). These sites of damaged bone provide a favourable environment for disseminated breast cancer cells, thereby facilitating the formation of bone metastases. Moreover,

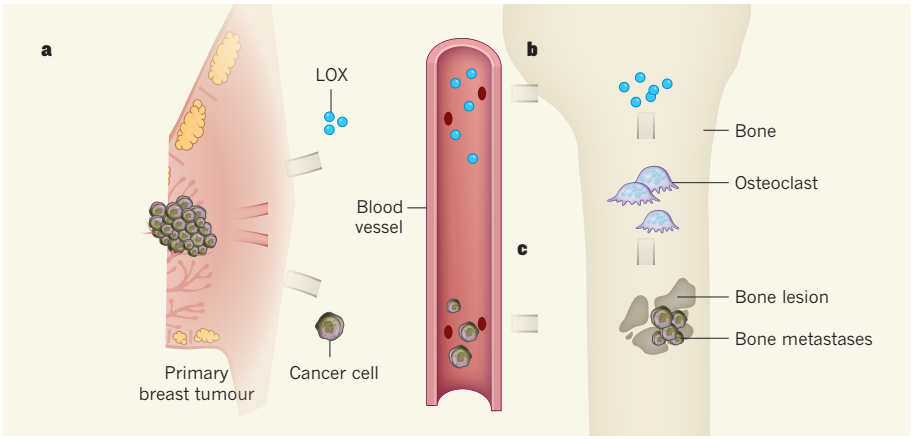

Figure 1 | Pre-metastatic niche formation in bone. **a**, Cox *et al.*[2] find that breast tumour cells that are exposed to hypoxic conditions secrete the enzyme lysyl oxidase (LOX) into the bloodstream. **b**, In bone, LOX activates cells called osteoclasts to enhance bone breakdown, resulting in the formation of bone lesions. **c**, These lesions create a pre-metastatic niche: breast cancer cells from the original tumour that are disseminated by the circulation are able to occupy this niche and form a metastatic tumour.

the authors demonstrate that such bone lesions can be created even in a tumour-free system: when they injected mice with factors secreted by hypoxic breast tumour cells, these soluble factors induced bone lesions that enhanced the formation of bone metastases by cancer cells circulating in the bloodstream. Thus, their study shows that systemic LOX, secreted by ER$^-$ breast tumours, drives the formation of a pre-metastatic niche in bones, which precedes and facilitates the formation of metastases (Fig. 1).

The pre-metastatic niche concept suggests that a hospitable microenvironment is formed in target organs before the arrival of metastatic tumour cells and enables their invasion, survival and proliferation[8]. Although the notion of tumour cells as 'seeds' that require a fertile 'soil' for their growth was suggested more than a century ago[9,10], the mechanisms that enable this soil to be prepared have only emerged gradually over recent years. It was not clear whether the earliest changes in incipient metastatic niches are accomplished systemically, by soluble factors secreted from the primary tumour[11], or by the presence of a small number of disseminated tumour cells, or through both processes. Cox and colleagues' exciting discovery provides evidence supporting the systemic nature of pre-metastatic niche formation and contributes to our understanding of systemic regulation of cancer progression and metastasis.

The study is limited by its use of only one model of transplantable mammary tumour, rather than a genetically engineered model in which the breast tumour arises in the mouse. However, there is a lack of models in immune-competent mice in which such tumours spontaneously metastasize to bones. Another limitation is an interesting issue that remains unresolved: why is the secretion of LOX by hypoxic breast cancer cells predominantly linked with bone relapse in patients with ER$^-$ breast cancer? Although hypoxia-related signalling was previously shown to drive breast cancer metastasis[5], a detailed dissection of the link between breast cancer subtype, hypoxia and tumour-cell attraction to bone is yet to be performed.

Elucidating the early interactions between disseminated tumour cells or their soluble products and their new microenvironment is an essential prerequisite for the development of effective targeted therapies. Target molecules are likely to be organ-specific, because the complex components and interactions of tissues vastly differ in different organs (such as bone versus brain). Adding to this complexity, this new study suggests that biomarkers that predict potential risk for organ-specific metastases are also specific for different tumour subtypes.

Interestingly, several studies have indicated that drugs that prevent bone destruction (such as bisphosphonates and the monoclonal antibody denosumab) are efficient co-therapies for preventing bone metastasis[1,12]. Therefore, the knowledge gained from Cox and colleagues' findings may open new horizons in the treatment of patients with breast cancer after removal of the primary tumour. Analysis of the expression of LOX may provide both a molecular tool to stratify patients by their propensity for bone metastasis and a target for preventive treatment for patients at a higher risk of bone metastasis. ■

Neta Erez *is in the Department of Pathology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, 69978 Israel.*
e-mail: netaerez@post.tau.ac.il

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HIGH-ENERGY PHYSICS

Proton smasher spots rare particle decays

The extremely rare decays of particles known as neutral *B* mesons have been observed at CERN's Large Hadron Collider. The result may be a glimpse of physics beyond that of the standard model of particle physics. SEE LETTER P.68

DARIA ZIEMINSKA

For more than three decades, physicists have been looking for the decay of the 'strange *B* meson' particle into a pair of muons, the heavy cousins of electrons. The process is incredibly rare, and harder to find than the famous Higgs particle, the discovery of which at the Large Hadron Collider at CERN, near Geneva, Switzerland, was celebrated worldwide in 2012. The standard model of elementary particle physics[1] makes an exact prediction of the number of particle-decay events researchers should observe in an experiment. Anything more than the predicted value means potential trouble for the standard model. On page 68 of this issue, researchers working on the CMS and LHCb collaborations[2] at the Large Hadron Collider describe a joint analysis of data from proton collisions that set the decay rate of the strange *B* meson at about three in one billion — in agreement with the standard-model prediction. However, they find that the decay rate of another type of