Physicists reveal random nature of metastasis

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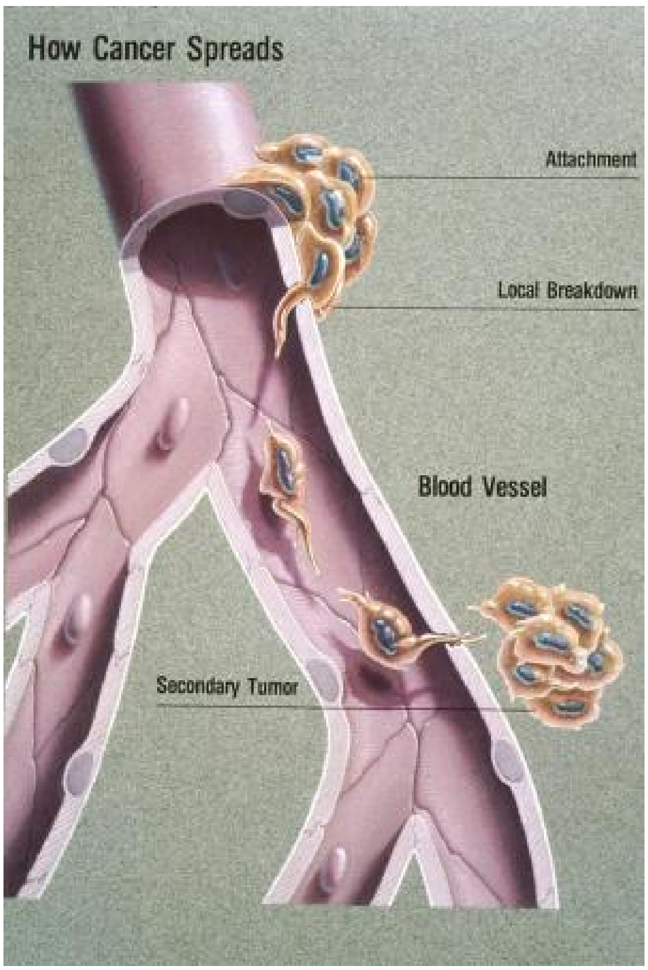

Illustration showing hematogeneous metastasis. Credit: National Cancer Institute

The spreading of a cancerous tumour from one part of the body to another may occur through pure chance instead of key genetic mutations, a new study has shown.

Physicists from the University of Dundee and Arizona State University have used a statistical model to show that the formation of a new secondary tumour—commonly known as a metastasis—could just as likely derive from "common" cancer cells that circulate in the bloodstream, as from "specialist" cancer cells.

Their results, which have been published today, 18 July, in IOP Publishing's journal *Physical Biology*, could spur new ways of thinking about cancer research, demonstrating that statistical physics may be as fundamental as complex genetics when studying the occurrence and treatment of metastatic disease.

In the conventional view of metastasis, only certain "specialist" cancer cells from the primary tumour can successfully metastasise. These cells have been compared to decathletes due to their ability to perform a number of different tasks, such as invade local tissue, enter, survive in, and leave the bloodstream, and colonise new tissue environments.

This view explains the inefficiency of metastasis and why it often takes years to cause death in most patients—it is highly improbable that a cell would possess all of the genetic mutations required to carry out all of the above functions.

In their study, the researchers also considered the possibility that a large number of "common" cancer cells that are free flowing in the bloodstream may, on very rare occasions, cause metastasis by pure chance.

The co-author of the study, Professor Timothy Newman from the University of Dundee, said: "If we use a military metaphor, a key mission can be accomplished using either a handful of highly trained special forces—in this case the specialist cells—or a huge number of untrained infantry—the common cancer cells—in which case a handful of ordinary soldiers will, by sheer luck, be successful."

The researchers used methods from statistical physics and probability theory to calculate the probability of such rare events caused by common cancer cells and the timescales of how fast these events could occur. They found that successful metastatic growth from common cells, although rare, would proceed extremely rapidly, and appear deterministic.

In particular, their results showed that in the early stages of metastatic growth, the growth of a new colony of cancer cells formed by a specialist cell with just the right amount of mutations was statistically indistinguishable from a colony that formed from a common cell which happened to "get lucky".

"If one could magically observe the early growth of a metastasis, we show there would be no way of telling from the growth dynamics whether the tumour was seeded by a special forces cell or a lucky infantryman," continued Professor Newman.

Co-author Dr Luis Cisneros added: "If we allow ourselves to consider the role of randomness then we open the door to perceiving surprising effects of the statistical fluctuations that may not be expected by naïve reasoning."

The researchers also used very crude physiological data to estimate that the rare events caused by common cells would lead to semi-stable metastases in the size range of about 50 cells, which was striking as metastases of this size have been previously observed in experiments on mice and zebrafish.

Such tiny metastases would be too small to observe using medical imaging in human patients, but could possibly be found through fine examination of biopsied tissue, which the researchers are looking to investigate in future studies.

Professor Newman concluded: "Our research is an example to the cancer research community that sometimes one needs to pause and step back from the genetic details of cancer and carefully consider in parallel other approaches and paradigms."

"Genetics is undoubtedly important in cancer, but not exclusively so, and there are equally fundamental concepts at higher levels which underpin cancer progression. Perhaps physicists, and others from outside the cancer research area, can help provide more insights along these lines, which may be game-changing."

More information: Quantifying metastatic inefficiency: rare genotypes versus rare dynamics, Cisneros L H and Newman T J 2014 *Phys. Biol* 11 046003. iopscience.iop.org/1478-3975/11/4/046003/article

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