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### **Weizmann Institute Scientists' New Technique Gets to the Root of Cancer**

In two complementary studies, Weizmann Institute scientists have developed a new method for reconstructing a cell's "family tree," and have applied this technique to trace the history of the development of cancer.

The quest to understand a cell's path of descent, called a cell lineage tree, is shared by many branches of biology and medicine as gleaning such knowledge is key to answering many fundamental questions, such as whether neurons in our brain can regenerate, or whether new eggs are created in adult females.

So far, only tree lineages of tiny organisms, such as worms, which possess only a thousand cells, or "branches," have been determined. Now, Prof. Ehud Shapiro of the Institute's Biological Chemistry, and Computer Science and Applied Mathematics Departments, together with Doctoral students Dan Frumkin and Adam Wasserstrom have developed a novel way to reconstruct, in principle, trees for larger organisms, including humans.

The human body is made of about 100 trillion cells, all of which are descendants of a single cell – the fertilized egg (zygote). Cells that have undergone a small number of cell divisions are relatively close descendants (akin to branches representing children and grandchildren etc., on a family tree), while some cells may have undergone hundreds or even thousands of divisions ("distant cell generations"). Knowing the number of cell divisions since the zygote, known as the depth of cells, would enable scientists to address questions about the behavior of the body under physiological and pathological conditions.

Until now, estimates of cell depth were based on theoretical calculations and assumptions, but Shapiro provides a practical way of determining cell depth precisely. The concept behind their new method is simple: Previous research indicated that each time a cell divides, harmless mutations are introduced, and that "cell relatives" of distant generations tend to acquire more mutations, drifting away from the original DNA sequence of the zygote. Inspired by this, the team developed a non-invasive, accurate and systematic way, involving DNA amplification and computer simulations, to quantitatively estimate cell depth on the basis of the number of mutations in microsatellites (repetitive DNA sequences), and has applied it to several cell lineages in mice.

According to the team's estimates, as reported in *PLoS Computational Biology*, the average depth of B cells – a type of immune cell – is related to mouse age, suggesting a rate of one cell division per day. In contrast, various types of adult stem cells underwent fewer divisions, supporting the notion that they are relatively quiescent.

Shapiro and Frumkin, in collaboration with Prof. Gideon Rechavi from the Sheba Medical Center and others then decided to apply this method to reconstruct, for the first time, the family tree of a cancer cell. “Despite several decades of scientific research, basic properties of the growth and spread of tumor cells remain controversial. This is surprising, since cancer is primarily a disturbance of cell growth and survival, and an aberrant growth pattern is perhaps the only property that is shared by all cancers. However, because the initiation and much of the subsequent development of tumors occurs prior to diagnosis, studying the growth and spread of tumors seems to require retrospective techniques and these have not been forthcoming,” explains Shapiro.

Therefore, by reconstructing a cancer cell lineage tree and performing an analysis of mutations accumulated in the cells, scientists would be able to trace back and reveal several aspects of the tumor’s developmental history. Shapiro: “We intend to apply this method to study key questions in human cancers, including when and where does a tumor initiate? The progression from pre-malignant to malignant states. At what stage does metastasis occur? Can the depth of tumor cells serve as a prognostic marker for cancer severity? And does chemotherapy target a subset of cells characterized by distinct lineage features (e.g. greater depth)?”

So far, their findings, featuring on the cover of the July 15<sup>th</sup> issue of *Cancer Research*, show that cancer cells (extracted from tissue sections of a mouse lymphoma by laser micro-dissection) had almost double the number of branched generations (i.e., had divided almost twice as many times) compared to adjacent normal lung cells in the same amount of time. They were also able to calculate the age of the tumor and characterize its growth pattern. Further analysis was sufficient to corroborate the long-standing hypothesis on the single-cell origin of cancer.

The scientists believe cell lineage studies of cancer can greatly enhance our understanding of, and eventually lead us to the root of cancer.

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*Prof. Shapiro is the incumbent of the Harry Weinrebe Chair of Computer Science and Biology*

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