Treating cancer as a chronic disease

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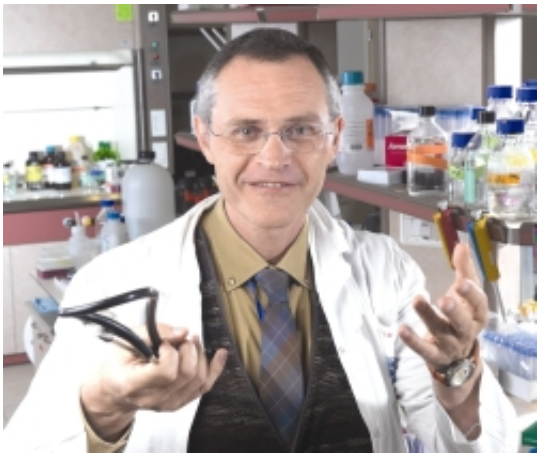

Professor Karl Skorecki

New research from the Technion-Israel Institute of Technology Rappaport Faculty of Medicine and Research Institute and the Rambam Medical Center may lead to the development of new methods for controlling the growth of cancer, and perhaps lead to treatments that will transform cancer from a lethal disease to a chronic, manageable one, similar to AIDS.

By placing cancer cells in and near a growth developed from a population of human stem cells, scientists have demonstrated that the cancer cells grow and proliferate more robustly when exposed to human cells than they do in a typical petri dish or mouse model. The cancer cell population is also more diverse than had previously been understood. The research was published in the current advanced online issue of the

journal *Stem Cells*. Maty Tzukerman, Rambam senior research scientist and the project leader and senior co-author on the report, says that this model will facilitate targeted drug discovery aimed at blocking the cancer cell self-renewal process.

Previous studies have determined that some tumor cells appear to be differentiated, while others retain the self-renewal property that makes cancer so deadly. According to Technion Professor Karl Skorecki, director of Medical Research and Development at Rambam Health Care Campus and senior co-author on the report, this new research attempts to understand how cancer grows, and to find ways to halt the runaway replication.

In order to mimic the human cancer environment as closely as possible, the research team developed a teratoma - a tumor made of a heterogenous mix of cells and tissues - by enabling the differentiation of human embryonic stem cells into a variety of normally occuring human cell lines on a carrier mouse. The human cellular teratoma constitutes a new platform of healthy human cells for monitoring the behavior and proliferation of human cancer cells.

For this study, the team took cells from one woman's ovarian clear cell carcinoma and injected them either into or alongside the human stem cell-derived environment. "We noticed very early on, rather strikingly, that the human cancer cells grow more robustly when they are in the teratoma environment compared to any other means in which we grew them, such as in a mouse muscle or under the skin of a mouse," says Skorecki.

The scientists were able to tease out six different kinds of self-renewing cells, based on behavior - how quickly they grow, how aggressive they are, how they differentiate - and on their molecular profile. This was a previously unknown finding, that one tumor might have such a diversity

of cells with crucial fundamental growth properties. Tzukerman explains that the growth of the cancer cell subpopulations can now be explained by their proximity to the human cell environment.

The researchers cloned and expanded the six distinct cell populations and injected them into the human stem cell teratomas. One key observation is that some cells, which were not self-replicating in any other model, became self-replicating when exposed to the human cells.

Skorecki said that while he wasn't surprised that the human environment affected the growth, he was in fact surprised by the magnitude of the effect: "We've known for years now that cancers are complex organs, but I didn't think the power of the human stem cell environment would be so robust, that it would make such a big difference in how the cells were grown."

The researchers point out that they do not yet know the cues that particularly enhance the cancer's proliferation, and the team is now working on isolating the factors from human cells that promote such plasticity and self-renewing properties. The scientists explain that this may eventually allow physicians to manage cancer as a chronic disease: instead of one therapy against the entire tumor, researchers may develop a method to tease out the variety of self-renewing cell lines of a particular tumor and determine what allows each to thrive, then attack that mechanism.

Skorecki and Tzukerman say that an important next step in this line of cancer research will be to identify and develop ways of blocking the factor or factors that promote this essential self-renewing property of cancer, thus relegating many forms of cancer to controllable, chronic diseases.

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