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Scientists explain the persistence of melanoma through 'dynamic stemness'

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Scientists at The Wistar Institute offer a new explanation for the persistent ability of melanoma cells to self-renew, one of the reasons why melanoma remains the deadliest form of skin cancer. The concept of the "dynamic stemness" of melanoma can explain why melanoma cells behave like both conventional tumor cells and cancer stem cells.

The researchers write in the May 14 issue of the journal *Cell* that—contrary to other published reports—melanoma does not appear to follow the hierarchic cancer stem cell model, where a single malignant "mother cell" both reproduces to produce new mother cells and differentiates to produce the bulk tumor population. Instead, all melanoma cells equally harbor cancer stem cell potential and are capable of inducing new tumors. Their findings reveal the unique biology of melanoma, and suggest that melanoma requires a new therapeutic approach.

"Targeting only the bulk tumor population, as most conventional anticancer therapies do, is pointless in melanoma, in that each cell can act as a seed for the tumors to rebound," said Meenhard Herlyn, D.V.M., D.Sc., professor and leader of Wistar's Molecular and Cellular Oncogenesis Program. "The other implication is that we should stop hunting for a cancer stem cell, because it won't be there."

The traditional view of cancer holds that cancers arise following a random accumulation of malignant events, e.g. mutations, gradually imparting enough growth advantages that a cell can grow unchecked.

Over the last decade, scientists have developed a cancer stem cell concept that explains how the slow growth and persistence of mother cells allow tumors to persist following treatment. Melanoma, for one, seems to follow a third path, dynamic stemness, where the stem cell-like behavior is not confined to mother cells alone, Herlyn says.

In the study, Herlyn and his colleagues describe a slow-growing subpopulation of melanoma tumor cells, defined by the protein JARID1B, which is required for tumor maintenance. Genetically blocking the ability of cells to express—or produce—this protein "exhausts" the tumor, preventing its proliferation. Yet unlike classic cancer stem cells, this subpopulation is highly plastic: JARID1B-expressing cells can turn off the gene, and JARID1B-non-expressing cells can turn it on.

Their findings suggest that melanoma requires a two-pronged therapeutic approach, says Herlyn. One is needed to target the bulk of the tumor, while another one should specifically target the slow-growing, JARID1B-positive subpopulation. "It's a dual therapy that we are proposing," said Herlyn.

According to the study's lead author, Alexander Roesch, M.D., of the Regensburg University Medical Center in Germany and a visiting scientist in the Herlyn laboratory at The Wistar Institute, the growth could explain the disease's notorious therapy resistance. "A slow-growing JARID1B-positive subpopulation of tumor cells, immune to most therapies, can spontaneously convert to a fast-growing JARID1B-negative population, which can rapidly replenish the tumor," Roesch said.

The present study arose when Roesch discovered a link between the potential of JARID1B to decrease proliferation of melanoma cells and control stemness. He decided to see whether JARID1B could be a

marker of slow growing melanoma stem cells. Initially, the results were promising, he says. JARID1B-expressing cells were slow-growing (as stem cells often are), and rare, accounting for about 5 percent of the tumor population. "At this point we were really happy because we thought we had found a cancer stem cell marker," Roesch said.

But then, two unexpected results occurred. First, Roesch found that all melanoma cells were equally capable of initiating tumors in a mouse model, regardless of whether they expressed JARID1B or not. Second, he found that JARID1B expression did not conform to the traditional model of stem cell development - cells that expressed the gene could turn it off, and cells that didn't, could turn it on. In other words, the gene's expression was plastic, rather than stable. "Basically, our data suggest that every melanoma cell can serve as source for indefinite replenishment of the tumor," said Roesch.

At the moment, the researchers do not suggest that the cancer stem cell model is wrong in any other tumors; their results apply only to melanoma, which may represent a special case.

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