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Blood cancer: Poorer prognosis due to genetic diversity of tumor cells

Blood cancers such as acute myeloid leukemia (AML) commonly exhibit the loss, exchange, or extra copies of chromosomes or portions of them. The blood of patients often contains various "daughter clones" of cancer cells with diverse chromosomal defects. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and the University Hospitals of Heidelberg and Dresden have now shown for the first time that the presence of daughter clones in AML indicates an unfavorable progression of the disease.

Tumors are considered to be "clones", i.e., common descendants of a single, mutated cell. However, cancer cells are not as uniform as one might expect from a single clone parent. Analyses of individual cells from a single tumor have often revealed an amazing genetic diversity. The majority of the differences in the genetic material affect only individual building blocks of genes. However, in many cancers, patients' tumor cells also differ from each other in terms of large aberrations of chromosomal structure. Losses, exchanges or extra copies of entire chromosomes or parts of them can be seen under the microscope. So-called daughter clones (subclones) with diverging chromosome aberrations are particularly common in blood cancers.

"Chromosomal aberrations are frequent in acute myeloid leukemia (AML)," says Professor Dr. Alwin Krämer, who leads a Clinical Cooperation Unit of the German Cancer Research Center and Heidelberg University Hospital. "We also find distinct subclones of cancer cells in many patients. However, it was unknown whether this has any bearing on the progression of the disease in AML."

As a project of the Study Alliance Leukemia (SAL), Krämer and his coworkers have studied the appearance of the chromosomes, called the "karyotype", of cancer cells in more than 2,600 AML patients. The researchers detected chromosomal abnormalities in approximately 50 percent of the cases. In about one third of these, they found subclones that were distinct from each other in terms of chromosomal aberrations.

In most cases it was possible to trace the ancestry of the various clones. They were mostly "daughters" that could be distinguished from the mother clone; they had undergone a new, additional chromosomal abnormality. In some cases, a single mother clone had split off into three or more offspring clones. However, the researchers also found complex karyotypes where multiple daughter clones with various chromosomal abnormalities had arisen.

A statistical evaluation showed that the presence of subclones is associated with an unfavorable progression of the disease. In patients classified as high-risk, based on specific genetic characteristics, subclone formation turns out to be an additional, independent risk factor for an unfavorable progression. The detection of heterogeneous subclones, particularly in AML patients under 60 years of age, is therefore an independent prognostic factor for physicians.

"The formation of subclones helps tumors survive," Alwin Krämer explains. "They enlarge their genetic spectrum, thereby increasing the chances that they will resist chemotherapy." This hypothesis is supported by the observation that patients with an extremely large number of distinct daughter clones have an even poorer prognosis than patients who have only a few.

“These patients particularly benefit from stem-cell transplantation,” says Krämer. This type of treatment is based on immunological mechanisms, and leukemia cells seem to have greater difficulty escaping it by genetic diversification than they do when patients undergo chemotherapy.

For the first time, this analysis of AML karyotypes confirms the link between the presence of daughter clones, i.e., a tumor’s genetic diversity, and a cancer prognosis. “We assume that this phenomenon may also play a role in the ultimate health effects of other types of cancer for which heterogeneous karyotypes have been described.”

Tilmann Bochtler, Friedrich Stölzel, Christoph E. Heilig, Christina Kunz, Brigitte Mohr, Anna Jauch, Johannes W.G. Janssen, Michael Kramer, Axel Benner, Martin Bornhäuser, Anthony D. Ho, Gerhard Ehninger, Markus Schaich and Alwin Krämer for the Study Alliance Leukemia (SAL): Clonal heterogeneity as detected by metaphase karyotyping is an indicator of poor prognosis in acute myeloid leukemia. Journal of Clinical Oncology 2013, DOI: 10.1200/JCO.2013.50.7921

A picture for this press release is available on the Internet at:
http://www.dkfz.de/de/presse/pressemitteilungen/2013/images/Kraemer_AML_2.jpg
Caption: Bone marrow smear of acute myeloid leukemia. Alwin Krämer, German Cancer Research Center

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