The genomic landscape of chronic myelomonocytic leukemia and its modulation by demethylating agents

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ABSTRACT

The response of chronic myelomonocytic leukemia patients to hypomethylating agents, either 5-azacytidine or 5-aza-2’-deoxycytidine, is transient. Since the mechanism of action of these drugs is not yet clear, we explored their genetic and epigenetic effects. We first performed a comprehensive analysis of the genome of 66 chronic myelomonocytic leukemia cases using whole exome (N=49) or whole genome (N=17) sequencing for paired leukemic-control DNA, with validation of recurrently mutated genes in 180 samples. Then, serial analysis of whole exome sequence in 17 cases was completed with serial RNA sequencing and DNA methylation analysis in 9 cases, including patients treated or not with hypomethylating agents. Chronic myelomonocytic leukemia genomes have an average of 14 +/- 5 mutations in coding sequences, 26 genes being mutated in two or more samples. Newly identified recurrent mutations were in *PHF6, DOCK2, NF1, ABCC9, HUWE1, and ASXL2*. A computational framework for extracting mutational signatures identified the signatures of three mutational processes. Serial sequencing of sorted monocyte DNA demonstrated the slow and linear accumulation of new gene mutations in the leukemic clone. Hypomethylating agents did not decrease the mutation allele burden in peripheral blood cells of responding patients. Dramatic changes in DNA methylation and gene expression were detected in responding patients, not in those with a stable disease. These results strongly argue for a dominant epigenetic activity of hypomethylating agents, without cytotoxic activity.

ABOUT THE SPEAKER

Eric Solary, 59 year-old, is MD, full-Professor in Haematology at Paris-Sud University, head of research in Gustave Roussy Comprehensive Cancer Center, and director of team 4 in Inserm Unit 1170 « Normal and pathological haematopoiesis ». He is teaching clinical and biological haematology as well as cell biology at Paris-Sud 11 faculty of Medicine. He is the former Scientific Director of the Canceropole Ile de France and the present President of the Scientific Committee of the Foundation ARC, a charity dedicated to cancer research funding. Eric Solary’s research has been dedicated initially to leukemic cell resistance to cytotoxic drugs, then cell death mechanisms and the link between cell death and differentiation in the hematopoietic system. His current research is focused on monocyte response to cytokines and chronic myeloid malignancies, especially chronic myelomonocytic leukemia.

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