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Overcoming CML acquired resistance: Impact of cell differentiation and CD38 expression

Wen Yong Chen
Beckman Research Institute, USA

Acquired resistance through genetic mutations is a major obstacle in targeted cancer therapy, but the underlying mechanisms are poorly understood. Using chronic myeloid leukemia (CML) as a disease model, we studied mechanisms of CML acquired resistance to tyrosine kinase inhibitors. By examining genome-wide gene expression and Exome sequencing of CML cells before and after developing genetic resistance, we identified key changes in cellular differentiation status when CML cell acquired genetic resistance. Forced differentiation overcame CML acquired resistance by altering CD38 expression and cellular NAD metabolism, which led to inhibition of SIRT1 functions and error-prone DNA damage repair in CML cells and blocking mutation acquisition. Our study sheds novel insight of cancer acquired resistance and has clinical implication of using differentiation agents to overcome drug resistance to tyrosine kinase inhibitors.

WeChen@coh.org