29ème congrès du CHO
11 au 14 octobre 2023
Giens, Var, France

POSTER 2: CDK6 inhibition unlocks the vitamin D differentiation response in AML

Antonia Boudet[1], Lise Brault[1], Edwige Voisset[1], Paraskevi Kousteridou[1,], Sébastien Letard[1], Sophie Lopez[1], Paulo De Sepulveda[1]

1 : Centre de Recherche en Cancérologie de Marseille - Aix Marseille Université, Institut Paoli-Calmettes, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Centre National de la Recherche Scientifique : UMR7258, Institut National de la Santé et de la Recherche Médicale : U1068, Institut Paoli-Calmettes : UMR7258, Aix Marseille Université : UM105

Acute Myeloid Leukemia, the most common acute leukemia in adults, has a 5-year survival of 35–40% in patients under 60 years and 5–15% in older patients. It is a heterogeneous disorder due to acquired genetic modifications by stem and progenitor cells. As cells accumulate mutations, early immature myeloid cells fail to differentiate and eventually invade the bone marrow, interfering with the renewal of mature blood cells. Relapse and resistance to standard treatments are the primary causes of mortality, largely attributed to the genetic and phenotypic heterogeneity of leukemic cells. Therefore, there is a crucial need for novel treatments that target all the diverse type of cells of the leukemia.

Regardless of their mutation status, all AML cells are dependent on CDK6 (cyclin dependent kinase 6), a kinase involved in cell cycle regulation. Calcitriol, the active form of vitamin D, promotes normal hematopoietic differentiation. However, in the context of AML, cells are largely insensitive to calcitriol. In this work, we describe unique features of the association of CDK6 inhibition with calcitriol on AML cells.

CDK6 inhibitors combined with calcitriol synergize to increase monocytic differentiation, and decrease the pool of leukemic progenitors on various AML cell lines. Furthermore, this combination is effective on primary samples from patients. Transcriptome analysis confirmed the activation of differentiation signatures upon treatment, as well as the activation of other cellular processes. The mechanism of action of the synergy observed with combined treatment

seems to rely on chromatin remodeling, allowing the restoration of the vitamin D response in AML cells. Our project aims to redefine the use of vitamin D and the repositioning of CDK4/CDK6 inhibitors in the context of AML.