Секция «Экспериментальные исследования»

Inhibition of CDK8/19 Transcriptional Kinases As a New Therapeutic Strategy in Acute Myelogenous Leukemia

Научный руководитель – Shtil Alexander Albertovich

Rodionova Maria Dmitrievna
Student (master)
Санкт-Петербургский национальный исследовательский университет информационных технологий, механики и оптики, Санкт-Петербург, Россия
E-mail: demettoria@gmail.com

The acute myelogenous leukemia (AML) is a rare although dangerous malignancy with a high mortality rate. Elderly (>60 years old) patients comprise a sizable cohort. Chemotherapy using anthracyclines and cytarabine frequently causes general toxicity which is especially intolerable in these patients. AML has been considered a tumor pathogenetically related to super-enhancers (SE), the genome regions enriched with transcription factors and Mediator complexes [1]. The kinase module of Mediator is represented by the cyclin dependent kinase 8 (CDK8) or its paralog CDK19, the enzymes that promote RNA polymerase II traverse along the DNA template. In agreement with the deleterious cellular effects of inactivation of SE associated proteins, treatment with submicromolar concentrations of CDK8/19 inhibitors Senexin B (SenB) or 15w caused an apoptotic death of MV-4-11 and KG-1 human AML cells. Apoptosis developed rather slowly, with caspase activation, poly(ADPriboso)polymerase cleavage and DNA fragmentation (accumulation of subG1 events as determined by flow cytometry) by day 5. Importantly, the two CDK8/19 inhibitors prevented the emergence of resistance to cytarabine in the course of co-treatment of MV-4-11 cells. Furthermore, SenB and 15w synergized with cytarabine in killing MV-4-11 cells. Given that CD8/19 inhibitors are well tolerated in the adult organism, combinations of these drug candidates with the conventional chemotherapeutic agents emerge as a new mechanism-based approach to AML treatment. With these combinations a similar antitumor efficacy is achievable with lower doses of cytarabine. In contrast, the Kasumi-1 AML cell line was intrinsically insensitive to SenB and 15w regardless of the expression of the wild type CDK8. These observations set the stage for the search of a molecular determinant(s) of AML responsiveness to CDK8/19 inhibition. Once such a predictor is identified, the use of non-toxic CDK8/19 antagonists in selected patients is expected to be prospective for prevention of establishment of drug resistance as well as for attenuating the side effects of conventional cytotoxic chemotherapy.

This study was supported by the Megagrant (Agreement no. 14.W03.31.0020 between the Ministry of Science and Education of the Russian Federation and Institute of Gene Biology, Russian Academy of Sciences).

References

1) Pelish H.E. et al. Mediator kinase inhibition further activates super-enhancer-associated genes in AML // Nature. 2015. № 526. P. 273–276.