células foram transduzidas com shRNA mediado por lentivírus. A viabilidade celular foi determinada pelo ensaio de MTT, clonogenicidade pelo ensaio de formação de colônias autônomas e apoptose por marcação com anexina V/PI e citometria de fluxo. Expressões de genes e proteínas foram avaliadas por qPCR e Western blot. **Resultados:** A expressão de *STMN1* está aumentada em amostras de pacientes com LPA ($p < 0,05$). A expressão diferencial de *STMN1* está associada a processos de ligação a macromoléculas, sinalização mediada por receptores celulares e transdução de sinal. A GSEA identificou 23 assinaturas associadas à expressão diferencial de *STMN1*, entre elas, alvos de E2F, alvos de MYC, ponto de verificação G2/M, reparo de DNA, glicólise e sinalização PI3K/AKT/mTOR. *STMN1* é altamente expressa em progenitores hematopoiéticos iniciais e reduz durante a diferenciação celular, incluindo subpopulações granulomonocíticas. A fosforilação de STMN1 é predominante no *pool* de células enriquecidas com mitose. Em células NB4 e NB4-R2, o silenciamento de STMN1 diminui o crescimento clonal autônomo ($p < 0,05$), mas não afeta a apoptose e a diferenciação induzidas por ATRA. As células NB4 e NB4-R2 apresentam alta sensibilidade ao paclitaxel (IC_{50} de 3,6 nM e 1,8 nM, respectivamente). O crescimento clonal autônomo é significativamente reduzido pelo paclitaxel ($p < 0,05$), o qual aumenta os níveis de marcadores de estabilidade dos microtúbulos (acetil-α-tubulina) e de dano em DNA (γ-H2AX e CDKN1A). **Discussão:** A alta expressão de *STMN1* em pacientes com LPA foi confirmada em uma coorte independente. Os dados da análise genômica indicam que a expressão de STMN1 está associada a assinaturas gênicas relacionadas à proliferação e ao metabolismo em LPA. Nossos resultados destacam a contribuição de STMN1 para clonogenicidade de células leucêmicas. **Conclusão:** Em resumo, nosso estudo adiciona novos *insights* sobre as funções da STMN1 e dinâmica de microtúbulos em LPA. **Financiamento:** CNPq, CAPES e FAPESP.

https://doi.org/10.1016/j.htct.2021.10.305

THE MCL-1 INHIBITOR AZD5991 DISPLAYS A PROMISING TARGETED THERAPY FOR ACUTE MYELOID LEUKEMIA

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Aims: MCL-1 protein is an anti-apoptotic member of BCL-2 protein family. In hematological neoplasms, increased MCL-1 gene expression or protein activity is related to disease relapse, poor prognosis and resistance to chemotherapy, especially to Venetoclax, an BCL-2 inhibitor. The present study aimed at evaluating the *MCL-1 gene* expression in AML patients as well as investigating the effects of MCL-1 protein inhibition in myeloid cells. **Methods:** Analysis of *MCL-1 gene* expression was performed in a cohort of 286 AML patients (OHSU/Nature 2018 study at cbioportal.org). Leukemia myeloid cell lines (U937, KG1a, OCI-AML3) were treated with increasing concentrations of the MCL-1 inhibitor compound AZD5991 (AstraZeneca) for 48, 72 and 96h for determination of the 50% inhibiting concentration (IC_{50}). Apoptosis (annexin-V stain), reactive oxygen species (ROS) production (DFCHA dye) and autophagy (acridine orange dye) were assessed by flow cytometry, after 48h of treatment. Coculture assays were performed by adding leukemia cells onto a monolayer of HS5 mesenchymal stromal cells, followed by treatment with AZD5991 for 48h. Statistical analyzes were performed using ANOVA, Mann-Whitney or Kruskal Wallis tests. *p-value* < .05 was considered significant. **Results:** Increased *MCL-1 gene* expression in AML patients with adverse cytogenetic risk was observed when compared to patients with favorable or intermediate cytogenetic risk ($p < .001$). All leukemia cell lines showed dose and time-dependent sensitivity with AZD5991. IC_{50} values of 4.3, 3.4 and 9.2μM in U937; 20.0, 15.2 and 14.9μM in KG1a; and 550, 380 and 420nM in OCI-AML3, for 48, 72 and 96h, respectively. Treatment with AZD5991 (0.5-20μM) in OCI-AML3, U937 and KG1a cells significantly reduced cell viability (69.2%, 50.3%, 40.6%) and increased apoptosis (68.2%, 90.1%, 92.2%) rate in a time and dose-dependent manner, with greater intensity in OCI-AML3 cells. AZD5991 was able to reduce ROS production at 15.1% and 17.2% in U937, 10.3% and 5.6% in KG1a, 59.4% and 45.8% in OCI-AML3, in monoculture and coculture, respectively ($p < .05$). Similarly, there was a reduction in the formation of acidic vesicles (autophagic process) at 43.0% and 19.0% in U937, 40.5% and 19.0% in KG1a, 62.6% and 18.8% in OCI-AML3, in monoculture and coculture, respectively ($p < .05$). Increased cell percentage in G0/G1 phases of cell cycle was also observed. Western blot analyses showed decreased MCL-1, Bax and Bak and increased Bim. **Discussion and conclusion:** MCL-1 overexpression is related with AML progression, and associated with poor prognosis (Li et al. Onco Targets Ther. 2019;12:3295-3304). Our analysis from OHSU data bank showed that patients with adverse cytogenetic risk presented higher *MCL-1* gene expression that could induce resistance to pharmacological therapies. Our *in vitro* studies demonstrated that the MCL1 inhibitor AZD5991 induced apoptosis and reduced viability of leukemia cells, possibly by MCL-1-Bak complex disruption and subsequent Bak-dependent mitochondrial apoptotic pathway activation. The diminished MCL-1 availability in mitochondria, probably caused lower ROS production and impaired autophagy (Mukhopadhyay et al. Apoptosis. 2014;19:555-66). Therefore, these findings provide important tools for further investigations and highlight that MCL-1 inhibitor could be a promising compound for AML treatment due to its potent antitumor activity and may represent a potential therapeutic strategy. **Funding:** FAPESP e CNPq.

https://doi.org/10.1016/j.htct.2021.10.306