Flavins-induced Cell Cycle Arrest and Apoptosis of Human Myeloid Leukemia Cells

Souza, A.C.S.[1]*; Santos, V.G.*[1]*; de Jesus, M.B.* [1]*; de Paula, E.* [1]*; Aoyama, H.* [1]*; Ferreira, C.V.* [1]

[1]Departamento de Bioquímica, Instituto de Biologia, UNICAMP, Campinas, SP. email: anacss@yahoo.com

Flavins are known to be versatile compounds that function as electrophiles and nucleophiles, with covalent intermediates of flavin and substrate frequently involved in catalysis. Another important characteristic is the photosensitizer action of flavins (riboflavin and FMN). The photochemical aspects of flavins involve two major reactions, i.e., normal photolysis and photoaddition which produce three photoproducts: lumichrome, formyllumiflavin and lumiflavin. The aim of this work was to evaluate the effect of flavin photoproducts on human myeloid leukemia (HL60) cells viability, cell cycle and apoptosis induction. For this purpose the riboflavin or FMN were irradiated with UV-light and their photoproducts were tested. Our results show that flavin photoproducts presented an expressive cytotoxic effect on HL60 cells, as demonstrated by the MTT reduction assay (IC50 values of 5 and 10 μM for FMN and riboflavin, respectively). In order to increase the riboflavin solubility, this compound was complexed with beta-cyclodextrin. The complexation increased the solubility of riboflavin in the culture medium but did not affect the photoproducts formation after UV-irradiation, once we observed an IC50 value similar to that of free riboflavin (15 μM). Flavin photoproducts induced cell cycle arrest in HL60 cells treated for 24h. We observed overexpression of p21 and downregulation of proliferating cell nuclear antigen (PCNA), two proteins that control cell cycle progression. Differential activation of caspases was detected: activation of caspase 3 was about 4-fold higher than the activation of caspase 9 when the cells were treated with 10 μM of photoproducts. This result suggests that the participation of mitochondria in the apoptosis cascade activation by the photoproducts was not predominant and probably death receptor could also be involved. Our results suggest that riboflavin, FMN as well as their photoproducts could be promising candidates in the leukemia chemotherapy.

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