Fludarabine induced changes in p63 and p73 expression and p53 protein binding partners

INTRODUCTION

The critical requirement for p53 in determining sensitivity to fludarabine is highlighted by the extremely poor response rates of CLL patients with mutated p53 to fludarabine-based regimens. The p53 family includes two other transcription factors, p63 and p73, with significant sequence homology to p53 and overlapping functions in drug induced apoptosis (1). However, it is clear that in CLL, p63 and p73 do not adequately compensate for a lack of p53 in mediating sensitivity to fludarabine.

The aim of this study was to investigate the effects of fludarabine nucleoside (2-FaraA) treatment on the abundance of p53, p63 and p73 in the three sub-cellular compartments (nucleus, mitochondria and cytoplasm) in model cell lines with wild-type p53 (RAJI, Burkitt lymphoma and IM9, lymphoblastoid) or mutated p53 (MEC1, CLL and U266, mieloma). In addition, the binding partners of p53 were also investigated in Raji cells before and after treatment.

METHODS

RESULTS

CONCLUSIONS

Table 1: p53 binding partners of p53 in Raji cells with no 2-FaraA

Table 2: p53 binding partners in Raji cells with 2-FaraA (3 µM, 24 h)

Cell growth, 2-FaraA treatment, was h & lysis

Cellular tumor antigen p53 Tumor suppressor

H2A histone family, member Z Suppresses the p53 and p21 transcription and senescence responses.

Receptor for activated C kinase 1 (Rack1) Tumor suppressor

UBiquitin C Ubiquitination

Topoisomerase (DNA) I The reaction catalyzed by topoisomerases leads to the conversion of one topological isomer of DNA to another

Glucose-6-phosphate dehydrogenase , the first and rate-limiting enzyme of the PPP, and prevents the formation of the active dimer

p53, inhibits the pentose phosphate pathway (PPP). Through the PPP, p53 suppresses glucose consumption, NADPH production and biosynthesis. The p53 protein binds to glucose-6-phosphate dehydrogenase and enhances p53 translation in response to ultraviolet light irradiation

Enhances p53 translation in response to ultraviolet light irradiation

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Suppresses the p53 and p21 transcription and senescence responses.

UV irradiation p53 activates transcription of the human nicotinamide ribonucleotide transhydrogenase, the first and rate-limiting enzyme of the PPP, and prevents the formation of the active dimer

Required for DNA recombination, repair and replication. The activity of RP-A is mediated by single-stranded DNA binding protein (by similarity)

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Topoisomerase (DNA) II alpha Tumor suppressor

Ubiquitin C Ubiquitination

Phosphoprotein B23, numatrin

Topoisomerase (DNA) II alpha Tumor suppressor

Nucleophosmin (nucleolar phosphoprotein B23, numatrin)

Complement component (3b/4b)

Heat shock protein 90kDa alpha (cytosolic), class A member 1 Molecular chaperone, has ATPase activity (by similarity)

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