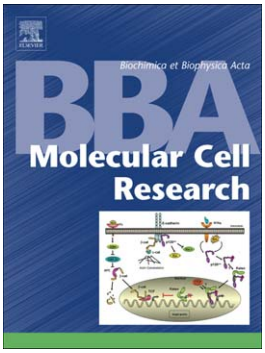

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Melanoma antigen-D2: a nucleolar protein undergoing delocalization during cell cycle and after cellular stress

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ABSTRACT

Melanoma antigen D2 (MAGE-D2) is recognized as a cancer diagnostic marker, however it has poorly characterized functions. Here, we established its intracellular localization and shuttling during cell cycle progression and in response to cellular stress. In normal conditions, MAGE-D2 is present in the cytoplasm, nucleoplasm and nucleoli. Within the latter, MAGE-D2 is mostly found in the granular and the dense fibrillar components, and it interacts with nucleolin. Transfection of MAGE-D2 deletion mutants demonstrated that Δ203-254 leads to confinement of MAGE-D2 to the cytoplasm, while Δ248-254 prevents its accumulation in nucleoli but still allows its presence in the nucleoplasm. Consequently, this short sequence belongs to a nucleolar localization signal. MAGE-D2 deletion does not alter the nucleolar organization or rRNA levels. However, its intracellular localization varies with the cell cycle in a different kinetic than nucleolin. After genotoxic and nucleolar stresses, MAGE-D2 is excluded from nucleoli and concentrates in the nucleoplasm. We demonstrated that its camptothecin-related delocalization results from two distinct events: a rapid nucleolar release and a slower phospho-ERK-dependent cytoplasm to nucleoplasm translocation, which results from an increased flux from the cytoplasm to nucleoplasm. In conclusion, MAGE-D2 is a dynamic protein whose shuttling properties could suggest a role in cell cycle regulation.

Key words: Melanoma antigen protein; nucleolus; cell cycle; cellular stress; camptothecin; MAP kinases.

Abbreviations: CPT, camptothecin; CTA, cancer/testis antigen; DFC, dense fibrillar component; DRB, 5, 6-dichloro-1-beta-D-ribofuranosylbenzimidazole; eGFP,