ADVERSE DRUG REACTIONS, INCLUDING SJS, TEN

UPREGULATION OF PLASMA EXOSOMAL MIR-200A-3P CONTRIBUTES TO EPIDERMAL NECROLYSIS IN SEVERE DRUG ERUPTIONS

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Introduction: Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are acute cutaneous adverse drug reactions. Although one of the primary histologic features of SJS/TEN is keratinocyte apoptosis, its exact mechanism remains unknown.

Objectives: We investigated the role of plasma exosomal-derived microRNAs (miRNAs) in the pathogenesis of severe drug eruptions and evaluated the possibility that miRNA can be a disease marker.

Materials and Methods: Exosome-derived miRNAs were isolated and characterized from plasma of patients. Deep sequencing analyses were performed to identify pathogenic miRNAs. The results were confirmed with quantitative real-time PCR, in situ hybridization, transient transfection of small interfering RNAs (siRNA) or miRNA mimics into cultured keratinocytes, flow cytometry, immunoblotting, luciferase assay and immunohistochemistry.

Results: Deep sequencing analysis and real-time PCR using plasma exosomal-derived miRNAs demonstrated that the miR-200a-3p level was increased in the patients with SJS/TEN and were correlated with areas of skin erythema or erosion in patients with drug eruptions. Plasma-derived exosomes from patients were internalized by keratinocytes and promoted the induction of apoptosis. Additionally, transfection of miR-200a-3p mimic into keratinocytes resulted in increased induction of apoptosis. The miR-200a-3p mimic also downregulated the expression of mucosa-associated lymphoid tissue 1 (MALT1). A luciferase assay with the MALT1 3' untranslated region showed MALT1 is directly targeted by miR-200a-3p. Transfection with MALT1 siRNA induced keratinocyte apoptosis and caspase activity. Furthermore, miR-200a-3p induced endoplasmic reticulum (ER) stress characterized by the up-regulated levels of phosphorylated PERK, eIF2α and CHOP, and mitochondrial dysfunction characterized by the reduction of mitochondrial membrane potential and the release of cytochrome c, which promoted the cleavage of caspase-3, -9 and PARP.

Conclusions: Our results indicated that downregulated MALT1 caused by miR-200a-3p overexpression mediates intrinsic keratinocyte apoptosis through ER stress- and

mitochondria-dependent apoptotic pathways in patients with SJS/TEN. Plasma exosomal miR-200a-3p levels can be a useful disease marker for drug eruptions.