HHV-6-derived microRNAs in the serum of DIHS/DRESS patients

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Introduction

Drug-induced hypersensitivity syndrome/ Drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS)

- A particular type of severe cutaneous adverse drug reaction
- Associated with the reactivation of human herpesvirus 6 (HHV-6)

MicroRNA (miRNA)

- Non-protein-coding small RNA in the size range of 19-25 nucleotides
- Important roles in biological processes (immune response, cell development, cell differentiation, organogenesis, growth control and apoptosis)
- Many members of the herpesvirus family have their own miRNAs, which may regulate key viral genes.
- In vitro study shows that hhv6b-miR-Ro6-1, 2, 3 and 4 (HHV6-miR-1, 2, 3 and 4) are detected in HHV-6 infected cell.
- The precise role of these miRNAs in regulating HHV-6 latency and reactivation is largely unknown.

Hhv6b-miR-Ro6-2	↔	immediate early (IE)
Hhv6b-miR-Ro6-3		(expressed as early as 6h following infection)
Hhv6b-miR-Ro6-1	↔	immediate early (IE) or early (E)
		(Detected 2 days later than Hhv6b-miR-2,3)
Hhv6b-miR-Ro6-4	↔	Detected following 4 days of infection

Purpose of study

- To investigate expression level of four HHV-6 miRNAs in serum of patients with DIHS/DRESS at the acute stage.

Method

A summary of clinical and laboratory features of patients with DIHS/DRESS

Patient No.	Sex	Age	Causative drug	DRESS score	Duration of fever (>38.0° C) (days)	Type of skin eruption
1	F	84	allopurinol	7		3 Erythroderma
2	M	60	trimethoprim-sulfamethoxazole	8		10 Erythroderma
3	F	84	allopurinol	6		5 Erythroderma
4	F	73	carbamazepine	4		0 Erythroderma
5	M	39	carbamazepine	5		8 Erythroderma
6	F	15	carbamazepine	6		1 Erythroderma
7	M	50	modafinil	5		5 Diffuse MPE
8	F	77	allopurinol	6		0 Erythroderma
9	M	68	trimethoprim-sulfamethoxazole	5		1 Diffuse MPE
10	F	83	isonicotinic acid hydrazide	7		5 Erythroderma

Result

Up-regulation of HHV-6-derived miRNAs in the serum of DIHS/DRESS patients

The maximum levels of hhv6b-miR-Ro6-1, -2, -3, and -4 in serum were significantly higher in DIHS/DRESS than in MPE patients and healthy controls. *p<0.05.

Correlation between DRESS scores and HHV-6 miRNAs in the serum of DIHS/DRESS patients

DRESS scores correlated with the serum levels of hhv6b-miR-Ro6-1, -2, and -3, respectively.

Time course of HHV-6 miRNA expressions in each patient with DIHS/DRESS

(a) Case1. HHV-6 reactivation was confirmed by detecting HHV-6 DNA in PBMCs on day 25 after onset. The expression of hhv6b-miR-Ro6-2 in serum was detected on day 19, while hhv6b-miR-Ro6-4 and -1 were detected on days 25 and 33, respectively.

(b) Case 2. HHV-6 reactivated on day 16 after onset. Hhv6b-miR-Ro6-2 was expressed on day 10, while hhv6b-miR-Ro6-3 and -1 were expressed on the same day when HHV-6 DNA was detected.

(c) Case 6. The expression of HHV-6 DNA and hhv6b-miR-Ro6-2 and -3 was detectable on day 9 after onset, while hhv6b-miR-Ro6-4 was detected on day 21 following hhv6b-miR-Ro6-2 expression.

Correlation between HHV-6 miRNAs and type of skin eruption

Patient No.	Serum levels of HHV-6 miRNAs (copies/ml)				Type of skin eruption
	hhv6b-miR-Ro6-1	hhv6b-miR-Ro6-2	hhv6b-miR-Ro6-3	hhv6b-miR-Ro6-4	
2	389.6	1409.3	590.3	34.0	Erythroderma
10	2.3	608.1	100.1	7.9	Erythroderma
3	131.1	297.5	246.1	423.2	Erythroderma
5	20.6	258.5	175.2	1.0	Erythroderma
6	1.9	215.9	17.5	96.3	Erythroderma
1	646.4	172.0	79.0	277.9	Erythroderma
8	31.7	122.7	10.6	4.0	Erythroderma
4	7.9	50.9	32.4	54.7	Erythroderma
9	1.1	47.0	6.2	0.1	Diffuse MPE
7	24.0	3.7	266.4	2.2	Diffuse MPE

When the expression levels of hhv6b-miR-Ro6-2 in DIHS/DRESS patients were listed in descending order, the first eight patients with higher levels of hhv6b-miR-Ro6-2 had erythroderma, while the last two patients with lower levels of hhv6b-miR-Ro6-2 had diffuse MPE. Hhv6b-miR-Ro6-2 may reflect the type of skin eruption.

Correlation between the duration of fever (>38° C) and HHV-6 miRNAs in the serum of DIHS/DRESS patients.

The duration of fever correlated with serum levels of hhv6b-miR-Ro6-2 and -3, respectively.

Summary

- Four HHV-6 miRNAs were detected in some DIHS/DRESS patients, but not in MPE patients and healthy controls.
- Serum levels of hhv6b-miR-Ro6-2 increased before or at the same time as the detection of HHV-6 DNA, while serum levels of hhv6b-miR-Ro6-1 and/or 4 significantly increased a few weeks later in some patients with DIHS/DRESS.
- Some HHV-6 miRNAs in the serum are useful indicators of the severity of DIHS/DRESS.
- Hhv6b-miR-Ro6-2 may be an early and specific biomarker for predicting the reactivation of HHV-6.
- The detection of the miRNAs of HHV-6 in DIHS/DRESS may reflect the reactivation of HHV-6.

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