Genetic Variant of Aldo-keto Reductase (AKR) 1C3 in Japanese Psoriasis Patients

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Background

The aldo-keto reductase (AKR) 1C3, a NAD(P)H-dependent oxidoreductase, is known to be up-regulated in differentiated human epidermis. In atopic dermatitis (AD) lesions, AKR1C3 is up-regulated and reduces loricrin expression (Mantel et al., 2011). In contrast, according to NCBI GEO profiles, AKR1C3 expression is dramatically down-regulated in psoriasis (PSO) lesions as compared to non-lesional skin or healthy controls. Although it is expected that AKR1C3 plays an important role in the pathogenesis of these chronic inflammatory skin diseases, its regulation in skin is only poorly understood.

Question

Expression of AHR is increased in lesional skin from patients with PSO and AD compared to those of normal skin from healthy controls.

Kim HO, et al: *Exp Dermatol.*, 2014

Why is AKR1C3 down-regulated despite increased AHR levels in PSO lesion?

Materials & Methods

DNA was isolated from **232 psoriasis patients** treated in Nagoya City Univ. The cohort included 171 males and 61 females (m:f=3:1). The average of PASI score is 25.6.

Patients by type)

Psoriasis Vulgaris (PV): 134, Psoriatic Arthritis (PsA):65, Generalized Pustular Psoriasis (GPP):19, Erythrodermic Psoriasis (EP):5, PsA+EP:2, PsA+GPP:6, PSA+GPP+EP:1

Below two SNPs were analysed by TaqMan SNP genotyping assay.

rs12529

Polymorphism: C/G,
Transversion Substitution Context
Sequence[VIC/FAM]
AGTGACAGGGAATGGATTCCAAACA[C/G]C
AGTGTGTAAGCTAAATGATGGCC

rs12387

Polymorphism A/G,
Transition Substitution Context Sequence
[VIC/FAM]
GACCAGCCTTGGAAACTCACTGAA[A/G]
AAAGCTCAATTGGACTATGTTGACC

Results ② Immunohistochemistry for AKR1C3

Immunohistochemistry for AKR1C3 (red) and Loricrin (green).

Results ③ Serum AKR1C3 Activity Assay by ELISA

Enzyme-Linked Immuno Sorbent Assay (ELISA) for human AKR1C3: MBS7220102 is performed using patients' serum.

There is no significant difference in serum AKR1C3 activity between each SNPs.

Preliminary Study ① AKR1C3 expression is AHR-dependent

Materials:
Benzo[a]pyrene (BaP; AHR agonist)
β-Naphthoflavone (BNF; AHR agonist)

AKR1C3 expression is upregulated upon exposure to AHR agonists.
Genetic inhibition of AHR abrogated AKR1C3 expression on mRNA & protein level.
(also visit poster # 208)

Hypothesis

Psoriasis is generally thought to have genetic aspects. Around one-third of patients report a family history and identical twin studies suggest a 70% chance of onset if the other twin has psoriasis. **We hypothesized that the polymorphism of the AKR1C3 may attenuate AHR's effect on its expression and is one of the genetic predispositions to psoriasis.**

Results ① SNP genotyping assay

rs12529

	samples	C(%)	G(%)	Fisher's exact test	Odds ratio	95% CI
current study	232	13.6	86.4	P-value		
ss69068306	90	6.6	93.3	0.01359	0.45	0.24-0.86
ss71643788	88	5.6	94.3	0.005	0.38	0.19-0.77

rs12387

	samples	G(%)	A(%)	Fisher's exact test	Odds ratio	95% CI
current study	232	13.6	86.4	P-value		
ss2827707	172	8.1	91.9	0.0178	0.56	0.35-0.90
ss66361131	90	6.7	93.3	0.0035	0.38	0.19-0.76

SNPs of rs12529 or rs12387 was observed twice as much as Japanese healthy cohort.
SNPs rs12529 and rs12387 were always observed in same cases in our Japanese psoriasis patient cohort.

Conclusion & Discussion

SNPs of rs12529/rs12387 are observed often in psoriasis patients and cause down-regulation of AKR1C3 in psoriasis lesional epidermis.

It may cause a shift towards Th1-driven inflammation.
The identified mechanism might be relevant with regards to the etiology of psoriasis.

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