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Possible Role of Endoplasmatic Reticulum Stress in Psoriasis Vulgaris

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Abstract

Plaque psoriasis is a chronic immune-mediated inflammatory skin disease. The role of cytokines in the development of psoriasis is well known and has been studied for decades. Endoplasmic reticulum (ER) stress is the cellular response to the disturbed homeostasis in the ER. ER stress is involved in different human pathologies, including chronic inflammatory and degenerative conditions. The aim of our study was to explore whether the single nucleotide polymorphisms (SNPs) in ER stress related genes are associated with a higher risk for plaque psoriasis. We studied 29 SNPs in the following ER stress genes: *ATF6* (chr1), *HSPA5* (chr9), *HSP90B1* (chr12), *ERN1* (chr17), *XBP1* (chr22). Single marker analysis resulted in significant associations with the *HSP90B1* gene (rs17034977, p=0.0232) and with the *ERN1* gene (rs9916168, p<0.0001). Haplotype analysis revealed that the AGCCCG block in the *HSP90B1* gene differed statistically significantly between patients and controls (p=0.0197). Our study suggests that the variations in the ER stress related genes may contribute to the genetic susceptibility to psoriasis and the genes under investigation may be involved in the pathogenesis of this inflammatory disease.

Keywords: ER stress; Psoriasis; Unfolded protein response; Susceptibility

Introduction

Psoriasis is a chronic inflammatory disease affecting predominantly the skin with the involvement of autoimmune mediated mechanisms. It affects about 2 to 3% of the Caucasian population. Typical pathogenic features include an increased renewal of epidermal keratinocytes, the enlargement of the germinating compartment papillomatosis, altered epidermal differentiation, angiogenesis, lymphangiogenesis and inflammatory infiltration. Despite the progress in our understanding of underlying pathomechanisms, the ultimate cause of psoriasis remains elusive. The genetic contribution to disease is substantial and recent large-scale association studies have identified 37 psoriasis risk regions, with *HLA-C*06* being the main risk gene [1-3].

The endoplasmic reticulum (ER) is a sophisticated luminal network in which protein synthesis, maturation, folding, and transport take place. Homeostasis in the ER is monitored and maintained *via* unfolded protein response (UPR). A number of biological, psychological or pathological stimuli can perturb protein folding in the ER, leading to accumulation of unfolded or misfolded proteins in the ER lumen – a condition referred to as "ER stress" (Figure 1) [4,5]. In response to increased demands of producing secreted or membrane proteins, cells adapt themselves to the stress conditions *via* UPR; i.e., attenuation of general translation, induction of ER chaperones and foldases, and activation of ER-Associated Degradation (ERAD) to eliminate immature proteins [6,7].

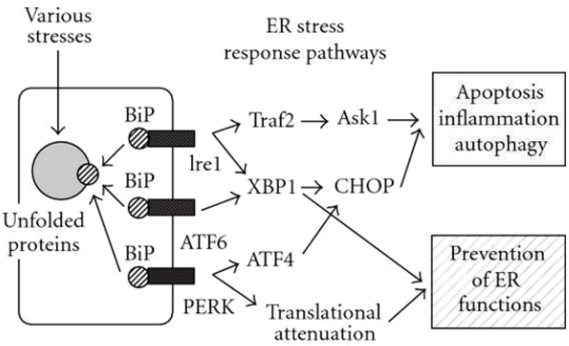

Figure 1: The major signal transduction pathway in the ER stress response [8].

Three major transducers for sensing ER stress have been identified on the membrane of the ER; i.e., RNA-dependent protein kinase-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring ER-to-nucleus signal kinase 1 (IRE1). These proteins bear domains protruding into the ER lumen, which sense ER stress, coupled to cytosolic effector domains. ATF6 is a sensor molecule on the ER membrane which is responsible for the sensing of unfolded proteins. Upon ER stress, the inactive form of ATF6 (p90ATF6) is transported to the Golgi apparatus and is activated by a two-step cleavage by Site-1 protease and Site-2 protease, to produce the active

form of ATF6 (p50ATF6). The free ATF6 fragment migrates to the nucleus to activate transcription [9,10]. IRE1 in humans is encoded by the *ERN1* gene. IRE1 [11] excise an intron from XBP1 mRNA, generating a spliced version of mRNA coding for a more potent form of a UPR transcription factor. XBP1 is a potent inducer of a subset of UPR target genes [5]. It is required for ER expansion and thedevelopment and survival of a variety of secretory cells as previously noted, as well as the adaptation of cells to a variety of stressful tissue environments such as that associated with hypoxia and calcium and glucose deprivation, among others [12].

The ER stress response has been recognized in a wide range of diseases, including rheumatoid arthritis, cancer, hypoxia and neurodegenerative disorders [13-15]. The aim of this study was to investigate a potential genetic association of ER stress related genes for psoriasis vulgaris in Estonian psoriasis patients.

Materials and Methods

Study subjects

Unrelated plaque psoriasis patients of the Estonian population (n=566, age range 18-89 years, mean age of onset 28.1 years) were enrolled at the Department of Dermatology, University of Tartu, as described [16]. Psoriasis patients were also divided into two subgroups based on the age of onset of the disease. Those with the onset before 40 years of age were considered as eraly onset psoriasis patients (n=434, age range 18-84 years, mean age of onset 20.9 years) and those with the onset of disease at the age of 40 years and later were considered as late onset psoriasis patients (n=132, age range 41-89 years, mean age of onset 51.8 years).

The control cohort was comprised of healthy unrelated individuals (n=308) without a personal or family history of psoriasis. Control subjects were recruited from among medical students, health care personnel and patients presenting at the dermatological outpatient clinic with either facial teleangiectasis or skin tags.

The clinical parameters of study participants are shown in Table 1. The Ethics Review Committee on Human Research of the University of Tartu approved the study and written informed consent was obtained from all participants.

Variable	Plaque psoriasis (N=566) frequency (%)	Early onset (N=434) frequency (%)	Late onset (N=132) frequency (%)
Gender			
Male	304	234	69
Female	262	199	63
Family History	246 (43.46)	216 (49.77)	30 (22.73)
PASI score			
≤ 10	161 (28.45)	111 (25.58)	49 (37.12)
11-20	165 (29.15)	123 (28.34)	43 (32.58)
≥ 21	240 (42.4)	200 (46.08)	40 (30.3)
BSA			
<10%	121 (21.38)	85 (19.58)	36 (27.27)
11-30%	190 (33.57)	141 (32.49)	49 (37.12)
>31%	255 (45.05)	208 (47.93)	47 (35.61)
Seasonality			
Spring-Summer	42 (7.42)	336 (77.42)	70 (53.03)
Autumn-Winter	406 (71.73)	27 (6.22)	15 (11.36)
None	105 (18.55)	62 (14.29)	43 (32.58)
Do not Know	13 (2.3)	9 (2.07)	4 (3.03)
Nail Involvement	277 (48.94)	233 (51.38)	54 (40.91)
PSA	127 (22.44)	107 (24.65)	20 (15.15)

Table 1: Demographic data of psoriatic patients.

Genotyping

DNA was obtained from peripheral blood leucocytes by standard salting-out method. Single nucleotide polymorphisms (SNPs) were analyzed using the SNPlex Genotyping System [17]. SNPlex Genotyping System utilizes a suite of pre-optimized universal assay reagent kits and a set of SNP-specific ligation probes allowing the genotyping of up to 48 SNPs in a single reaction. This system is based on the oligonucleotide ligation/PCR assay (OLA/PCR) with a universal ZipChute probe detection for high-throughput SNP genotyping. Flourescently labelled ZipChute probes are hybridized to complementary ZipCode sequences that are part of genotype-specific amplicons. These ZipChute probes are eluted and detected by electrophoretic separation on 3730 Genetic Analyzer. The GeneMapper 3.7 software was used for automated allele calling of all possible SNPs in each DNA sample.

SNPbrowser version 3.5 was used for the SNP selection and SNPlex assay pool design. Selection conditions were as follows – LD Map database was from Applied Biosystems, SNP selection was based on density with spacing criterion around 10 kb, minor allele frequency cut-off 5% and non-synonymous SNPs always included.

Statistical Analysis

For statistical analysis of single marker associations R program (http://www.r-project.org) was used. For haplotype analysis we used SHEsis program. A p-value<0.05 was considered statistically significant for all analyses. The significance level (p-value) was corrected by Bonferroni multiple comparisons analysis. Cases and controls were considered separately.

Results

We genotyped 29 SNPs in five ER stress related genes (namely *ATF6*, *HSPA5*, *HSP90B1*, *ERN1* and *XBP1*) in the total of 566 psoriasis vulgaris patients and 308 healthy control individuals. Psoriasis patients were divided into two different groups- early and late onset, as described above. Genotype distributions of the analyzed polymorphisms of the studied genes were in Hardy-Weinberg equilibrium both in the group of patient with psoriasis and the control group. Comparison of genotypic frequencies between cases and controls in the psoriasis group resulted in two statistically significantly associated SNPs. Namely, HSP90B1 (rs17034977, p-0.0233) and ERN1 (rs9916168, p<0.0001) (Table 2).

Chr	Gene	SNP	Plaque psoriasis	early onset	late onset	PASI ≤10	PASI 11-20	PASI ≥21	BSA ≤10%	BSA 11-30%	BSA ≥31%	Seasonality spring-summer	Seasonality autumn-winter	PsA	Family association
1	ATF6	rs10917876	0.7173	0.7288	0.7599	0.2682	0.5775	0.4928	0.1598	0.3282	0.2845	0.6189	0.5773	0.246	0.0762
		rs2070151	0.4987	0.6996	0.4746	0.5549	0.9906	0.2314	0.6221	0.9741	0.2056	0.6196	0.1882	0.1873	0.7865
		rs1503815	0.9487	0.98	0.7132	0.1578	0.5034	0.6306	0.2213	0.4765	0.5555	0.93	0.7131	0.2054	0.1155
		rs2340721	0.9418	0.8304	0.7109	0.4495	0.9188	0.8077	0.0986	0.4145	0.9874	0.0181	0.1457	0.3919	0.1723
		rs2341474	0.5797	0.7772	0.4038	0.6762	0.9527	0.3795	0.7227	0.951	0.348	0.7085	0.1757	0.2319	0.5465
		rs10753679	0.8691	0.8314	0.9889	0.6633	0.7787	0.4058	0.4387	0.6194	0.6866	**0.0016**	0.2902	0.6142	0.6638
		rs10918279	0.6486	0.5937	0.943	0.4199	0.7575	0.5659	0.3072	0.7377	0.8519	**0.0008**	0.2253	0.6971	0.299
		rs2499854	0.9674	0.911	0.7718	0.899	0.5343	0.5211	0.3938	0.3006	0.8213	**0.0079**	0.1589	0.3044	0.7549
9	HSPA5	rs599063	0.5149	0.7513	0.1749	0.7056	0.6936	0.7865	0.7421	0.5558	0.8495	0.8142	0.3596	0.7607	0.9826
		rs10125922	0.7012	0.8393	0.3592	0.7059	0.807	0.1621	0.4153	0.9731	0.2647	0.5621	0.7926	0.4865	0.0895
12	HSP90B1	rs1165678	0.8684	0.7701	0.7786	0.3875	**0.0358**	0.3682	0.1023	0.1824	0.3589	0.4429	0.6297	0.5087	0.2239
		rs1920413	0.962	0.967	0.607	0.8484	0.7415	0.3414	0.1208	0.6292	0.5853	0.5484	0.9876	0.7796	0.1555
		rs4964375	0.2546	0.4649	0.078	0.3508	0.374	**0.0082**	0.7762	0.9177	**0.0438**	0.6859	0.3336	0.2562	0.2294
		rs1165687	0.5198	0.4273	0.5225	0.3457	0.4342	0.0944	0.4323	0.897	0.1153	0.4359	0.2273	0.2738	0.5439
		rs17034977	**0.0232**	0.125	**0.0088**	0.5141	0.8587	**0.0022**	0.3446	0.5472	**0.0018**	**0.0528**	0.1132	0.4861	**0.04732**
		rs2583251	0.603	0.6307	0.6055	0.24	0.3993	0.6989	**0.0599**	0.4404	0.9707	0.5662	0.6976	0.2727	0.3587
17	ERN1	rs196904	0.6618	0.8414	0.4417	0.3635	0.4453	0.3988	0.5358	0.6714	0.353	0.2821	0.8434	0.6195	0.6231
		rs77684	0.7239	0.9267	0.3117	0.2156	0.4808	0.7829	0.4984	0.7614	0.614	0.1211	0.5493	0.5679	0.492
		rs7216531	0.6205	0.7893	0.4864	0.2604	0.4023	0.4045	0.4555	0.3816	0.4643	0.8224	0.7667	0.7806	0.3015
		rs196941	0.7572	0.8974	0.5018	0.1805	0.3753	0.8932	0.4084	0.8522	0.7388	0.1014	0.5266	0.7787	0.5352
		rs880069	0.8195	0.7823	0.668	0.3522	0.4166	0.8739	0.6151	0.8565	0.8048	0.1107	0.4209	0.5739	0.7152
		rs2172679	0.0655	0.1465	0.2062	0.0782	0.775	0.3862	0.281	0.3621	0.3572	0.7231	0.6213	0.6226	**0.0381**
		rs9911085	0.3916	0.4556	0.6638	0.2459	0.8341	0.9942	0.5588	0.5219	0.9071	0.1777	0.5895	0.8588	0.4718
		rs9916168	**<0.0001**	**0.0005**	**0.0314**	0.4099	0.1026	**0.0367**	0.6291	0.0742	**0.0297**	0.4523	**0.0015**	0.1617	**0.0008**
22	XBP1	rs5762795	0.6007	0.6534	0.4122	0.114	0.3754	0.1062	0.8087	**0.0023**	**0.0374**	**0.0303**	0.4164	0.9407	0.5543
		rs2267131	0.255	0.3421	0.4075	0.2665	0.2866	0.5899	0.2574	0.3499	0.6806	0.6243	0.9125	0.9809	**0.0225**
		rs2239815	0.8025	0.6761	0.6639	0.2029	0.3788	0.1258	0.7891	**0.0047**	**0.0306**	**0.0242**	0.2795	0.9809	0.8309
		rs2269577	0.4765	0.3677	0.6288	0.1132	0.3184	0.1873	0.6863	**0.0026**	**0.0477**	**0.0349**	0.1796	0.9637	0.5281
		rs5762814	0.2867	0.3499	0.5029	0.2881	0.3217	0.611	0.2858	0.326	0.6436	0.614	0.9318	0.9824	**0.0282**

Table 2: Associations of ER stress genes in Psoriasis Vulgaris patients (*P-value<0.05 was considered statistically significant for all analyses.

Comparison of genotypic frequencies between cases and controls in the early and late onset psoriasis groups revealed that ERN1 (rs9916168) was statistically significant both the early and late onset psoriasis group (p=0.0005 and p=0.0314, respectively), whereas HSP90B1 (rs17034977) gave statistically significant association only in the late onset psoriasis group (p-0.0088) (Table 2). These differences remained significant after the Bonferroni correction (giving p=0.0004 and p=0.031 for *ERN1* gene and p=0.025 for *HSP90B1* gene, respectively).

Halophytes of the *HSP90B1* gene	Psoriasis patients (%) (N=566)	Control samples (%) (N=308)	OR (95%CI)	p-value	PASI ≥ 21	BSA ≥ 31%	Seasonality (autumn-winter)
AACCCG	5.0	4.3	1.138 (0.670-1.935)	0.6316	0.7512	0.8985	0.4472
AGCCAG	12.0	11.7	1.010 (0.717-1.424)	0.9546	0.6466	0.7144	0.6104
AGCCCG	3.9	6.6	0.561 (0.343-0.917)	**0.0197**	**0.0013**	**0.0031**	**0.0100**
AGTAAG	12.7	12.4	1.014 (0.726-1.417)	0.9338	0.9100	0.8852	0.9421
AGTCAA	12.0	10.6	1.130 (0.794-1.609)	0.4967	0.7076	0.9624	0.6889
AGTCAG	15.1	13.4	1.134 (0.824-1.561)	0.4405	0.2708	0.4187	0.3281
GATAAG	35.5	35.7	0.966 (0.765-1.220)	0.084	0.5570	0.7285	0.6231

Table 3: Haplotype distribution of *HSP90B1* gene polymorphisms in Psoriasis Vulgaris patients and controls (*P-value<0.05 was considered statistically significant for all analyses).

We also performed stratified association analyses based on disease activity (Psoriasis Area and Severity Index - PASI score and Body Surface Area - BSA) and seasonality, age of onset and associated nail and joint involvement. The rs17034977 in the *HSP90B1* gene showed statistically significant association with severity of psoriasis –PASI ≥ 21 (p=0.0023) and BSA ≥ 31% (p=0.0018). These differences remained significant even after the Bonferroni correction (giving p=0.002 for PASI ≥ 21 and p=0.0017 for BSA ≥ 31%, respectively). Statistically significant tendency for association was also found with the prevalence within the family (p=0.0473) and with seasonality (spring-summer prevalence, p=0.0528). Differences in the prevalence within the family and seasonality lost statistically significant association after the correction for multiple testing. *ERN1* gene showed association with PASI ≥ 21 (p=0.03676), BSA>31% (p=0.0297) and seasonality (autumn-winter prevalence, p=0.0015). All these associations remained significant after the Bonferroni correction (p=0.037, p=0.03 and p-0.015, respectively). Despite the fact that studied SNPs of ATF6 and *XPB1* gene were not associated within the total psoriasis group, they showed associations with clinical manifestations of psoriasis. SNPs rs2340721, rs10753679, rs10918279 and rs2499854 of *ATF6* gene showed association with seasonality (p=0.0182, p=0.0016, p=0.0009, p=0.0079, respectively). Differences were also found with rs5762795 of the *XBP1* gene that was significantly associated with BSA score 11-30% (p=0.00235) and with BSA score >31% (p=0.0375). We could not show statistically significant changes in the psoriatic arthritis group (Table 2).

Haplotype analysis for the genes under investigation was performed and analysis for the *HSP90B1* gene revealed seven haplotype blocks (Table 3). Haplotype block AGCCCG differed statistically significantly between patients and controls and emerged as a risk haplotype with OR, 95%CI, and P-value of 0.561, 0.343-0.917, 0.0197. The AGCCCG haplotype block was also statistically significantly associated with different clinical parameters of psoriasis, namely PASI (PASI ≥ 21) (p=0.0013), BSA (BSA ≥ 31%) (p=0.0031), and seasonality (p=0.0100).

Haplotype analysis for the *ATF6*, *ERN1*, *HSPA5* and *XBP1* gene was performed, but no statistically significant associations in haplotype blocks was found (data not shown).

Discussion

The purpose of this study was to analyze ER stress related genes and to assess their impact on the risk of plaque psoriasis in the Estonian population. ER stress and the attendant UPR can lead to cell death and ER stress is related to chronic inflammatory diseases [18,19]. Moreover, the conditions that lead to an increase in protein misfolding or a decrease in the ability of the cell to handle these proteins in the ER can result in cellular dysfunction and cause different types of diseases [18,20-26]. ER stress pathways are also linked to the mechanisms involved in immunity and inflammation. ER stress may be both a trigger and a consequence of chronic inflammation. Chronic inflammation is often associated with diseases that arise because of primary misfolding mutations and ER stress. Similarly, ER stress and activation of the UPR is a feature of many chronic inflammatory diseases [8]. Psoriasis is a chronic inflammatory disease arising through the interplay between genetic risk variants and the environment. The number of psoriasis susceptibility variants has increased with the development of large-scale genetics and, so far, primarily the genes shared between psoriasis phenotypes have been captured [1].

We found no previous data about the possible associations between psoriasis vulgaris and ER stress genes. However, in this study, we showed that ER stress genes were associated with genetic susceptibility to plaque psoriasis. ERN1 (rs9916168) and HSP90B1 (rs17034977) [27] were significantly associated within the group with plaque psoriasis compared to the healthy control individuals. Thus, we conclude that the ER stress associated genes may play a role in the development of plaque psoriasis.

ERN1 is endoplasmic reticulum to nucleus signaling 1 and it is a human homologue of the yeast *Ire1* gene product. This gene is important in altering gene expression as a response to an endoplasmic reticulum-based stress signal [28]. *ERN1* has quite diverse functions that are all related to the regulation of ER stress response. This gene is involved in the broader regulation of cell fate during unfolded protein response [29]. Therefore, it is involved in quite diverse cellular functions. *ERN1* senses bacterial proteins invading ER and activate innate immune response [30]. *ERN1* has also been shown to be involved in inflammation and in neurodegeneration [17,31,32]. For instance, the role of ER stress in the pathogenesis of rheumatoid arthritis is well established [14]. XBP1, CHOP and GRP78 have all been shown to be involved in the development of rheumatoid arthritis [33,34]. In several studies the role of ER stress in synovial damage has been shown. Therefore, ER stress can be involved in the psoriatic arthritis that is very common in psoriasis patients, however in our study group we were unable to show it. Moreover, ER stress and the *ERN1* gene are involved in the Toll-like receptor-mediated signaling during RA. Macrophages from the synovial fluid of rheumatoid arthritis patients have significantly activated *IRE1a*. Myeloid–specific deletion of the *IRE1a* gene protected mice from inflammatory arthritis [35].

Another association was found with the *HSP90B1* gene, which is an ER chaperone and regulates the activity, stability and subcellular localization of a large number of client proteins to which it binds in a selective manner together with associated cofactors [7]. In our study, we found that the *HSP90B1* gene SNP rs17034977 was significantly associated with psoriasis vulgaris. This may support the fact that HSP90B1 is induced by the accumulation of misfolded proteins and it facilitates cell repair by stabilizing and refolding denaturated proteins after stress [6].

There is a good reason to belive that ER-stress is involved in psoriasis as increased ER-stress is a feature of epridermal differentiation [36,7]. The increased epidermal proliferation typical for psoriatic epidermis will increase the burden of ER-stress and thus ER-stress signaling. ER-stress is also increased during UV-A and UV-B irradiation of mammalian epidermis and dermis [37,38]. As UV-B therapy improves psoriasis and thus over-activates UV-induced ER-stress, it is hard to belive that ER-stress is the underlying pathomechanism in psoriasis. Nevertheless, the role of ER-stress in psoriasis and genetic susceptibility to disease pathophysiology is interesting link to ER-stress-mediated inflammatory responses [39,40]. Our findings provide a new insights into the association between ER stress related genes and psoriasis vulgaris. However, the role of ER stress response in the pathogenesis of this disease remains to be defined.

Conflict of Interest

The authors have declared no conflicts of interest.

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