Autoimmunity Reviews 18 (2019) 211–213

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Letter to the Editor: Protein phosphatase 1 subunit Ppp1r15a/GADD34 is overexpressed in systemic lupus erythematosus and related to the expression of type I interferon response genes

ARTICLE INFO

Keywords:
Endoplasmic reticulum stress
GADD34
Interferon
Protein phosphatase 1 subunit Ppp1r15a
Systemic lupus erythematosus
Unfolded protein response

Dear Editor,

With this letter we would like to highlight the key role of unfolded protein response during the course of systemic lupus erythematosus and the relation between endoplasmic reticulum stress and a type I interferon response in lupus patients.

The endoplasmic reticulum (ER) is the subcellular compartment where transmembrane and secreted proteins are synthesized. In physiological or pathological situations, such as oxidative stress or viral infections, the accumulation of misfolded proteins in the ER leads to the activation of different intracellular signaling pathways known as unfolded protein response (UPR) [1]. GADD34 (growth arrest and DNA damage-inducible protein) is a regulatory subunit of PP1a phosphatase induced by the PERK-mediated signaling pathway, which dephosphorylates the α subunit of the translation initiation factor eIF2 and induces a negative feedback loop of UPR, allowing the recovery of protein synthesis, essential for cell survival [2]. If ER homeostasis is not restored, the UPR induces apoptosis *via* CHOP (C/EBP homologous protein)-mediated pathway through the transcription of proapoptotic genes [3]. The UPR is more than just an adaptive response to unfolded protein accumulation in the ER. Indeed, UPR signaling pathways intersect with innate and adaptive immune responses at many levels, being involved in immunoglobulin synthesis, and in the differentiation and survival of immune cells such as plasma cells and dendritic cells [4,5]. The activation of UPR has been highlighted in several human pathologies such as metabolic diseases [6], neurodegenerative diseases [7], cancer [8], as well as in inflammatory and autoimmune diseases [9,10]. Interestingly, GADD34 has been shown to be necessary for type I IFN production *in vitro* by dendritic cells and fibroblasts exposed to double-strand RNA and *in vivo* in a murine model in response to a viral infection [11,12]. More recently, GADD34 expression has been shown to be responsible for a biochemical cycle permitting pulses of IFN-β synthesis in murine ds-RNA activated cells undergoing protein translation inhibition [13]. Furthermore, UPR activation has been described as a danger signal alone, that could trigger inflammation directly or indirectly, even independently of pathogens [14]. In this context, GADD34 might be a key molecule in inflammatory process in human pathologies as well, such as in autoimmune diseases and in particular in systemic lupus erythematosus (SLE), in which proinflammatory cytokines and especially IFNs have a pathogenic role.

We report a case-control study on GADD34 gene expression in PBMC of patients ($n = 58$) suffering from SLE satisfying the SLICC (Systemic Lupus International Collaborating Clinics) [15] and age- and sex-matched healthy controls ($n = 30$). The level of GADD34 gene expression, as well as IFN-α, IFN-β and type-I IFN response genes in PBMC was measured by quantitative PCR after reverse transcription reaction.

A descriptive analysis of SLE patients and healthy controls was performed. The disease activity was evaluated according to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. Lupus activity has been classified in: “no activity” (SLEDAI = 0), “low activity” (SLEDAI between 1 and 5), “mild activity” (SLEDAI between 6 and 10) and “high activity” (SLEDAI ≥11) [16]. Seventeen patients had lupus with no activity (in remission), twenty-eight patients with a low activity, nine patients with a mild activity, and one patient with a high activity (for three patients not enough data were available to calculate disease activity). Clinical manifestations were mainly articular (88%) and cutaneous symptoms (82%). The presence of autoantibodies in the serum of the patients was evaluated: antinuclear antibodies were present in 83% of patients and anti-dsDNA antibodies in 46% of the patients. A comparative analysis of GADD34 expression level in PBMC of SLE patients and healthy controls was carried out. GADD34 gene expression was found significantly higher in the SLE patient group than in the control group (p-value < .0001) (Fig. 1). Considering the threshold of a fold increase ≥2 compared with healthy controls, overexpression of GADD34 was found in 30 among the SLE patients (prevalence of 52%); no overexpression of GADD34 was observed in PBMC of healthy subjects. The expression of CHOP, which is also involved in the PERK-mediated signaling pathway, has been analyzed. Interestingly, CHOP is also overexpressed in the PBMC of SLE patients, and related to the expression of GADD34 (Fisher's exact test, $p < .001$). The overexpression of both GADD34 and CHOP in SLE patients strengthens the evidence of the involvement of UPR and in particular of the signaling pathway mediated by PERK in lupus patients. Nevertheless, the mechanism of the UPR activation in autoimmune diseases and in especially in SLE, remain to be elucidated.

SLE is a chronic disease whose evolution is characterized by

https://doi.org/10.1016/j.autrev.2018.09.007
Received 24 September 2018; Accepted 30 September 2018
Available online 19 December 2018

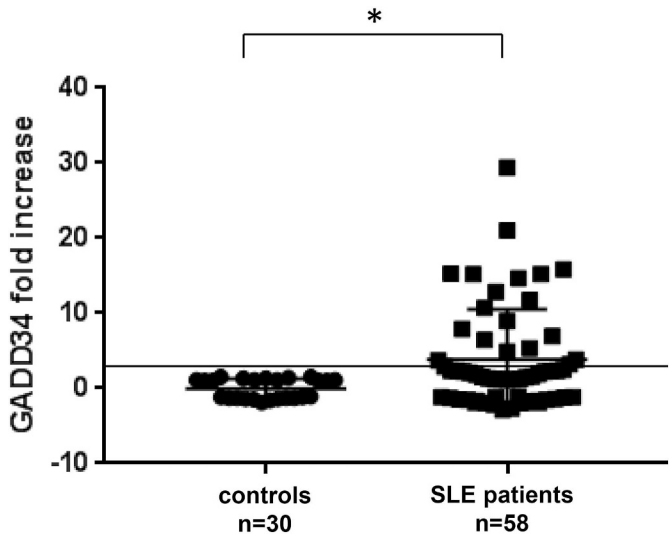

Fig. 1. Comparative analysis of GADD34 gene expression in SLE patients and the control group, *Fisher's exact test*, * $p < .0001$; GADD34 fold increase threshold ≥2 is represented.
Median values of GADD34 gene expression were: 1.01 [−1.23; 1.36] for controls and 1.84 [1.16; 5.25] for SLE patients. Statistical analyses were performed using Mann-Whitney test, median [25th; 75th].

Table 1
GADD34 overexpression is related to type I IFN and type I IFN response genes.

		GADD34 non-overexpressing SLE patients	GADD34 overexpressing SLE patients	*p* value
IFN-α (*n* = 42)	Overexpressed	7	23	=0.001
	Non overexpressed	10	2	
IFN-β (*n* = 41)	Overexpressed	6	19	0.0086
	Non overexpressed	11	5	
ISG15 (*n* = 53)	Overexpressed	9	31	< 0.001 (1,14 10^{-5})
	Non overexpressed	12	1	
IFIH1 (n = 42)	Overexpressed	3	22	< 0.001 (1,06 10^{-5})
	Non overexpressed	14	3	

Fisher's exact test.

alternating periods of activity and remission. Therefore, the search for new prognostic biomarkers is necessary to allow early and adapted management of the disease flares. Considering the important variability of the level of GADD34 expression and the heterogeneity of the activity of the disease among patients, a follow-up of GADD34 expression and clinical evolution of SLE patients during time are currently under evaluation in a more important cohort of patients (clinical trial NCT02455089).

The involvement of type I IFN genes and type I IFN response genes has been highlighted in the pathogenesis of lupus [17–20]. The expression of the following genes in the PBMC of our cohort of SLE patients has been analyzed: IFNα, IFNβ, ISG15, OAS1, MX1, IP10, IFI27, IFIT3, IFI44 and IFIH1. OAS1, MX1 and IP10 genes were not overexpressed in our cohort of patients, while IFNα, IFNβ, ISG15, IFI27, IFIT3, IFI44 and IFIH1 were overexpressed in SLE patients. GADD34 has been shown to be necessary for the production of proinflammatory cytokines such as IFN-β *in vitro*, as well as *in vivo* in a viral murine model [11,12]. Interestingly, we found that GADD34 overexpression in PBMC of patients with SLE is related to the overexpression of type I IFN genes IFN-α and IFN-β and to type I IFN response genes ISG15 and IFIH1 (Table 1). These results show a relation between GADD34 expression and a type I IFN response in lupus patients, providing an insight of the importance of the link between ER stress signaling pathways and type I IFN signature in SLE, suggesting that GADD34 might be a key molecule in inflammatory process in human pathologies as well.

Acknowledgements

We thank Adeline Russo who participated in performing experiments.

Declaration of interest

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Hetz C. The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat Rev Mol Cell Biol 2012;13(2):89–102.
[2] Novoa I, Zeng H, Harding HP, Ron D. Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2alpha. J Cell Biol 2001;153(5):1011–22.
[3] Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, Jungreis R, et al. CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. Genes Dev 2004;18(24):3066–77.
[4] Reimold AM, Iwakoshi NN, Manis J, Vallabhajosyula P, Szomolanyi-Tsuda E, Gravallese EM, et al. Plasma cell differentiation requires the transcription factor XBP-1. Nature 2001;412(6844):300–7.
[5] Janssens S, Pulendran B, Lambrecht BN. Emerging functions of the unfolded protein response in immunity. Nat Immunol 2014;15(10):910–9.
[6] Ozcan L. Endoplasmic reticulum stress in cardiometabolic disorders. Curr Atheroscler Rep 2012;14(5):469–75.

[7] Lin W, Popko B. Endoplasmic reticulum stress in disorders of myelinating cells. Nat Neurosci 2009;12(4):379–85.
[8] Wang S, Kaufman RJ. The impact of the unfolded protein response on human disease. J Cell Biol 2012;197(7):857–67.
[9] Kaser A, Lee A-H, Franke A, Glickman JN, Zeissig S, Tilg H, et al. XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. Cell 2008;134(5):743–56.
[10] Clavarino G, Adriouach S, Quesada J-L, Clay M, Chevreau M, Trocmé C, et al. Unfolded protein response gene GADD34 is overexpressed in rheumatoid arthritis and related to the presence of circulating anti-citrullinated protein antibodies. Autoimmunity 2016;49(3):172–8.
[11] Clavarino G, Cláudio N, Dalet A, Terawaki S, Couderc T, Chasson L, et al. Protein phosphatase 1 subunit Ppp1r15a/GADD34 regulates cytokine production in polyinosinic:polycytidylic acid-stimulated dendritic cells. Proc Natl Acad Sci U S A 2012;109(8):3006–11.
[12] Clavarino G, Cláudio N, Couderc T, Dalet A, Judith D, Camosseto V, et al. Induction of GADD34 is necessary for dsRNA-dependent interferon-β production and participates in the control of Chikungunya virus infection. PLoS Pathog 2012;8(5):e1002708.
[13] Dalet A, Argüello RJ, Combes A, Spinelli L, Jaeger S, Fallet M, et al. Protein synthesis inhibition and GADD34 control IFN-β heterogeneous expression in response to dsRNA. EMBO J 2017;36(6):761–82.
[14] Reverendo M, Mendes A, Argüello RJ, Gatti E, Pierre P. At the crossway of ER-stress and proinflammatory responses. FEBS J 2018. https://doi.org/10.1111/febs.14391.
[15] Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64(8):2677–86.
[16] Kuhn A, Meuth AM, Bein D, Amler S, Beissert S, Böhm M, et al. Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI): a modified outcome instrument for cutaneous lupus erythematosus. Br J Dermatol 2010;163(1):83–92.
[17] Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J. Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. Science 2001;294(5546):1540–3.
[18] Niewold TB, Clark DN, Salloum R, Poole BD. Interferon alpha in systemic lupus erythematosus. J Biomed Biotechnol 2010;2010:948364.
[19] Crow MK. Type I interferon in the pathogenesis of lupus. J Immunol 2014;192(12):5459–68.
[20] Chiche L, Jourde-Chiche N, Whalen E, Presnell S, Gersuk V, Dang K, et al. Modular transcriptional repertoire analyses of adults with systemic lupus erythematosus reveal distinct type I and type II interferon signatures. Arthritis Rheumatol 2014;66(6):1583–95.

Caroline Plazy[a], Chantal Dumestre-Pérard[a,b], Françoise Sarrot-Reynauld[c], Pierre Audoin[d], Jean-Louis Quesada[d], Philippe Pierre[e], Laurence Bouillet[c], Jean-Yves Cesbron[a,b], Giovanna Clavarino[a,b,*]

[a] *Laboratoire d'Immunologie, Pôle de Biologie, Centre Hospitalier Universitaire Grenoble Alpes, CS 10217, 38043 Grenoble, Cedex 9, France*
[b] *BNI Team, TIMC-IMAG UMR5525, Université Grenoble Alpes, CNRS, BP170, 38042 Grenoble, Cedex 9, France*
[c] *Clinique Universitaire de Médecine Interne, Pôle pluridisciplinaire de Médecine et de Gérontologie clinique, Grenoble University Hospital, CS 10217, 38043 Grenoble, France*
[d] *Direction de la Recherche Clinique et de l'Innovation, Pôle Recherche, Grenoble University Hospital, CS 10217, 38043 Grenoble, France*
[e] *Centre d'Immunologie de Marseille-Luminy, Aix Marseille Université UM2, Inserm U1104, CNRS UMR7280, 13288 Marseille, France*
E-mail address: gclavarino@chu-grenoble.fr (G. Clavarino).

* Corresponding author at: Laboratoire d'Immunologie, Pôle de Biologie, CHU de Grenoble, CS 10217, 38043 Grenoble, Cedex 9, France.