Journal of King Saud University – Science 32 (2020) 1434–1436

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Original article

Involvement of nuclear factor kappa-B in development of neonatal onset multisystem inflammatory disease

Fei Yu *, Min Chen, Li Zhou

Department of Community Family Health, Maternal and Child Health Hospital of Hubei Province, Wuhan, Hubei 430070, China

ARTICLE INFO

Article history:
Received 24 October 2019
Revised 18 November 2019
Accepted 26 November 2019
Available online 5 December 2019

Keywords:
Nuclear factor kappa-B
Multisystem inflammatory disease
Diagnosis
Polymorphism

ABSTRACT

The present study investigated the relationship between nuclear factor-κB1 gene (NFkB1) and neonatal onset multisystem inflammatory disease (NOMID) among Chinese neonates. We therefore aimed to investigate whether nuclear factor kappa-B involved in development of NOMID among Chinese neonates. Patients with confirm diagnosis of NOMID or healthy neonates was enrolled at Maternal and child health hospital of Hubei province, China. Involvement of poly (ADP-ribose) polymerase-1 (PP-1) and nuclear factor-κB1 was assessed using PCR techniques with the help of DNA sample. A total of 220 Chinese neonates with NOMID, and 220 healthy neonates were completed study. We note that the involvement of del/ins of NFkB1 gene in development of NOMID among Chinese neonates. GG and G SNPs of PP-1 were found responsible for developing NOMID and the individuals with GA SNPs protect responsible for protecting from NOMID. Thus, nuclear factor-κB1 and PP-1 involved in cause of NOMID, and considering as risk of developing is approx. 2 times higher compared to healthy subjects. Our study result shown that polymorphism of nuclear factor-κB1 and PP-1 is involved in development of NOMID in China. Our study suggested that NFkB1 and PP-1 is a possible target for treatment of NOMID; the treatment targeting nuclear NFkB1 and PP-1 is useful for effective patient care. Our study results encourage conducting large trial evaluating role of NFkB1 and PP-1 polymorphism in NOMID.

1. Introduction

Neonatal onset multisystem inflammatory disease (NOMID) is a rare inflammatory disease in neonates, and most common causes of morbidity, mortality, and increase economic burden to people (Prieur and Griscelli, 1981; Prieur et al., 1987; Feldmann et al., 2002). The key clinical symptoms among neonates are increase body temperature (fever), development of rashes, hearing loss and psychological impedance. It is characterized by global prevalence of NOMID is approximately 5% of neonates, with higher mortality rates in developing countries China. It is a key reason of death in neonates: over 1 million deaths per year are attributable to NOMID (Aksentijevich et al., 2002; Stojanov and Kastner, 2005; Agostini et al., 2004; Manji et al., 2002). Epidemiological studies have shown, however, that the prevalence of NOMID in neonates is higher than assumed (Agostini et al., 2004). NOMID is a genetic disorder, which is due to the mutation of autoinflammatory, these results in multisystem inflammatory disease (Prieur and Griscelli, 1981). NOMID is flattering an important public health concern throughout the world and accounts for premature morbidity and mortality (Prieur et al., 1987). The prevalence of NOMID is increasing quickly in recent years in China, accounts for >5% of the overall population (Feldmann et al., 2002). Furthermore, the occurrence of NOMID in Asia is projected to upsurge obviously in subsequent 20 years due to growing occurrence of obesity.

The role of nuclear factor kappa-B (NF-κB) in activating inflammatory mediators, mainly cytokines and inflammatory mediators and it also trigger the range of vital cellular functions. (Wang et al., 2002; O'Connor et al., 2003; Yu et al., 2006; Kanneganti et al., 2006; Grenier et al., 2002; Dowds et al., 2004). The functional role of NF-κB in NOMID was not assessed in Chinese patients. Therefore, this pilot investigation designed to assess whether NF-κB is involved in NOMID in Chinese individuals. The results of present investigation study may encourage conducting large multicentric trials which assess the relationship of NF-κB and PP1 in Chinese patients with NOMID. We hypothesize the

* Corresponding author.
E-mail address: VeronikaCocke@yahoo.com (F. Yu).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jksus.2019.11.038
1018-3647/

relationship between NF-κB and PP1 with NOMID among Chinese neonates. Therefore, the present studye aimed to investigate the relationship of NF-κB and PP1 as one of the possible threat in the cause of NOMID among Chinese neonates.

2. Materials and methods

2.1. Samples and collection

Subjects with confirm diagnosis of NOMID or healthy individuals was enrolled at maternal and child health hospital of Hubei province, China. The patients with any other pathology, which consulting physician or doctor feels may affect the result of study or patients who were received forbidden concomitant medicines or experiencing any other surgery were excluded, in view of influence of study consequence and subject's safety were also excluded from the study.

2.2. Involvement of NF-κB and PP1

Involvement of NF-κB and PP1 was analyzed by PCR methods using plasma DNA samples. In this study, the subjects of either gender with confirm diagnosis of NOMID or healthy individuals with no sign of NOMID (control group) were enrolled. This study was conducted at single center in china. Institutional ethics committee was obtained, and consent from parents of each enrolled subjects was obtained in writing. All subjects were enrolled in this study after satisfying pre-defined eligibility criteria.

2.3. Gene expression studies

Nuclear factor kappa-B and PARPs genotype area were intensified in 25 μl reaction volume with alkaline pH consists of buffer solution, one unit of enzyme (polymerase) and $MMgCl_2$ (Beg and Baltimore, 1996). Polymerase chain reaction was executed using augmented order of rotations. The PCR product was placed at room temperature for digestion. Likewise, other nuclear factor genes were amplified using same reagents.

2.4. Relationship between NFkB1 and NOMID

The present pilot/preliminary investigation was designed to investigate the relationship between NFkB1 and NOMID among Chinese neonates. Hence, there was no formal calculation of sample size. In the present preliminary investigation, we have planned to recruit at least 200 Chinese neonates with NOMID in each treatment group. The finding of present study may benefit to scientific community and helps to design large clinical trial to investigate the relationship between NFkB1 and NOMID among Chinese neonates across globe. The data which falls in numerical category data and shows bell shaped were analyzed by student *t* test for the independent group, and paired *t* test for the dependent group. The data which falls in numerical category data and shows non-bell shaped were analyzed by Mann Whitney after normality assessment. Quantitative data were presented using Mean (SD). Categorical data were presented as percentage/proportion of patients and were analyzed using fisher exact test or chi-square test based on size of data. $P < 0.05$ were as difference between comparisons of interest was statistically significant. Statistical analysis was performed using version 6.2 of Graph Pad Prism.

3. Results

A total of 270 Chinese patients (NOMID: 135 patients and healthy neonates: 135) were enrolled at Maternal and child health hospital of Hubei province. All patients completed study, and data of both the groups (were analyzed using appropriate statistical analysis. Mean (SD) age of NOMID group of neonates was 2.3 (0.5) weeks whereas it was 3.1 (0.7) weeks in healthy subjects. Baseline characteristics in both the groups were comparable (Table 1).

We observed that the participants with GA genotype were vulnerable of NOMID; risk of NOMID was 2 higher in as than participants without GG genotype ($p < 0.001$). We found that the participants with A allele are also vulnerable for increased risk of NOMID; risk of NOMID was 1.7 times more in these patients than subject with no G allele ($p < 0.001$). We also notice the involvement of other genotype such as GG and GA among NOMID patients (Table 2). We found the positive relationship of PARPs polymorphisms with NOMID when assessed association between NOMID and PARPs polymorphisms among participants with NOMID. There was no evidence of polymorphism of PARPs than the participants of NOMID with healthy subjects. The participants with C allele were more vulnerable of NOMID; risk of NOMID was 1.5 times greater among participants having allele of C in comparison to subjects with no C allele.

GG and G SNPs of PARPs were found responsible for developing NOMID and the individuals with GA SNPs protect responsible for protecting NOMID. Thus, PARPs involved in NOMID and risk of developing is approx. 1.5 times higher compared to healthy subjects. In our study results shows involvement of TT, CC, GA, GG, AA and CT genotype of PARPs C410T. In our study, threat of developing NOMID was more amongst neonates with del/ins polymorphism. We noted the association of del/ins in developing NOMID (Table 3).

4. Discussion

Identification of potential target for treatment of NOMID is utmost important for effective patient care, this helps in modifying the risk factor associated with NOMID with improve patient care (Dowds et al., 2004). In this study, a total of 135 Chinese subject with neonatal onset multisystem inflammatory disease, and 135 Chinese subject without NOMID were completed study. In our study, GG and G SNPs of PARPs were found responsible for developing NOMID and the individuals with GA SNPs protect responsible for protecting from NOMID. We also observed that the involvement of del/ins (d/i) gene of NFκB1. This shows the role of d/i of NFκB1 in developing NOMID. In our study, threat of developing NOMID was more in neonates with del/ins polymorphism. We noted the association of del/ins in developing NOMID. Thus, NFκB1 and PARPs involved in NOMID and risk of developing is approx. 2 times higher compared to healthy subjects. Subjects with GG genotype were susceptible for developing of NOMID; risk of NOMID was approximately more than 1 times higher than when compared to individuals who had no GG DNA gene. The subject

Table 1
Patient characteristics.

Variables	Neonatal onset multisystem inflammatory disease Subjects N = 135	Healthy Subjects N = 135
Age (in weeks), Mean (SD)	2.3 (0.5)	3.1 (0.7)
Gender, n		
Male	90	100
Female	45	35
Body weight, kg	4.16 (1.17)	4.7 (1.16)

N = total number of patients in each group. n = number of patients in each group.

Table 2
Involvement of PARPs genotype in NOMID subjects and healthy subjects.

	NOMID Subjects N = 135	Healthy Subjects N = 135	OR (95% CI) p value
Genotype – G1672A			
Existence – GG	49	41	2.63 (2.26–5.14) 0.067
Existence – GA	38	43	1.27 (1.22–3.18) 0.017
Existence – AA	32	35	2.12 (1.34–3.12) 0.072
Allele – G1672A			
Allele G	312	215	1.40 (1.47 –2.72)
Allele A	36	79	<0.0001
Genotype – C410T			
Existence – CC	53	48	3.74
Existence – CT	65	72	1.11 (1.42–4.15) 0.016
Existence – TT	67	76	1.03 (1.22–2.22) 0.071
Allele – C410T			
Allele C	45	49	1.13 (1.33–2.13)
Allele T	32	42	0.064

Table 3
Involvement of nuclear factor-κB genotype in NOMID subjects and healthy subjects.

	NOMID Subjects N = 135	Healthy Subjects N = 135	OR (95% CI) p value
NF-κB1 gene			
Existence – INS-INS	63	58	0.7 (1.62–2.10) 0.16
Existence – DEL-INS	96	40	1.9 (0.75–1.22) 0.03
Existence – DEL-DEL	54	56	1.03 (1.12–1.10) 0.14
Allele occurrence in NF-κB1 gene			
ALL INS	132	139	0.91 (1.22–2.01)
ALL DEL	34	38	0.13
NF-κBIA gene			
Existence – AA	41	39	0.7 (0.7–1.2) 0.13
Existence – AG	53	34	1.14 (0.14–1.83) 0.03
Existence – GG	74	42	2.1 (0.9–4.8) 0.04
Allele (ALL) occurrence in NF-κBIA gene			
ALL A	131	130	1.7 (1.1–2.1)
ALL G	43	38	0.12

with GG gene remained vulnerable of NOMID; risk of NOMID was 1.5 higher in NOMID subjects with GG gene than subjects without GG gene ($p < 0.001$). Moreover, the subjects with G allele were vulnerable for greater threat of NOMID; threat of NOMID was 1.3 time more in these patients than subject with no G allele ($p < 0.001$). We also notice the involvement of other genotype such as AA and GA among NOMID subjects. We found the positive relationship of NFκB1 and PARPs polymorphisms with NOMID when assessed association between NOMID. There was no evidence of polymorphism of NFκB1 and PARPs in NOMID than subjects without NOMID. Subjects with C allele were more vulnerable of NOMID; risk of NOMID was 1.5 times greater among participants having allele of C in comparison to subjects with no C allele (Beg and Baltimore, 1996). Our study result shown that polymorphism of NFκB1 and PARPs is involved in development of NOMID in Chinese individuals. In summary, polymorphism of NFκB1 and PARPs involved in development of NOMID in China. Our study suggested that NFκB1 and PARPs is a potential target for treatment of NOMID; the treatment targeting NFκB1 and PARPs is useful for effective patient care. Our study results encourage large study role of NFκB1 and PARPs polymorphism in NOMID.

5. Conclusion

The results of study shows that polymorphism of NFκB1 and PARPs is involved in development of NOMID among Chinese individuals. Our study suggested that NFκB1 and PARPs is a potential target for treatment of NOMID, the treatment targeting NFκB1 and PARPs is useful. Our study results encourage conducting large study which evaluates role of NFκB1 and PARPs polymorphism in NOMID patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

All authors would like to thank the subjects for their participation in this study.

References

Agostini, L., Martinon, F., Burns, K., McDermott, M.F., Hawkins, P.N., Tschopp, J., 2004. NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity 20, 319–325.

Aksentijevich, I., Nowak, M., Mallah, M., et al., 2002. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. Arthritis Rheum. 46, 3340–3348.

Beg, A.A., Baltimore, D., 1996. An essential role for NF-κB in preventing TNF-α-induced cell death. Science 274, 782–784.

Dowds, T.A., Masumoto, J., Zhu, L., Inohara, N., Nunez, G., 2004. Cryopyrin-induced interleukin 1beta secretion in monocytic cells: enhanced activity of disease-associated mutants and requirement for ASC. J. Biol. Chem. 279, 21924–21928.

Feldmann, J., Prieur, A.M., Quartier, P., et al., 2002. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am. J. Hum. Genet. 71 (1), 198–203. https://doi.org/10.1086/341357.

Grenier, J.M., Wang, L., Manji, G.A., et al., 2002. Functional screening of five PYPAF family members identifies PYPAF5 as a novel regulator of NF-kappaB and caspase-1. FEBS Lett. 530, 73–78.

Kanneganti, T.D., Ozoren, N., Body-Malapel, M., et al., 2006. Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/Nalp3. Nature 440, 233–236 [PubMed].

Manji, G.A., Wang, L., Geddes, B.J., et al., 2002. PYPAF1, a PYRIN-containing Apaf1-like protein that assembles with ASC and regulates activation of NF-kappa B. J. Biol. Chem. 277, 11570–11575.

O'Connor, W., Jr., Harton, J.A., Zhu, X., Linhoff, M.W., Ting, J.P. Cutting edge: CIAS1/cryopyrin/PYPAF1/NALP3/CATERPILLER 1. 1 is an inducible inflammatory mediator with NF-kappaB suppressive properties. J. Immunol. 2003;171:6329–6333.

Prieur, A.M., Griscelli, C., Lampert, F., et al., 1987. A chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome: a specific entity analysed in 30 patients. Scand. J. Rheumatol. Suppl. 66, 57–68.

Prieur, A.M., Griscelli, C., 1981. Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. J. Pediatr. 99, 79–83.

Stojanov, S., Kastner, D.L., 2005. Familial autoinflammatory diseases: genetics, pathogenesis and treatment. Curr. Opin. Rheumatol. 17, 586–599.

Wang, L., Manji, G.A., Grenier, J.M., et al., 2002. PYPAF7, a novel PYRIN-containing Apaf1-like protein that regulates activation of NF-kappa B and caspase-1-dependent cytokine processing. J. Biol. Chem. 277, 29874–29880.

Yu, J.W., Wu, J., Zhang, Z., et al., 2006. Cryopyrin and pyrin activate caspase-1, but not NF-kappa B, via ASC oligomerization. Cell Death Differ. 13, 236–249.