Journal of Neuroimmunology 411 (2026) 578833

Contents lists available at ScienceDirect

Journal of Neuroimmunology

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

Full Length Article

Exploratory analysis of B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL) across migraine phases

Nisha Smithi [a,1], Pooja Singh [b,1], Swathika Rajendran [a], Harini Purushothaman [a], Ameena Bee [a], Vishnupriya Gurumoorthy Mani [a], Sowmiya Mari [a], Deepa Avadhani [c], Rajesh Kumar Gandhirajan [b], Murugesan Arumugam [a,*]

[a] Department of Pharmacology, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai 600116, Tamil Nadu, India
[b] Department of Human Genetics, Sri Ramachandra Faculty of Biomedical Sciences and Technology, Porur, Chennai 600116, Tamil Nadu, India
[c] Department of Neurology, Sri Ramachandra Medical college & Hospital, Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai 600116, Tamil Nadu, India

ARTICLE INFO

Keywords:
Migraine
Headache
Autoimmunity
Migraine pathophysiology
BAFF
APRIL

ABSTRACT

Emerging evidence suggests that imbalanced T-cell activity and immune dysfunction may contribute to migraine pathogenesis. However, the specific immune pathways remain unclear, particularly the role of B cells. To explore B-cell–related mechanisms, this study focused on two key members of the tumor necrosis factor (TNF) family, namely B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL), which play critical roles in B-cell survival and regulation. This study examined BAFF and APRIL expression in peripheral blood samples from migraine patients during pre-ictal, ictal, and post-ictal phases ($n = 9$) and in healthy controls ($n = 9$). BAFF levels increased during the ictal phase ($p = 0.011$) and declined in the post-ictal phase, whereas APRIL remained consistently downregulated relative to controls. The divergent patterns of BAFF and APRIL reveal a novel B-cell–related immune signature that may contribute to migraine pathogenesis. These preliminary findings support further studies to confirm these patterns and investigate the functional role of the BAFF–APRIL pathway in migraine.

1. Introduction

Migraine is a chronic and complex neurological disorder, and its underlying pathophysiology remains not yet fully elucidated (Puledda et al., 2023; Arumugam and Narayan, 2019). Despite this limited understanding, the classic neurovascular model has provided valuable insights into migraine mechanisms (Silberstein, 2004; Mungoven et al., 2021). However, the exact origin of pain remains poorly understood. Recent evidence suggests that additional factors, including genetic susceptibility, hormonal influences, and autoimmune mechanisms, may also contribute to migraine development (Arumugam and Narayan, 2019; Amiri et al., 2022; Khan et al., 2021).

Among these, the role of the immune system has gained increasing attention, supported by emerging data and evolving hypotheses (Ha and Chu, 2024; Arumugam et al., 2024; Subalakshmi et al., 2025). Earlier, our clinical investigations strengthened this concept by demonstrating reduced levels of regulatory T cells (Tregs) and altered T-cell subsets in migraine patients compared with healthy controls (Arumugam et al., 2024; Arumugam and Parthasarathy, 2016). In line with these findings, other studies have reported polymorphisms in the FOXP3 gene, further indicating a possible autoimmune component in migraine pathophysiology (Faraji et al., 2023; Sugumar et al., 2024).

These observations suggest that immune alterations in migraine may disrupt cytokine balance and promote inflammatory processes. Immune dysregulation in migraine has also been associated with altered cytokine profiles (Yamanaka et al., 2023). Elevated levels of pro-inflammatory cytokines such as IL-6, IL-1β, TNF-α, and IL-8 with reduced IL-4 levels reflect an imbalance in immune signaling (Yamanaka et al., 2023; Munno et al., 2001; Thuraiaiyah et al., 2022). Additionally, increased concentrations of immunoglobulins, particularly IgA and IgM (Ha and Chu, 2024; Shimomura et al., 1992), indicate a role of B-cell activity in migraine pathogenesis.

* Corresponding author.
E-mail address: murugesan.a@sriramachandra.edu.in (M. Arumugam).
[1] Authors contributed equally.

https://doi.org/10.1016/j.jneuroim.2025.578833
Received 11 November 2025; Accepted 28 November 2025
Available online 30 November 2025

Extending this line of thought, attention has shifted to two members of the TNF superfamily, namely B Cell Activating Factor (BAFF) and A Proliferation-Inducing Ligand (APRIL). They regulate B- and T-cell function and are strongly implicated in autoimmune diseases including systemic lupus erythematosus (Mackay et al., 1999; Vincent et al., 2014) and rheumatoid arthritis (Moura et al., 2011; Shabgah et al., 2019). BAFF stimulates cytokines such as IL-10 (Saulep-Easton et al., 2016) and IL-6 (Yoshimoto et al., 2011) and promotes the differentiation of Th17 cells (Zhou et al., 2011). Th17 cells produce IL-17 A and IL-17F, which are key drivers of acute and chronic inflammation in autoimmune diseases (Tabarkiewicz et al., 2015) and have also been associated with migraine (Chen et al., 2022). Furthermore, BAFF enhances antibody production, including IgA (Li et al., 2014) and IgM (Granja and Tafalla, 2019). Similarly, APRIL contributes to the generation of IgA (Xiao et al., 2011) and IgM (Simón et al., 2021) antibodies and has been linked to cytokines such as IL-6 (Makita et al., 2020) and Th17 cells (Xiao et al., 2008).

While BAFF and APRIL normally regulate cytokine and antibody production, their overexpression can lead to excessive cytokine and antibody levels, which may contribute to the progression of autoimmune diseases (Evans et al., 2023). However, their precise role in migraine has not yet been explored. Determining the involvement of these ligands in migraine may provide an important connection between B-cell and T-cell activity in immune pathways. Such knowledge would not only clarify the role of immune proteins in migraine etiology but also strengthen understanding of its association with autoimmunity. Therefore, the present study aims to examine BAFF and APRIL levels in migraine patients across the pre-ictal, ictal, and post-ictal phases to study the role of the immune system in migraine pathogenesis.

2. Materials and methods

2.1. Ethics approval and study trial registration

The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Institutional Human Ethics Committee of Sri Ramachandra Institute of Higher Education and Research (CSP/24/JUL/150/281). The study was also registered with the ICMR Clinical Trial Registry of India (CTRI/2024/09/074182).

2.2. Screening of volunteers

Initially, 28 migraine patients were screened and recruited from the Outpatient Unit of the Department of Neurology, Sri Ramachandra Institute of Higher Education and Research, Chennai, India. The volunteers were selected based on the responses obtained from the Proforma (Supplementary file 1), which was completed under the supervision of a trained neurologist who conducted the primary diagnosis and recruitment. Of these, nine individuals were included for further study, and nine healthy volunteers were also included as controls. The inclusion criteria for migraine patients were individuals aged above 18 years, without any comorbidities. The collected data included demographic details (name, age, sex), duration and frequency of migraine attacks, previous migraine medications, family history, and other associated conditions.

2.3. Methodology

2.3.1. Sample collection and peripheral blood lymphocyte isolation

Blood samples from migraine patients were collected at three different intervals according to previous literature (Peng and May, 2020). These included the migraine-free period (pre-ictal), a single sample during the attack (ictal phase), and within 24–48 h after the attack (post-ictal). For comparison, a single sample was also collected from healthy controls. Approximately 2 mL of heparinized whole blood was obtained from each participant. Peripheral blood lymphocytes were isolated by Ficoll density gradient centrifugation. The isolated cells were washed twice with phosphate-buffered saline, counted using trypan blue exclusion, and 3×10^6 cells were aliquoted for RNA and DNA extraction. Samples were stored at −80 °C until further use.

2.3.2. Primer designing for cDNA preparation

Human APRIL and BAFF qPCR primers was selected from ORIGENE Technologies, which provides predesigned and validated primer sequences. The BAFF primer pair targets the *TNFSF13B* gene, with the forward sequence ACCACGCGGAGAAGCTGCCAG and the reverse sequence CTGCTGTTCTGACTGGAGTTGC, producing a 133 bp amplicon. The APRIL primer pair targets the *TNFSF13* gene, with the forward sequence CGGAAAAGGAGAGCAGTGCTCA and the reverse sequence GCCTAAGAGCTGGTTGCCACAT, producing a 130 bp amplicon. The primer sequences were reconfirmed using the National Center for Biotechnology Information (NCBI) database to ensure target specificity and to verify that they do not cross-react with unintended sequences.

2.3.3. RNA extraction and cDNA synthesis

Total RNA was extracted from peripheral blood lymphocytes using the Trizol–chloroform method. RNA was precipitated with isopropanol, washed with 70 % ethanol, and dissolved in nuclease-free water. The purity and concentration of RNA were determined using a NanoDrop spectrophotometer (Implen™). For cDNA synthesis, 500 ng of RNA was reverse transcribed using reverse transcriptase with a combination of oligo dT primers and random hexamers, following the manufacturer's instructions (HiMedia™).

2.3.4. Quantitative PCR (qPCR) analysis

Gene expression of BAFF (*TNFSF13B*), APRIL (*TNFSF13*), and ACTB (housekeeping gene control) was quantified using SYBR Green–based qPCR (HiMedia™). Amplification reactions were set up in a 96-well plate with gene-specific primers, and each reaction was performed in triplicate to ensure reproducibility. The qPCR program consisted of an initial denaturation at 95 °C for 5 min, followed by 40 cycles of denaturation at 95 °C for 15 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s. A melt curve analysis was performed at the end of the run to confirm the specificity of the amplified products.

2.4. Statistical analysis

Relative expression levels of BAFF and APRIL were calculated using the comparative ΔΔCt method with ACTB as the internal control. Statistical analyses were performed using GraphPad Prism version 8.0.2. The normality of the variables was assessed using the Shapiro–Wilk test. The Mann–Whitney *U* test was used to compare independent variables. Data are presented as mean ± SEM and median (interquartile range). A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Descriptive analysis

The mean age of migraine patients was 21.11 ± 1.36 years, while that of the control group was 20.11 ± 0.78 years. Females were predominant in the migraine group, consistent with known migraine epidemiology. A positive family history of migraine was reported in 33.33 % of migraine patients, whereas none of the controls reported a family history of migraine or autoimmune disorders. Approximately seven out of nine migraine patients reported a typical attack duration of 3–4 h in the proforma (Table 1). However, during post-ictal phase sample collection, they noted that their pain had lasted for around six hours. This observation indicates that the duration of migraine attacks can be highly unpredictable.

Table 1
Demographic and clinical characteristics of migraine patients and healthy controls.

Variable	Summary of Migraine patients *N* = 09 n (%) [95 % CI]	Summary of healthy control N = 09 n (%) [95 % CI]
Age (Mean ± SD)	21.11 ± 1.36	20.11 ± 0.78
Sex		
Female	7 (77.78 %) [39.99, 97.19]	3 (33.33 %) [7.49, 70.07]
Male	2 (22.22 %) [2.81, 60.01]	6 (66.67 %) [29.93, 92.51]
Time Period of Persistence		
Nil	–	9 (100.00 %) [66.37, 1]
30 min	2 (22.22 %) [2.81, 60.01]	–
1 h	2 (22.22 %) [2.81, 60.01]	–
2 h	1 (11.11 %) [0.28, 48.25]	–
2–3 h	2 (22.22 %) [2.81, 60.01]	–
More than 24 h	1 (11.11 %) [0.28, 48.25]	–
3 days	1 (11.11 %) [0.28, 48.25]	–
Blood relations suffering from Migraine		
Yes	3 (33.33 %) [7.49, 70.07]	–
No	6 (66.67 %) [29.93, 92.51]	9 (100.00 %) [66.37, 1]
Blood relations suffering from any other Autoimmune Diseases		
Rheumatoid arthritis	1 (11.11 %) [0.28, 48.25]	–
No	8 (88.89 %) [51.75, 99.72]	9 (100.00 %) [66.37, 1]

3.2. Comparison of BAFF levels in migraine patients and healthy controls

The relative expression of BAFF was significantly higher in migraine patients across all phases compared to healthy controls, with the highest elevation observed during the ictal phase ($p = 0.011$). The pre-ictal ($p = 0.024$) and post-ictal ($p = 0.024$) phases also showed significantly higher levels than healthy controls (Fig. 1). However, as the data did not follow a normal distribution, non-parametric analysis was performed, and the median (IQR) values were used for statistical analysis (Supplementary File 2). The median (IQR) for healthy controls was 0.33 (0.08–0.41), whereas for the migraine phases (pre-ictal, ictal, and post-ictal) they were 0.78 (0.53–1.04), 1.17 (0.58–1.73), and 0.97 (0.41–1.62), respectively.

3.3. Comparison of APRIL levels in migraine patients and healthy controls

APRIL expression was downregulated in migraine patients compared to healthy controls. The levels remained generally low across all migraine phases, including the pre-ictal, ictal, and post-ictal periods (Fig. 2). Similar to BAFF, APRIL levels also did not follow a normal distribution. Therefore, the median (IQR) was used for statistical analysis (Supplementary File 2). Overall, the trend indicates reduced APRIL expression during migraine attacks, although these changes were not statistically significant.

4. Discussion

The present study examined the expression of two TNF superfamily members, BAFF and APRIL, across the pre-ictal, ictal, and post-ictal phases in migraine patients. The results showed that BAFF levels were significantly elevated in migraine patients compared to healthy controls, with a gradual rise from the pre-ictal phase, peaking during the ictal phase, and then declining in the post-ictal phase. This temporal pattern suggests dynamic regulation of BAFF expression, possibly reflecting phase-specific immune activation during migraine episodes.

Typically, BAFF is produced by myeloid cells such as monocytes, macrophages, dendritic cells, neutrophils, and astrocytes (Yoshimoto et al., 2011; Kim et al., 2011; Giordano et al., 2020; Krumbholz et al., 2005). Astrocytes in the Central Nervous System can release high levels of BAFF, particularly under autoimmune conditions like multiple sclerosis, through activation by inflammatory cytokines including IFN-γ and TNF-α (Krumbholz et al., 2005). This BAFF can further activate T cells and stimulate IFN-γ production, creating an inflammatory feedback loop (Scapini et al., 2010).

Supporting this, earlier research helps explain these findings, which showed that TNF-α is elevated in migraine patients (Han, 2019; Albanese et al., 2025). This suggests that TNF-α may help stimulate BAFF production. This is significant because BAFF activates two key immune pathways. First, it triggers dendritic cells to release proinflammatory signals including IL-6, TNF-α, IL-1β, and Th1 chemokines. Second, BAFF drives CD4 T cells to produce more IFN-γ and weakly stimulates anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 (Chang and Jelinek, 2006). Notably, this specific immune signature, which is characterized by high levels of IL-6, TNF-α, and IL-1β alongside low IL-4 and IL-5, has been consistently observed in migraine patients (Munno et al., 2001; Han, 2019; Aydın et al., 2015).

Moreover, elevated BAFF may interfere with the deletion of autoreactive B cells, a mechanism central to maintaining immune tolerance

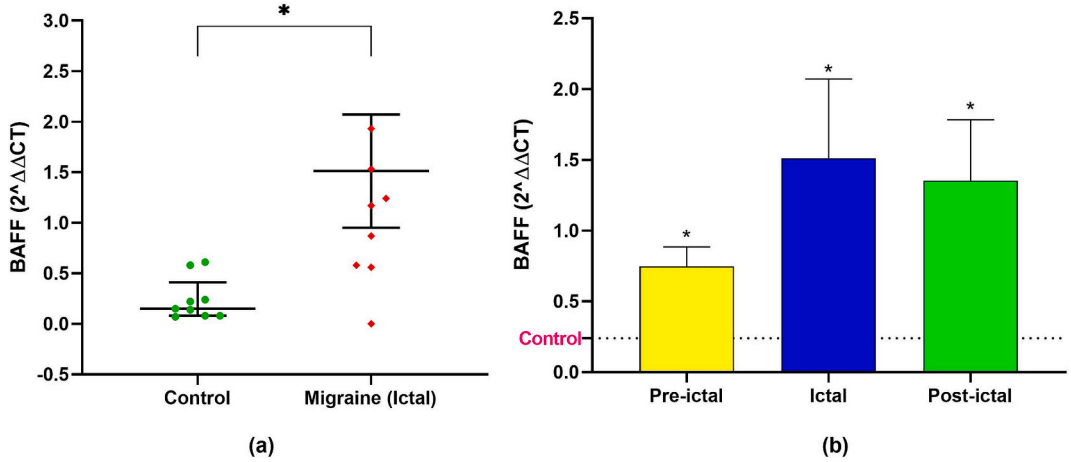

Fig. 1. BAFF expression in peripheral blood of migraine patients and healthy controls. (a) Relative mRNA expression level of BAFF (2ˆ-ΔΔCt) levels of the migraine attacks (ictal phase) versus healthy controls ($n = 9$). (b) Expression of BAFF during migraine phases as compared to control ($n = 9$). Results are given in the form of mean ± SEM (* indicate that the $p < 0.05$).

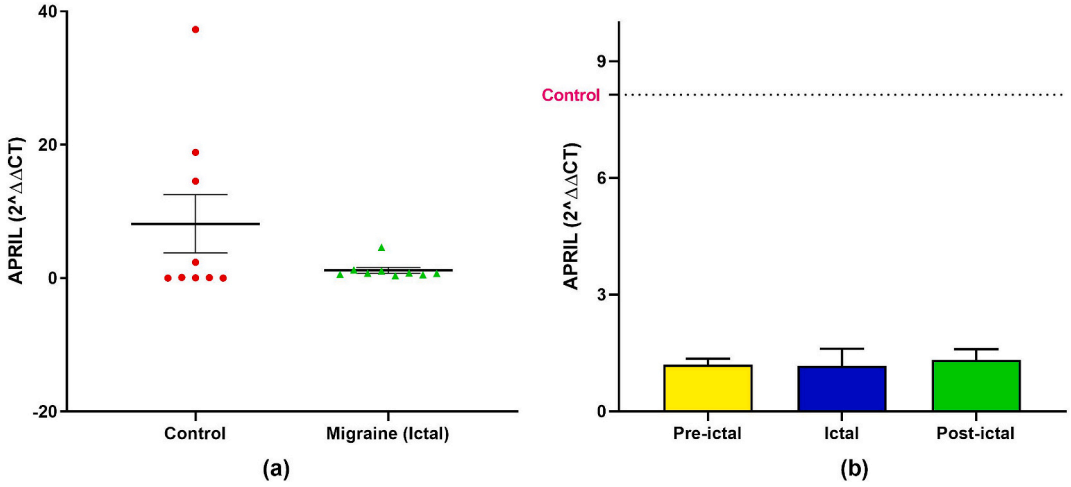

Fig. 2. APRIL expression in peripheral blood of migraine patients and healthy controls. (a)Comparison of the relative mRNA expression level of APRIL (2^-ΔΔCt) during migraine attacks (ictal phase) with that of healthy controls (n = 9). (b)The expression of APRIL across migraine phases with respect to healthy controls (n = 9). The data had been expressed in form of mean ± SEM.

(Thien et al., 2004). Such dysregulation can contribute to autoimmune-like processes, supporting the hypothesis that migraine involves complex immune alterations.

In contrast, APRIL levels were generally downregulated in migraine patients compared to controls. Although APRIL promotes B-cell survival and modulates Th17 responses, potentially contributing to autoreactivity in various autoimmune conditions (Simón et al., 2021; Makita et al., 2020), its specific mechanistic role in migraine remains unclear. In autoimmune disorders such as systemic lupus erythematosus, APRIL levels are often reduced, indicating a nuanced role in B-cell regulation and immune tolerance. Notably, regulatory B cells (Bregs) induced by APRIL secrete anti-inflammatory cytokines, including IL-10, which help counteract excessive autoreactive responses (Poznyak et al., 2025; Shimomura et al., 1992).

Similarly, in Sjögren's syndrome, serum APRIL levels may be elevated, yet its local expression in salivary glands remains lower than that of BAFF, suggesting a more limited contribution to tissue-specific inflammatory processes (Poznyak et al., 2025; Vallerskog et al., 2006; (Poznyak et al., 2025; Vallerskog et al., 2006; Vosters et al., 2012). This divergent expression likely reflects distinct regulatory pathways and immune targets for BAFF and APRIL, which may explain their contrasting behaviors during migraine episodes (Ng et al., 2004).

Taken together, the opposing behaviors of BAFF and APRIL highlight that migraine involves complex, multidimensional immune responses. BAFF seems to participate actively in inflammatory events during migraine attacks, whereas APRIL may play an indirect or counteracting role in maintaining basal immune homeostasis. Similar contrasting patterns have been observed in autoimmune diseases such as systemic lupus erythematosus and membranous nephropathy, where BAFF levels were elevated and APRIL levels downregulated (Vallerskog et al., 2006; Han et al., 2017). These findings align with the present results, suggesting a potential link between migraine pathophysiology and autoimmune-like processes.

The main limitations of this study include a relatively small sample size, which limits statistical power, and the lack of protein-level measurements, restricting a deeper mechanistic understanding. Additionally, the study focused on a single migraine episode and did not account for potential influences such as stress or hormonal fluctuations.

5. Conclusion

This study provides the first demonstration that BAFF levels are significantly elevated in migraine patients compared to healthy controls, while APRIL levels are downregulated, suggesting distinct roles for these factors in migraine. These findings highlight the complex interactions between immune mediators in migraine and provide evidence supporting a potential link to autoimmunity. The elevated BAFF levels indicate overproduction of cytokines and activation of T and B cells, pointing to specific immune pathways that may be further investigated. Future studies with larger sample sizes are warranted to better understand the role of the immune system and may provide solid evidence to focus on drug targets related to the BAFF pathway in migraine.

CRediT authorship contribution statement

Nisha Smithi: Formal analysis, Methodology, Resources, Software, Visualization, Writing – original draft. **Pooja Singh:** Methodology, Software, Validation, Visualization. **Swathika Rajendran:** Methodology, Resources, Software, Visualization, Writing – original draft. **Harini Purushothaman:** Investigation, Methodology, Resources, Writing – original draft. **Ameena Bee:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **Vishnupriya Gurumoorthy Mani:** Methodology, Resources, Writing – original draft, Writing – review & editing. **Sowmiya Mari:** Investigation, Methodology, Software, Visualization. **Deepa Avadhani:** Investigation, Methodology, Resources, Writing – review & editing. **Rajesh Kumar Gandhirajan:** Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. **Murugesan Arumugam:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The study was funded by Avicence Pharmaceutical private limited, Chennai, India through Corporate Social Responsibility (CSR) initiated small research grant.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.jneuroim.2025.578833.

Data availability

No data was used for the research described in the article.

References

Albanese, M., Ceci, V., Carrera, G., Selntigia, A., Exacoustos, C., Tiberi, M., Chiurchiù, V., 2025. Inflammatory cytokine signatures are associated with disease burden and comorbidity of episodic migraine and endometriosis. Neurology 12 (6), e200490.

Amiri, P., Kazeminasab, S., Nejadghaderi, S.A., Mohammadinasab, R., Pourfathi, H., Araj-Khodaei, M., Safiri, S., 2022. Migraine: a review on its history, global epidemiology, risk factors, and comorbidities. Front. Neurol. 12, 800605.

Arumugam, M., Narayan, S.K., 2019. Rethinking of the concepts: migraine is an autoimmune disease? Neurol. Psychiatry Brain Res. 31, 20–26.

Arumugam, M., Parthasarathy, V., 2016. Reduction of CD4+ CD25+ regulatory T-cells in migraine: is migraine an autoimmune disorder? J. Neuroimmunol. 290, 54–59.

Arumugam, M., Sugumar, S., Ganesan, P., 2024. The initiation of a migraine associated with a specific gene responsible for regulating immune function: hypothesis. Med. Hypotheses 188, 111382.

Sugumar, S., Suresh, J.A., Avadhani, D., Hazeena, P., Arumugam, M., 2024. A pilot study of FOXP3 Gene (rs2232365, rs3761547, and rs3761548) mutations in migraine patients. Immunol Genet J 7 (4), 274–280.

Aydın, M., Feyzi Demir, C., Arıkanoğlu, A., Bulut, S., İlhan, N., 2015. Plasma cytokine levels in Migraineurs during and outside of attacks. Eur. J. Gen. Med. 12 (4).

Chang, S.K., Jelinek, D.F., 2006. BLyS regulates adaptive immune responses by directly promoting dendritic cell maturation. In: Journal of Immunology, vol. 176. Amer Assoc Immunologists, Rockville Pike, Bethesda, MD 20814 USA, p. 9650 pp. S16-S16. April.

Chen, H., Tang, X., Li, J., Hu, B., Yang, W., Zhan, M., Xu, S., 2022. IL-17 crosses the blood–brain barrier to trigger neuroinflammation: a novel mechanism in nitroglycerin-induced chronic migraine. J. Headache Pain 23 (1), 1.

Evans, L.S., Lewis, K.E., DeMonte, D., Bhandari, J.G., Garrett, L.B., Kuijper, J.L., Dillon, S.R., 2023. Povetacicept, an enhanced dual APRIL/BAFF antagonist that modulates B lymphocytes and pathogenic autoantibodies for the treatment of lupus and other B cell–related autoimmune diseases. Arthritis Rheum. 75 (7), 1187–1202.

Faraji, F., Mosayebi, G., Bahrami, M., Shojapour, M., 2023. rs3761548 (C/a) and rs5902434 (del/ATT) polymorphisms of Foxp3 gene in Iranian patients with migraine. Egypt. J. Med. Genet. 24 (1), 18.

Giordano, D., Kuley, R., Draves, K.E., Roe, K., Holder, U., Giltiay, N.V., Clark, E.A., 2020. B cell activating factor (BAFF) produced by neutrophils and dendritic cells is regulated differently and has distinct roles in ab responses and protective immunity against West Nile virus. J. Immunol. (Baltimore, Md.: 1950) 204 (6), 1508–1520.

Granja, A.G., Tafalla, C., 2019. Different IgM+ B cell subpopulations residing within the peritoneal cavity of vaccinated rainbow trout are differently regulated by BAFF. Fish Shellfish Immunol. 85, 9–17.

Ha, W.S., Chu, M.K., 2024. Altered immunity in migraine: a comprehensive scoping review. J. Headache Pain 25 (1), 95.

Han, D., 2019. Association of serum levels of calcitonin gene-related peptide and cytokines during migraine attacks. Ann. Indian Acad. Neurol. 22 (3), 277–281.

Han, S.S., Yang, S.H., Jo, H.A., Oh, Y.J., Park, M., Kim, J.Y., Kim, D.K., 2017. BAFF and APRIL expression as an autoimmune signature of membranous nephropathy. Oncotarget 9 (3), 3292.

Khan, J., Al Asoom, L.I., Al Sunni, A., Rafique, N., Latif, R., Al Saif, S., Borgio, J.F., 2021. Genetics, pathophysiology, diagnosis, treatment, management, and prevention of migraine. Biomed. Pharmacother. 139, 111557.

Kim, H.A., Seo, G.Y., Kim, P.H., 2011. Macrophage-derived BAFF induces AID expression through the p38MAPK/CREB and JNK/AP-1 pathways. J. Leukoc. Biol. 89 (3), 393–398.

Krumbholz, M., Theil, D., Derfuss, T., Rosenwald, A., Schrader, F., Monoranu, C.M., Meinl, E., 2005. BAFF is produced by astrocytes and up-regulated in multiple sclerosis lesions and primary central nervous system lymphoma. J. Exp. Med. 201 (2), 195–200.

Li, W., Peng, X., Liu, Y., Liu, H., Liu, F., He, L., Peng, Y., 2014. TLR9 and BAFF: their expression in patients with IgA nephropathy. Mol. Med. Rep. 10 (3), 1469–1474.

Mackay, F., Woodcock, S.A., Lawton, P., Ambrose, C., Baetscher, M., Schneider, P., Browning, J.L., 1999. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J. Exp. Med. 190 (11), 1697–1710.

Makita, Y., Suzuki, H., Kano, T., Takahata, A., Julian, B.A., Novak, J., Suzuki, Y., 2020. TLR9 activation induces aberrant IgA glycosylation via APRIL-and IL-6–mediated pathways in IgA nephropathy. Kidney Int. 97 (2), 340–349.

Moura, R.A., Cascao, R., Perpétuo, I., Canhao, H., Vieira-Sousa, E., Mourao, A.F., Fonseca, J.E., 2011. Cytokine pattern in very early rheumatoid arthritis favours B-cell activation and survival. Rheumatology 50 (2), 278–282.

Mungoven, T.J., Henderson, L.A., Meylakh, N., 2021. Chronic migraine pathophysiology and treatment: a review of current perspectives. Front. Pain Res. 2, 705276.

Munno, I., Marinaro, M., Bassi, A., Cassiano, M.A., Causarano, V., Centonze, V., 2001. Immunological aspects in migraine: increase of IL-10 plasma levels during attack. Headache 41 (8), 764–767.

Ng, L.G., Sutherland, A.P., Newton, R., Qian, F., Cachero, T.G., Scott, M.L., Mackay, C.R., 2004. B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. J. Immunol. 173 (2), 807–817.

Peng, K.P., May, A., 2020. Redefining migraine phases–a suggestion based on clinical, physiological, and functional imaging evidence. Cephalalgia 40 (8), 866–870.

Poznyak, A., Gerasimova, E., Orekhov, N.A., Karimova, A.E., Vergun, M.A., Lapshina, K. O., Orekhov, A.N., 2025. Exploring the role of APRIL in autoimmunity: implications for therapeutic targeting in systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. Front. Immunol. 16, 1523392.

Puledda, F., Silva, E.M., Suwanlaong, K., Goadsby, P.J., 2023. Migraine: from pathophysiology to treatment. J. Neurol. 270 (7), 3654–3666.

Saulep-Easton, D., Vincent, F.B., Quah, P.S., Wei, A., Ting, S.B., Croce, C.M., Mackay, F., 2016. The BAFF receptor TACI controls IL-10 production by regulatory B cells and CLL B cells. Leukemia 30 (1), 163–172.

Scapini, P., Hu, Y., Chu, C.L., Migone, T.S., DeFranco, A.L., Cassatella, M.A., Lowell, C.A., 2010. Myeloid cells, BAFF, and IFN-γ establish an inflammatory loop that exacerbates autoimmunity in Lyn-deficient mice. J. Exp. Med. 207 (8), 1757–1773.

Shabgah, A.G., Shariati-Sarabi, Z., Tavakkol-Afshari, J., Mohammadi, M., 2019. The role of BAFF and APRIL in rheumatoid arthritis. J. Cell. Physiol. 234 (10), 17050–17063.

Shimomura, T., Araga, S., Kowa, H., Takahashi, K., 1992. Immunoglobulin k/Λ ratios in migraine and tension-type headache. Psychiatry Clin. Neurosci. 46 (3), 721–726.

Silberstein, S.D., 2004. Migraine pathophysiology and its clinical implications. Cephalalgia 24 (2_suppl), 2–7.

Simón, R., Díaz-Rosales, P., Tafalla, C., 2021. The ancient cytokine BAFF-and APRIL-like molecule regulates the functionality of teleost IgM+ B cells similarly to BAFF and APRIL. J. Immunol. 206 (8), 1765–1775.

Subalakshmi, S., Rushendran, R., Vellapandian, C., 2025. Revisiting migraine pathophysiology: from neurons to immune cells through Lens of immune regulatory pathways. J. NeuroImmune Pharmacol. 20 (1), 1–15.

Tabarkiewicz, J., Pogoda, K., Karczmarczyk, A., Pozarowski, P., Giannopoulos, K., 2015. The role of IL-17 and Th17 lymphocytes in autoimmune diseases. Arch. Immunol. Ther. Exp. 63 (6), 435–449.

Thien, M., Phan, T.G., Gardam, S., Amesbury, M., Basten, A., Mackay, F., Brink, R., 2004. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. Immunity 20 (6), 785–798.

Thuraiaiyah, J., Erritzøe-Jervild, M., Al-Khazali, H.M., Schytz, H.W., Younis, S., 2022. The role of cytokines in migraine: a systematic review. Cephalalgia 42 (14), 1565–1588.

Vallerskog, T., Heimbürger, M., Gunnarsson, I., Zhou, W., Wahren-Herlenius, M., Trollmo, C., Malmström, V., 2006. Differential effects on BAFF and APRIL levels in rituximab-treated patients with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Res. Ther. 8 (6), R167.

Vincent, F.B., Morand, E.F., Schneider, P., Mackay, F., 2014. The BAFF/APRIL system in SLE pathogenesis. Nat. Rev. Rheumatol. 10 (6), 365–373.

Vosters, J.L., Roescher, N., Polling, E.J., Illei, G.G., Tak, P.P., 2012. The expression of APRIL in Sjögren's syndrome: aberrant expression of APRIL in the salivary gland. Rheumatology 51 (9), 1557–1562.

Xiao, Y., Motomura, S., Podack, E.R., 2008. APRIL (TNFSF13) regulates collagen-induced arthritis, IL-17 production and Th2 response. Eur. J. Immunol. 38 (12), 3450–3458.

Xiao, Y., Motomura, S., Deyev, V., Podack, E.R., 2011. TNF superfamily member 13, APRIL, inhibits allergic lung inflammation. Eur. J. Immunol. 41 (1), 164–171.

Yamanaka, G., Hayashi, K., Morishita, N., Takeshita, M., Ishii, C., Suzuki, S., Go, S., 2023. Experimental and clinical investigation of cytokines in migraine: a narrative review. Int. J. Mol. Sci. 24 (9), 8343.

Yoshimoto, K., Tanaka, M., Kojima, M., Setoyama, Y., Kameda, H., Suzuki, K., Takeuchi, T., 2011. Regulatory mechanisms for the production of BAFF and IL-6 are impaired in monocytes of patients of primary Sjögren's syndrome. Arthritis Res. Ther. 13 (5), R170.

Zhou, X., Xia, Z., Lan, Q., Wang, J., Su, W., Han, Y.P., Zheng, S.G., 2011. BAFF promotes Th17 cells and aggravates experimental autoimmune encephalomyelitis. PLoS One 6 (8), e23629.