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Folate Receptor Beta Signaling in the Regulation of Macrophage Antimicrobial Immune Response: A Scoping Review

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Abstract

Introduction: Folate, vitamin B9, is a water-soluble vitamin that is essential to cellular proliferation and division. In addition to the reduced folate carrier, eukaryotic cells take up folate through endocytosis mediated by one of two GPI-anchored folate receptors (FRs), FRα or FRβ. Two other isoforms of FR exist, FRγ and FRδ, neither of which support endocytic activities of FR signaling. FRβ is expressed primarily by monocytes and macrophages and highly expressed on activated macrophages. Macrophage expression of FRβ suggests a role for this receptor in modulating function of these immune sentinels, particularly as they engage in inflammatory processes. Despite several studies suggesting that folates can suppress inflammatory responses of macrophages to proinflammatory stimuli, there appears to be a lack of basic research examining the role of FRβ in modulating macrophage responses to microbial sensing. We therefore conducted a scoping review to assess evidence within the published literature addressing the question, "what is known about the extent to which FRβ regulates macrophage responses to sensing, and responding to, microorganisms?". ***Methods:*** As a strategy for the study selection, we queried articles indexed in the research database PubMed and the search engine Google Scholar (up until August 12, 2023), including combinations of the research words: macrophage, folate receptor beta, *FOLR2*. ***Results:*** We identified 2 relevant articles out of 153 that are worth discussing here, none of which directly addressed our research question. ***Conclusion:*** There is an unmet need to better define the contribution of FRβ to regulating the macrophage response to microbes.

Introduction

Folate, vitamin B9, is a water-soluble vitamin essential for cells to generate nucleic acids and metabolic amino acids that are required for their proliferation and division [1]. Because eukaryotic cells cannot make folate, it is commonly delivered into cells through either the ubiquitously expressed reduced folate carrier (a facilitative anion exchange carrier encoded by the *SLC19A1* gene [2]) or a proton-coupled folate transporter (*SLC46A1* gene [3]), which is involved in dietary folate uptake from the intestine. However, another class of folate binding receptors are known collectively as

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folate receptors, which are expressed by highly specific cell types [1]. The folate receptor is a cell surface glycosylphosphatidylinositol-anchored glycoprotein, with three main isoforms in humans: FRα (encoded by the *FOLR1* gene), folate receptor beta (FRβ) (encoded by the *FOLR2* gene), and FRγ (encoded by the *FOLR3* gene) [1], of which the latter is a soluble secreted form because it lacks a glycosylphosphatidylinositol-anchoring signal. A fourth isoform, FRδ (encoded by *FOLR4*), does not appear to bind folate but is essential for mammalian fertilization [4]. FRα and FRβ can transport FA into cells through receptor-mediated endocytosis [1]. Notably, FRα is expressed by placental trophoblasts [1] and in the neural folds during neurulation [5]. Knockout of the *FOLR1* gene in the mouse leads to neural tube defects [6].

FRβ, with a subnanomolar affinity for folic acid (one of a family of structurally related folate compounds), is a surface marker of normal hematopoiesis of myelomonocytic lineage cells and is expressed primarily by monocytes and macrophages [1, 7]. Evidence suggests that FRβ is highly expressed on activated macrophages, which are implicated in the pathogenesis of human inflammatory diseases, such as rheumatoid arthritis, psoriasis, Crohn's disease, systemic lupus erythematosus, atherosclerosis, diabetes, ulcerative colitis, osteoarthritis, glomerulonephritis, and sarcoidosis [1]. The highly specific nature of FRβ expression on monocytes and macrophages has resulted in this receptor being targeted for cell-specific delivery of therapeutic agents and for localizing macrophages through in vivo imaging techniques [8–14].

Macrophage expression of FRβ suggests a role for this receptor in modulating the function of these immune sentinels, particularly as they engage in inflammatory processes. Despite several studies suggesting that folates can suppress inflammatory responses of macrophages (or macrophage-like cells) to proinflammatory stimuli [15–24], including some pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), there appears to be a paucity of studies specifically examining the role of FRβ per se in modulating macrophage responses to microbial sensing. We therefore conducted a structured, scoping review to assess evidence within the published, English language literature addressing the question, "what is known from the existing literature about the extent to which the FRβ regulates macrophage responses to sensing, and responding to, microorganisms?". The results suggest this is an area in need of further research.

Methods

We conducted a scoping review based on methods described by Peterson et al. [25] and consistent with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews [26]. The scoping review research question defined a priori was as follows: what is known from the existing literature about the extent to which the FRβ regulates macrophage responses to sensing, and responding to, microorganisms? To systematically answer this question, we sought to identify and review relevant studies that evaluated the interaction between the FRβ and the immune response to microorganisms in macrophages (either primary macrophages or cell lines). As a strategy for the study selection, we queried English-language articles indexed in one research database: PubMed and one search engine: Google Scholar, each searched through August 12, 2023, including combinations of the research terms: macrophage, folate receptor beta, and *FOLR2*. A separate protocol for this review does not exist. Specifically, we searched on PubMed using the following word combinations: "macrophage AND folate receptor beta"; "FOLR2 AND macrophage"; "FOLR2 AND folate receptor beta"; and lastly all three terms combined "FOLR2 AND folate receptor beta AND macrophage". Each combination of search terms resulted in differently sized lists of results which we cross-referenced against all the results generated for each combination of search terms to compile a final list of 144 research papers. The search engine Google Scholar (using the combination of the words FOLR2, folate receptor beta, and macrophage as PubMed search) resulted in an additional 9 papers that were not identified on our PubMed searches, for a total of 153 research papers reviewed here. Since Google Scholar is less stringent with its search strategy than a database like PubMed, the majority of resulting papers either lacked one or more of our search terms or focused on cancer biology (not related to pathogen recognition). To simplify the review process on Google Scholar, we excluded cancer-focused studies from further review and did not include them in our final list.

Two different screeners were used to identify all relevant PubMed articles based on the various combinations of the three search terms, and the preliminary publication list was reviewed by one additional person and results were compared regarding which publications would be included in our scoping review. One of the initial PubMed screeners completed the subsequent Google Scholar search, which was compared to the PubMed results to avoid duplicate results. There was consensus agreement reached on which articles to include based on group conversations among all three authors on this review paper. Publications were omitted if they did not include data from microorganisms or if they were review articles themselves. Sources of evidence were limited to quantitative research articles and not opinion articles or Websites. No additional data were requested from the authors of the primary sources because we did not evaluate data beyond published materials. We identified one additional study through references of the reviewed articles. Brief written summaries of each of the 153 articles included in the scoping review including reasons why each was included or excluded was generated (data not shown).

Table 1. Articles reviewed in-depth and either included or excluded

Authors	Reference No.	Publication year	Title	Form of review	Included/ excluded	Reason for exclusion
Moore et al.	[27]	2023	Single-cell RNA sequencing reveals unique monocyte-derived interstitial macrophage subsets during lipopolysaccharide-induced acute lung inflammation	Full article	Excluded	FRβ signaling was not studied
Lu et al.	[28]	2021	Targeting folate receptor beta on monocytes/macrophages renders rapid inflammation resolution independent of root causes	Full article	Excluded	No infectious disease correlated
Thomas et al.	[29]	2021	Phenotypic and functional characterization of first-trimester human placental macrophages, Hofbauer cells	Full article	Excluded	FRβ signaling was not studied
Muller et al.	[12]	2020	Can Nuclear Imaging of Activated Macrophages with Folic Acid-Based Radiotracers Serve as a Prognostic Means to Identify COVID-19 Patients at Risk?	Full article	Excluded	FRβ signaling was not studied; review paper
Zhang et al.	[30]	2020	Reprogramming of profibrotic macrophages for treatment of bleomycin-induced pulmonary fibrosis	Full article	Excluded	FRβ signaling was not studied
Kim et al.	[31]	2019	Anti-inflammatory actions of folate-functionalized bioactive ion-releasing nanoparticles imply drug-free nanotherapy of inflamed tissues	Full article	Excluded	FRβ signaling was not studied
Ohradanova-Repic et al.	[32]	2018	Extracellular Purine Metabolism Is the Switchboard of Immunosuppressive Macrophages and a Novel Target to Treat Diseases with Macrophage Imbalances	Full article	Excluded	FRβ signaling was not studied
Han et al.	[9]	2015	Molecular Imaging of Folate Receptor β–Positive Macrophages during Acute Lung Inflammation	Full article	Included	–
Sierra-Filardi et al.	[33]	2011	Activin A skews macrophage polarization by promoting a proinflammatory phenotype and inhibiting the acquisition of anti-inflammatory macrophage markers	Full article	Excluded	No infectious disease/microbe correlated
Xia et al.	[34]	2008	A functional folate receptor is induced during macrophage activation and can be used to target drugs to activated macrophages	Full article	Included	–
Nagai et al.	[35]	2010	Effect of an immunotoxin to folate receptor β on bleomycin-induced experimental pulmonary fibrosis	Full article	Excluded	No infectious disease/microbe correlated
Nagayoshi et al.	[36]	2005	Effectiveness of anti-folate receptor beta antibody conjugated with truncated Pseudomonas exotoxin in the targeting of rheumatoid arthritis synovial macrophages	Full article	Excluded	No infectious disease/microbe correlated

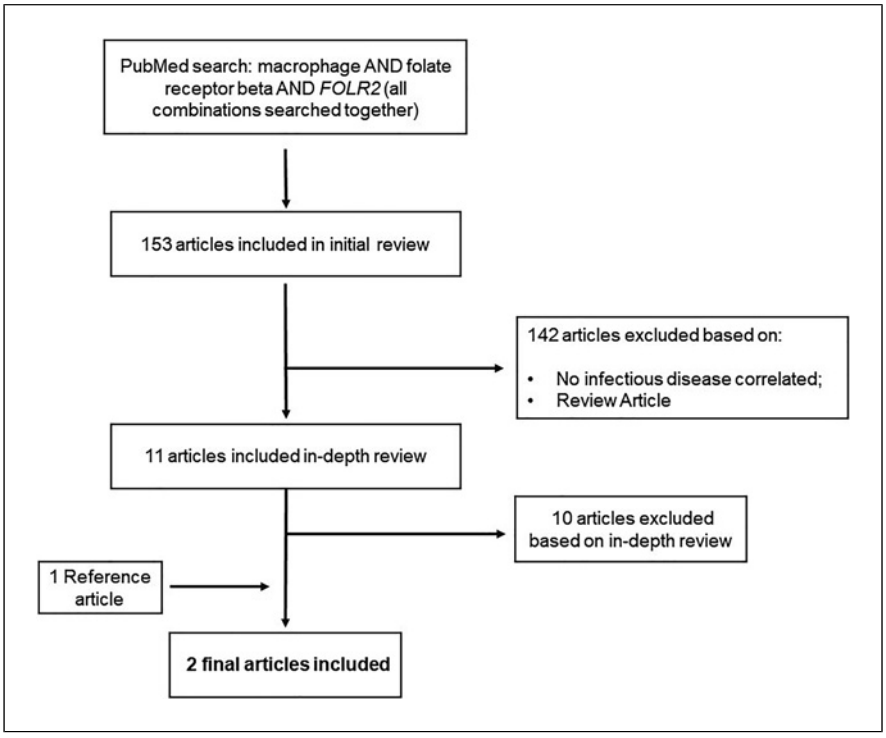

Fig. 1. Article flow: 153 articles were identified by searching the PubMed database and Google Scholar search engine, using combinations of the terms macrophage, folate receptor beta, *FOLR2*. After evaluating the abstracts, 142 articles were excluded. Of the 11 remaining articles, after in-depth review, 10 more articles were excluded. Finally, 1 article was added by the reference list, totaling 2 articles included in this scoping review.

Results

Scoping Review

From the first search, we obtained 153 total articles. A total of 142 articles were excluded based on abstract review because they were either literature review articles or did not include microorganisms. A deeper review of 11 studies resulted in 10 more articles being excluded because they were also found to be literature review articles, did not study FRβ signaling per se, or did not evaluate the response of macrophages to a microbe or part of a microbe. Table 1 summarizes the articles analyzed in-depth and the reasons why they were included or excluded [9, 12, 27–36]. One additional study was included upon review of the references of the included studies, comprising 2 articles selected for this scoping review. The study selection strategy is illustrated in Figure 1.

Review of Included Studies

Our search did not identify studies specifically examining the extent to which FRβ signaling modulated macrophage responses to intact microorganisms. However, we identified two studies relevant to this query that are worthy of summarizing below.

In 2009, Xia et al. [34] reported the induction of a functional FRβ receptor on mouse peritoneal macrophages that were recruited following the peritoneal injection of thioglycolate, live *Pseudomonas aeruginosa*, heat-killed *P. aeruginosa*, or zymosan. This study showed that FRβ expression appeared to be enriched by inflammatory stimuli, though a specific role for this receptor in altering the function or phenotype of the macrophages was not explored. In this study, 6- to 8-week-old C57BL/6 mice were used and macrophages were harvested from the peritoneal cavity after injection with saline (control), thioglycolate, zymosan, heat-killed or live *P. aeruginosa*. Analysis by flow cytometry revealed that compared to the non-stimulated (saline) control, each of these inflammatory stimuli induced macrophage-specific, cell surface expression of FRβ, with live bacteria being the strongest inducer (though dose-ranging studies of the stimuli were not presented) [34].

The increased expression of macrophage FRβ was accompanied by an increase in the expression of "M1" activation markers, including CD80, CD86, and Ly6C/G. In addition, following the injection of live bacteria there was an increase in the production of reactive oxygen species, positively correlating with the increase in FRβ. These studies also demonstrated the functional nature of FRβ in endocytosing folic acid [34]. As noted, this study did not directly address our primary research question.

In 2015, Han and colleagues [9] reported that FRβ expression was increased in mouse lung macrophages following acute inflammation induced in vivo with

Escherichia coli LPS. Bronchoalveolar lavage was used to obtain macrophages from mice 48 h after exposure to LPS [9]. In this context, macrophage expression of FRβ was increased, and through in vivo imaging with a fluorescent probe marker of folate uptake, it was possible to observe that the fluorescence in the spectral region of the mice reached its highest point at 48 h after the intratracheal LPS and was downregulated after the depletion of this cell type. Using flow cytometry, the investigators identified that this LPS-activated macrophage population was mostly proinflammatory, characterized by an "M1" profile. And while this study demonstrated the folate-based molecular imaging strategy as a useful approach for the detection of classically activated ("M1-like") monocytes and macrophages in vivo, the study again did not explore a causal link between FRβ signaling and macrophage phenotype in response to sensing a microorganism or PAMP.

Discussion

The receptor FRβ, with a subnanomolar affinity for folic acid, is a surface marker of normal hematopoiesis of myelomonocytic lineage cells and is expressed primarily by monocytes and macrophages [1, 7]. It is unknown why monocytes and macrophages require a unique folate binding receptor since the ubiquitously expressed reduced folate carrier is present on these cells, as is the proton-coupled folate transporter [37, 38]. We speculate that FRβ expression enriches the capacity for macrophages to compete for extracellular folates over neighboring cells, using the folate to shift the phenotype of the cell through effects on cell function, metabolism, and gene expression. Potential functions for FRβ include the importation of folates to serve canonical functions related to 1-carbon metabolism (nucleic acid synthesis, methylation cycles, methionine synthesis, etc.); epigenetic modifications shaping cell phenotype through changes in gene expression; and/or the regulation of macrophage innate immune behaviors (through as-yet undefined mechanisms) such as phagocytosis, intracellular microbial killing, reactive oxygen intermediate generation, and the release of DNA-rich extracellular traps.

It is notable that *FOLR2* expression is influenced by (and might influence) the inflammatory milieu. For example, *FOLR2* expression is increased in human monocyte-derived macrophages when they are differentiated toward an M2 phenotype with M-CSF but decreased when GM-CSF is used to polarize such cells toward an M1 phenotype [37, 39]. Consistent with this, M2-like tumor-associated macrophages also exhibit relatively high *FOLR2* expression [40]. Given the "M2-like," tolerogenic phenotype of macrophages at the maternal-fetal interface [41, 42], it is perhaps not surprising that *FOLR2* expression is high in these cells. However, studies also clearly indicate that pro-inflammatory stimuli (such as IL-6 or LPS) can induce *FOLR2* expression in some macrophages [9, 39], suggesting that some "M1-like"/immune-activated macrophages also express *FOLR2*. The expression of FRβ by activated macrophages is the basis of exploiting this feature to image rheumatoid arthritis activity [34, 43], for example. The current literature is therefore a bit confusing but shows that macrophage *FOLR2* expression is sensitive to autocrine and paracrine signaling.

Notably, an informal review of the literature reveals a number of studies reporting that macrophages supplemented with folic acid display reduced proinflammatory responses to inflammatory stimuli [15–20, 22–24], but existing studies have not, to the best of our knowledge, examined the receptors governing these phenotypic changes. We were surprised to find such a lack of peer-reviewed, published basic research defining the role of FRβ in the antimicrobial response of macrophages, given the high specificity of this receptor for this cell type and the importance of macrophages in antimicrobial innate immunity. It appears that very little is known about the extent to which the FRβ regulates macrophage responses to sensing, and responding to, microorganisms.

Our scoping review enabled the identification and evaluation of 153 English-language peer-reviewed, published research articles that correlated "folate receptor beta", "*FOLR2*", and "macrophage", but the vast majority of the identified articles investigated diseases other than those caused by microorganisms. Evaluating some articles more deeply, we verified that even those that used PAMPs, such as LPS, as a model did not evaluate how FRβ signaling interfered in the functionality of macrophages. In the end, we selected two articles worthy of in-depth review, which pertained to some degree to our central research question, neither of which directly addressed the interactions among macrophages, FRβ, and a microorganism.

Limitations exist within our scoping review process. First, the relatively negative results of our search strategy suggest that little-to-nothing is understood about the contribution of FRβ to microbial sensing by macrophage, but it is possible that our search strategy failed to identify relevant investigations that have indeed addressed this topic. Our use of one database (PubMed) and one search engine (Google Scholar) reduced but likely did not

eliminate the latter possibility. Second, we only included articles written in our native English language, so our results are generalizable to only that language and we may have missed critical studies published in other languages. Regardless of these limitations, it appears we have identified an area of immunology deserving further study.

Conclusion

In summary, we present the published research articles by Xia et al. [34] and Han et al. [9], which, despite showing a relationship between the increase in FRβ-expressing macrophages in models of infection or stimulation with PAMPs, did not identify how either receptor activation or receptor signaling modulates with cellular functionality. Despite several studies showing that folate regulates the inflammatory response and has an important action modulating these environments of intense activation of the immune system, it is still not clear how these folate compounds act on FRβ. Future studies that investigate in more depth the relationship between FRβ activation in the immune response to microorganisms are necessary and critical.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.M.A. conceptualized the article. A.C.C.C.B and L.M.R made the study selections. A.C.C.C.B generated the table and figure and wrote the first version of the manuscript. L.M.R and D.M.A reviewed and wrote the second/third versions of the article and revised the criteria for inclusion/exclusion of relevant literature.

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