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Deciphering the Role of Kruppel-like Factor 9 in Sepsis and Immunity: Perspectives from Joint Collective Omics Data and a Literature Review

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Abstract

Publicly available transcriptome profiling data show that the abundance of Kruppel-like factor 9 (KLF9) transcripts is elevated in neutrophils exposed to the plasma of septic patients. KLF9 is a transcription factor involved in regulating cancer cell proliferation, neurological development and reproduction, but its possible role in sepsis has not been reported in the literature. In the context of this review, further exploration of the public literature and transcriptional profiling records revealed the following: 1) KLF9 transcript abundance is also increased in vivo in patients with sepsis across multiple datasets. 2) KLF9 is one of the few members of the KLF family that can be induced by treatment with the broad-spectrum immune activator PMA/ionomycin. 3) Among other known roles, KLF9 contributes to increased oxidative stress and tissue injury via the repression of the levels of antioxidants such as thioredoxin reductase 2. A similar role can be inferred in neutrophils in the context of sepsis. Taken together, this gene-centric review of omics and bibliographic records identified potential gaps in biomedical knowledge about the role of KLF9 in sepsis and immunity and identified potential avenues for downstream investigation.

Keywords: *Immunity, KLF9, Neutrophils, Oxidative stress, Sepsis, Transcriptomics.*

Introduction

Context and Initial Observation

A hands-on training workshop was run remotely by instructors based in Doha, Qatar (BSAK and MA), involving colleagues from the Centre for Drug Discovery and Development, Sathyabama Institute of Science and Technology and the National Institute for Research in Tuberculosis (ICMR), both located

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in Chennai, India. A subject-matter expert from the University of Sydney in Australia was involved with the contextual interpretation (YZ). Public transcriptome datasets were used as a source of training material, with this particular module focusing on the interpretation of profiles obtained for a single candidate gene ("collective omics data" training module 1 – COD1, as described in an earlier publication [1]). KLF9 was selected among a pool of candidates based on a superficial screen that verified that a) the abundance of its RNA increased following neutrophil exposure to septic serum in vitro, as measured via transcriptome profiling (dataset with ID GSE49755, deposited in the NCBI GEO repository as part of earlier work and publication) [2], and b) literature describing its involvement in either sepsis or neutrophil immunobiology was minimal or lacking (Figure 1). A stepwise approach was adopted to further explore the role of KLF9 in the context of sepsis, combining an in-depth review of both the KLF9 literature and the KLF9 transcriptional profiles available in public transcriptome datasets deposited in the NCBI gene expression omnibus (GEO).

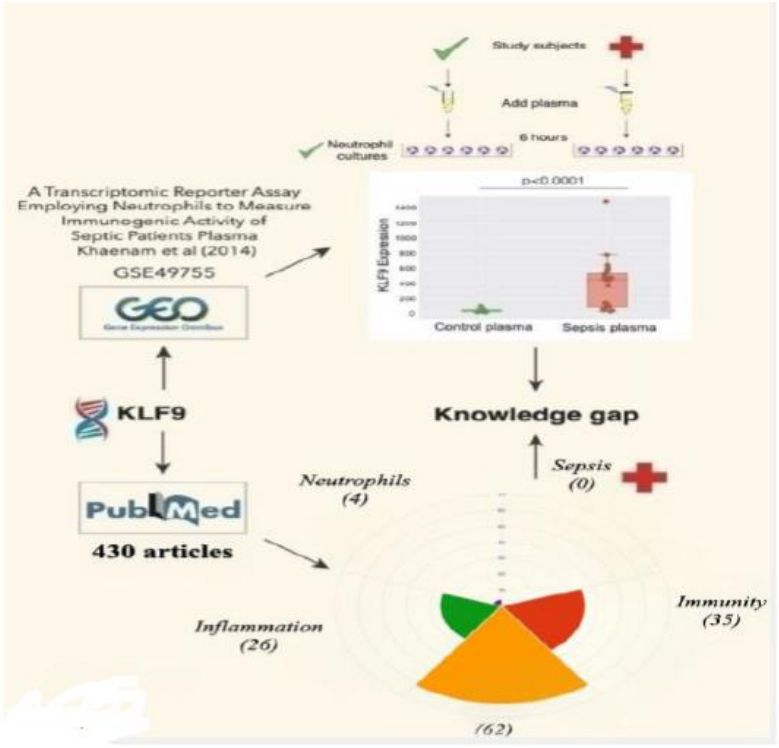

Figure 1. Initial Observation and Documentation of the Knowledge Gap.

The box plot above represents KLF9 transcript abundance in neutrophils cultured in vitro for 6 hours in the presence of the plasma of septic patients or uninfected controls ($p<0.0001$; excerpt from data deposited in GEO by Khaenam et al. under ID GSE49756. [2]). The polar plot below shows the title or abstract keywords associated with "sepsis", "neutrophils", "inflammation", "immunity" or "blood" in 430 articles that constitute the KLF9 literature. Those themes were selected based on their relevance to the experimental setting in which transcript upregulation was observed. The number of articles from the KLF9 literature linked to such themes is indicated in the plot and parentheses. It appears that the KLF9 literature neither mentions neutrophils nor sepsis.

Introduction to Sepsis and Neutrophils

As a first line of defence against pathogens, polymorphonuclear neutrophils are key players in the innate immune response. After transmigrating from the blood across endothelial cells and into infected tissues, neutrophils deploy a large arsenal of antimicrobial functions, including phagocytosis, the release of reactive oxygen species (ROS) and granular proteins, cytokine

production and the release of neutrophil extracellular traps (NETs) [3, 4]. These functions are critical for pathogen elimination and tissue repair during infection. Sepsis is defined as life-threatening organ dysfunction related to tissue damage caused by a dysregulated host response to infection. Sepsis-induced organ dysfunction is initially triggered by infection but is also driven by aberrant and deleterious host responses [5-7]. The management of sepsis consists of prompt recognition, the administration of broad-spectrum antibiotics, fluid resuscitation and vasopressor administration in cases of life-threatening hypotension. Even with optimal management, sepsis mortality remains high, reaching 20 to 30% [8, 9]. These observations raise the question of a new therapeutic approach by targeting the host response.

General Review of the KLF9 Literature

KLF9 is a member of the SP/KL family of transcription factors that bind CAC elements and GC-rich boxes in gene promoter regions (reviewed in [10, 11]). Structurally, members of this family are characterized by the presence of three Kruppel-like zinc fingers, which confer binding specificity. KLF9 is known to be able to either repress or activate the transcription of target genes, depending on the number of GC regions present in the promoter region [12].

Prevalent research themes among the KLF9 literature were identified via the following steps:

Step 1: Workshop participants were tasked with developing a PubMed query for retrieving KLF9-associated literature (incorporating all KLF9 official denominations as well as aliases listed in the OMIM, Entrez Gene and SwissProt databases):

KLF9 [tw] OR "Kruppel like factor 9" [tw] OR "Kruppel-like factor 9" [tw] OR BTEB [tw] OR BTEB1 [tw] OR "Basic Transcription Element-Binding Protein 1" [tw] OR "Transcription Factor BTEB1" [tw] OR "GC-Box-Binding Protein 1" [tw] OR "Krueppel-Like Factor 9" [tw] OR "Krueppel Like Factor 9" [tw] OR "BTE-Binding Protein 1" [tw] OR "Basic Transcription Element Binding Protein 1" [tw] OR "Basic Transcription Element Binding Protein" [tw] NOT (benzene OR silsesquioxanes OR borate OR "ethylene oxide" OR organosilane).

The above query returned **430 entries** as of December 2023. Arguments following the Boolean "NOT" were added to exclude false positive results (e.g., BTEB also stands for "1,4-bis(triethoxysilyl)benzene").

Step 2: participants conducted a general survey of the KLF9 literature to identify the main research themes. For this purpose, they extracted relevant keywords from the titles of articles that also contained the KLF9 official name symbol or aliases in titles ([tw] before the Boolean argument NOT was substituted by [it] in the query shown above, returning 193 "core" articles). Keywords belonging to multiple categories were selected: tissues, cells, disease, biomolecules, and molecular/cellular processes. They were next grouped based on semantic similarity/convergence, and their prevalence among the entire body of the KLF9 literature was determined. The following research "themes" and their respective query arguments retrieved more than 10 articles each (Figure 2 & Table 1): "Cancer", "Proliferation", "Nervous system", "Thyroid hormone", "Female reproductive system", "Corticoids", "Migration", and "Oxidative stress".

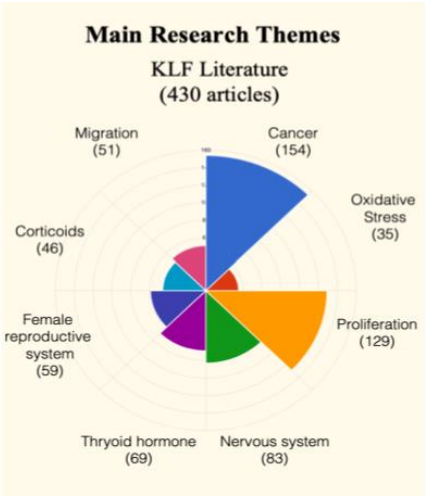

Figure 2. KLF9's Main Research Themes.

Biological concepts were extracted by manually curating the KLF9 literature (430 articles in total). The concepts that were found to be most prevalent included cancer, proliferation, nervous system, thyroid hormone, female reproductive system, corticoid, migration and oxidative stress. Each segment on the plot represents the number of articles in the KLF9 literature associated with those concepts. The query phrases used for the retrieval of the literature associated with each of those themes are provided in Table 1.

Table 1. Keywords and Query Phrases Used to Retrieve the KLF9 Literature Relevant to Specific Research Topics.

Theme	Keywords & query phrase	Number of articles
Cancer	AND (neoplasms [tw] OR neoplasms [tw] OR cancer [tw] OR tumour [tw] OR tumours [tw])	154
Proliferation	AND (proliferation [tw] OR proliferate [tw] OR proliferative [tw])	129
Nervous system	AND ("neurons"[tw] OR "neurons"[tw] OR nerve [tw] OR nervous [tw] OR brain [tw])	83
Thyroid hormone	AND ("Thyroid hormone"[tw] OR "Thyroid hormone receptor"[tw])	69
Female reproductive system	AND (pregnant [tw] OR pregnancy [tw] OR endometrium [tw] OR endometriosis [tw] OR progesterone [tw])	59
Corticoids	AND ("glucocorticoids"[tw] OR "Progesterone"[tw] OR "Corticoid"[tw])	46
Migration	AND (migration [tw])	51
Oxidative stress	AND ("Oxidative stress" [tw])	35

Each of these Themes is Elaborated Upon in the Following Sections:

Cancer & Proliferation

In cancer, KLF9 has generally been described as an oncosuppressor and is associated with reduced proliferation and tumour regression in different cancers, including hepatocellular carcinoma, gastric cancer, breast cancer and prostate cancer [13-18]. KLF9 tumour suppressive activity is chiefly mediated through the inhibition of

proliferation (the second most prevalent research theme in the KLF9 literature), but one report notably described the prevention of colorectal cancer through KLF9-dependent suppression of ISG15, an interferon-inducible apoptosis inhibitor [19].

Nervous System

A substantial body of literature documents the role of KLF9 in the development of the central nervous system and the response to injury or stress. The level of KLF9 transcript abundance is increased by multiple factors that play a role in CNS development and plasticity, including 1) thyroid hormone (T3), 2) corticosteroids released as a result of chronic stress, and 3) lysophosphatidic acid (LPA), a lipid derived from phospholipids that possesses signalling properties/activities [20]. However, the roles of KLF9 appear to be variable and seemingly contradictory. Induction of KLF9 by all three of these factors has been shown by one group to promote neural morphogenesis, stimulate the proliferation of neuronal cells and increase the number and length of neurites ("neurite outgrowth") [20-23]. More recently, a second group published several papers demonstrating a role for KLF9 in the inhibition of axon regeneration [24, 25].

Corticoids

KLF9 regulation by steroid hormones not only controls nervous system plasticity but is also involved in glucocorticoid-mediated liver gluconeogenesis [26], as well as in the response of endometrial cells to progesterone [27, 28].

Thyroid Hormones

The KLF9 gene contains a thyroid hormone response element [29], and a wide range of effects this hormone has on neurologic development and hematopoiesis are mediated by KLF9 [29-32]. Indeed, recent work by Zhang et al. demonstrated a role for KLF9 in erythroid cell maturation and lymphopoiesis, with the expression levels of KLF9 transcripts markedly decreased in the thymus in a pig model of hypothyroidism [32].

Female Reproductive System

KLF9 influences the transcriptional activity of progesterone and estrogen receptors in endometrial cells. Ablation of the KLF9 gene results in subfertility due to reduced embryo implantation, decreased uterine stromal PGR expression, attenuated uterine sensitivity to P [33,34], and defects in parturition [35 ,36].

Migration

A study by Zhong et al. investigated the impact of KLF9 on the migration of cancer cells via transwell migration assays and reported that pancreatic cancer cell lines, such as BxPC-3 and PANC-1 cells overexpressing KLF9, exhibited decreased migration ability in vitro [37].

Oxidative Stress

Elevation of KLF9 under conditions of oxidative stress has been reported in earlier studies [38-41]. While some studies provide evidence that KLF9 acts against the production of reactive oxygen species (ROS) induced by arsenic trioxide [39] or angiotensin II [40], two other studies contradict this observation and report that KLF9 promotes the accumulation of ROS [38, 41]. This topic is developed further as part of the discussion below.

Review of Changes in KLF9 Abundance in Sepsis Transcriptome Datasets

Steps were taken next to determine whether an increase in the abundance of KLF9 transcripts could be observed during sepsis in additional public datasets. *Datasets were selected based on their relevance before retrieving KLF9 profiles and computing fold changes and significance levels in abundance between cases and controls.* This ensures the absence of selection bias. Of the 8 microarray datasets initially selected, 2 did not include probes for KLF9. The remaining 6 significant differences between the septic and control

groups were found in 4 patients (Figure 3). However, 2 of the 4 experiments were repeats of the neutrophil serum exposure experiment, which served as a basis for our initial screen (GSE49756, GSE49757) [2]. Although these datasets were generated separately, they do not provide the same level of validation as a truly independent dataset. The other four datasets were generated in unrelated studies that were contributed to GEO by Pankla et al. (GSE13015) [42], Smith et al. (GSE25504) [43], Banchereau et al. (GSE30119) [44] and Parnell et al. (GSE54514) [45]. Overall, this screen revealed that changes in KLF9 transcript abundance can be observed in vivo in septic subjects in various study settings. However, to confirm this notion, KLF9 profiles were accessed in additional datasets. Differences could be found not only between septic subjects and controls but also markedly between children with systemic-onset juvenile idiopathic arthritis (SoJIA) (link = [46]). This disease is considered autoinflammatory and is driven by interleukin 1 [47]. It was also found to be significantly increased in the plasma of PBMCs from patients with ulcerative colitis or Crohn's disease (link = [48, 49]. More directly relevant to our original findings, the abundance of KLF9 transcripts was also increased upon exposure of PBMCs to the serum of patients with pneumococcal infections [50]. Notably, however, the abundance of KLF9 transcripts was not increased in response to plasma for patients with type 1 diabetes (T1D), which can likely be considered less immunogenic and does not reflect a systemic inflammatory process [51, 52].

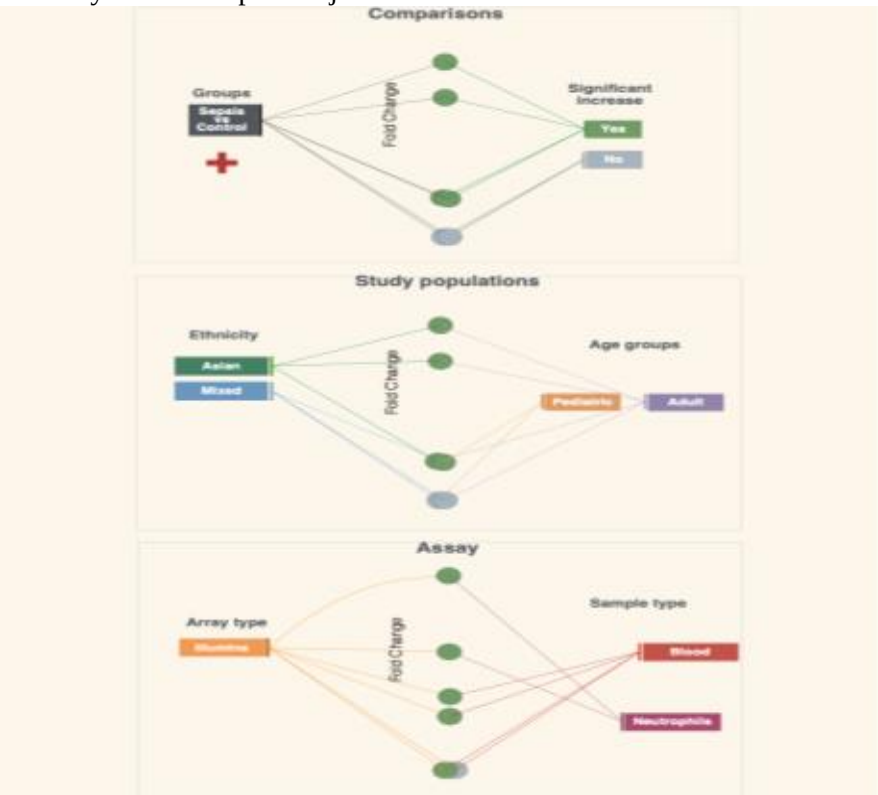

Figure 3. Increased KLF9 Expression in Sepsis is Observed in Four Out of Six Independent Datasets**.**

This graph shows the fold changes in the abundance of KLF9 in six independent datasets selected for subsequent investigation of the increase in the abundance of KLF9 RNA observed in neutrophils exposed to septic plasma (Figure 1). Each dataset is represented by a spot. The position of the spot on the vertical axis indicates the corresponding fold change in the abundance of KLF9 in the dataset. Spots are connected to dataset attributes (metadata). In the top panel, attributes relevant to the group comparisons that were performed

are shown (groups being compared, whether the increase in KLF9 abundance is statistically significant). In the middle and bottom panels, attributes describing the study populations and assay, respectively, are overlaid on the same graph. The datasets used and the corresponding GEO IDs are referenced in the text.

Screening and Review of the Literature Describing the Role of KLF9 in Immunity

A review of KLF9 profiles across a wide range of public datasets confirmed that the abundance of its transcripts increased during sepsis and under some systemic autoinflammatory conditions. The logical next step was investigating the extent of available biomedical literature describing the role of KLF9 and immunity. More specifically, themes related to the experimental setup in which differences were initially observed were sought among the KLF9 literature: these themes were "sepsis", "neutrophils", "inflammation", "immunity" and "blood".

No articles linked KLF9 and "sepsis" or "neutrophils", with 26 potentially linking KLF9 with "inflammation", 35 with "immunity" and 62 with "blood" (Figure 1). The nature of these associations is next examined in more detail.

Inflammation & Immunity

One of the most relevant publications is from Chinenov et al., who reported a role for KLF9 in promoting the anti-inflammatory program in macrophages via cooperation with the glucocorticoid receptor [53]. Other reports indirectly link KLF9 to inflammation through its involvement in the pathophysiology of endometriosis [54]. Overexpression of KLF9 reduces the division of B cells and converts memory B cells into "native-type" B cells. Studies have shown that the overexpression of KLF9 affects interferon gamma-related signals in fish models [55] and cancer cells [19].

Review of KLF9 Expression Profiles among Reference Transcriptome Datasets

Additional insights into the potential role played by KLF9 in immunity were sought by reviewing expression profiles in several reference datasets. Figure 4 represents the level of expression and restriction of 13 KLF family members across 6 blood leukocyte populations as measured by RNA sequencing (GXB link, all KLF family members listed: [56], dataset contributed by Linsley et al. with ID GSE60424 [57]). KLF6, KLF2, KL13 and KLF4 were the most highly expressed members of the family. Among those genes, KLF4 showed the greatest degree of restriction, being almost exclusively expressed in monocytes. This finding is consistent with the role described for this member of the KLF family as a key regulator of monocyte differentiation [58-60]. KLF6, which has the highest overall level of expression but is more ubiquitously expressed across leukocyte populations, is also known to play a role in myeloid cell differentiation and the promotion of inflammation [61, 62]. Other highly expressed family members are also known to play a role in immunity, with KLF13 being a promoter of T-cell survival and a regulator of IL2 and IL4 expression [63, 64]; KLF3 plays a role in B-cell programming and development [65, 66]. The abundance levels of KLF6, 3, 4 and 13 were increased to some degree in neutrophils exposed to septic serum despite a lack of preferential expression in this cell type (GXB link, all KLFs listed: [67]). As shown in Figure 4, the overall expression level of KLF9 in leukocytes was relatively low and was most prominent in lymphocytes and NK cells. The levels of neutrophils were the lowest of all leukocyte populations, but interestingly, they were increased in two of the three septic patients included in this study (GXB link, KLF9:[68]). Other KLF family members, including KLF8 (marked B-cell restriction), KLF10 (monocytes), KLF11 (monocytes, B cells), KLF5 (monocytes, neutrophils), KLF12

(lymphoid lineage cells), and KLF16 (all cell types), are expressed at intermediate or low levels. A role for KLF8 as a factor contributing to worse outcomes of chronic lymphocytic leukemia has been reported in the literature [69]. There appear, however, to be no other reports linking these members of the KLF family with B cells, despite a strong restriction of its expression in this cell type (known aliases were employed in our literature search, including BKLF3/"Basic Kruppel-Like Factor 3" and OR ZNF741/"Zinc Finger Protein 741").

The expression levels of KLF family members were also examined in reference datasets comprising profiles of blood samples stimulated in vitro with a wide range of pathogens and host-derived immune stimulators. One of the reference datasets employed included blood stimulated for 6 hours (from Obermoser et al. [70] x 4 subjects/condition: GSE30101), and the second dataset included blood stimulated for 2 hours (from Alsina et al. [71], x 13 subjects/condition: GSE25742). The KLF9 abundance did not change in response to stimuli in either dataset but was significantly increased by PMA/ionomycin, the positive control used in GSE25742 (GXB link for KLF9:[72,73]). Phorbol 12-myristate 13-acetate (PMA) directly activates the protein kinase C (PKC) signalling pathway. In combination with ionomycin, an ionophore that increases intracellular calcium levels, it is commonly used for nonspecific activation of lymphocytes and induction of the production of cytokines such as IL2 and IL4, as well as interferons and effector molecules such as perforin (and this was indeed the case in the dataset in which KLF9 induction by PMA/ionomycin was observed (GXB link for IL2, IL4, IFNG and PRF1: [74-77]. Notably, only 4 of the 12 KLF family members listed in this dataset are inducible by PMA/ionomycin in whole blood (Figure 5). In addition, KLF9 induction by PMA/ionomycin was observed for KLF4, KLF10, KLF6 and KLF5. Strikingly, from the information available in Figure 5, all the genes are predominantly expressed in monocytes, except KLF9, which is predominantly expressed by lymphoid cells. The significance of this observation is unclear, but it offers some clues concerning the mechanisms regulating the expression of KLF9 in immune cells. The fact that it was found to be induced only by PMA/Ionomicyn and not by whole bacteria, pathogens or host-derived stimuli also suggests that neutrophil activation is not sufficient to drive KLF9 expression but that it may be driven by other factors present in septic serum.

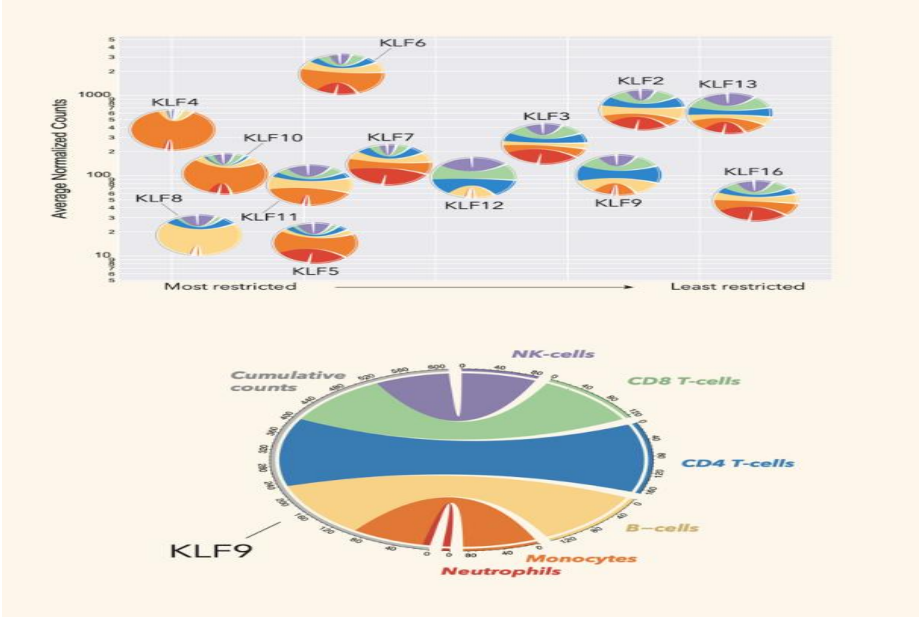

Figure 4. The abundance of KLF9 Family Member Transcripts among Blood Leukocyte Populations

Each chord diagram (circle) represents the relative transcript abundance of a given gene across six leukocyte populations: neutrophils, monocytes, B cells, CD4+ T cells, CD8+ T cells and NK cells. The colours associated with each cell population are shown in the KLF9 diagram (bottom). The predominance of a given colour in a diagram indicates a tendency of expression of the KLF family member in question to be preferentially restricted to the corresponding leukocyte population. Chord diagrams were generated via the circle R package. [91] And overlaid on a plot generated via the Plotly web application.

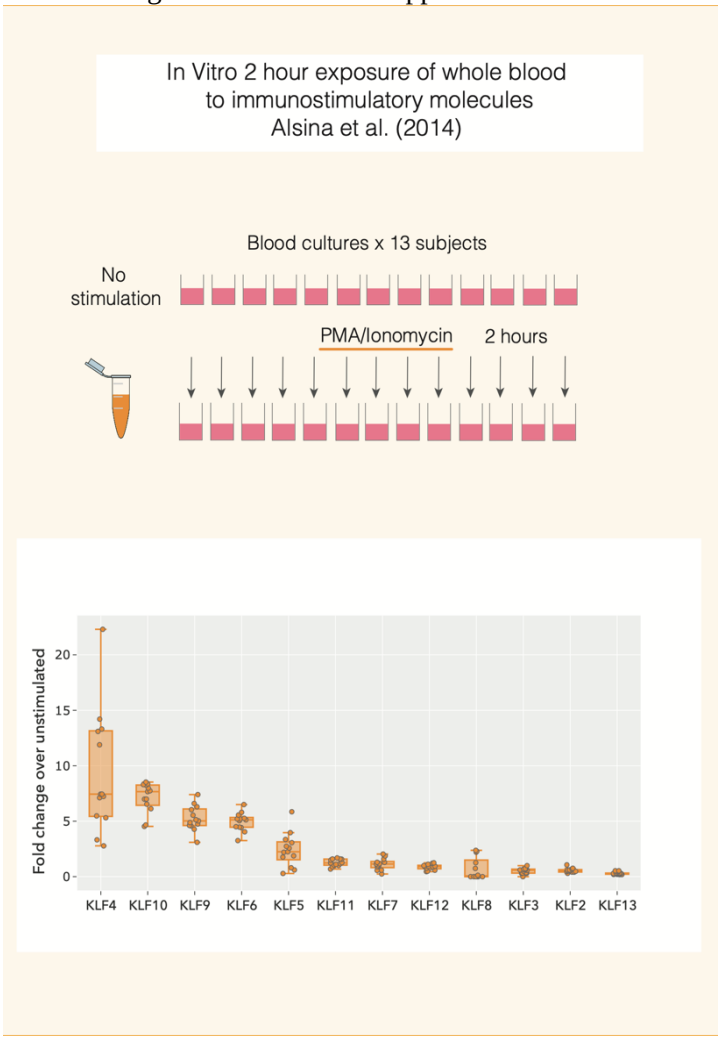

Figure 5. Changes in the Transcript Abundance of KLF Family Members in Blood Following Stimulation with PMA/Ionomycin.

The data presented are made available publicly by Alsina et al. under the NCBI GEO accession number GSE25742. Fresh whole blood from thirteen healthy subjects was incubated for 6 hr at 37°C with PMA/ionomycin. The expression profiles were generated via Illumina bead chips. The results shown are the fold changes for individual subjects over the average unstimulated values.

Another incidental observation, which in itself could also further warrant investigation of the role of KLF9 in immunity, was made while reviewing the expression profile of KLF9 in monocytes and dendritic cells exposed in vitro to a panel of immune stimulators. The data clearly show that the abundance of KLF9 transcripts is dramatically increased upon stimulation of human dendritic cells with LPS, as is MGL (meningococcal polysaccharide vaccine - Menomune), which is one of the 13 vaccines whose immunogenicity was tested in vitro in this study (GXB link [78], dataset

contributed by Banchereau et al. with ID GSE44721 [79]). No changes in the abundance of KLF9 transcripts were observed when monocytes were stimulated under the same conditions.

Inferring a Role of KLF9 in the Context of Sepsis

Additional evidence from both the literature and public transcriptome datasets could further advance our understanding of the role of KLF9 in immunity in general, particularly in the context of sepsis and neutrophil immunobiology. One approach consisted of performing full-text searches in Google Scholar (since PubMed searches are restricted to titles and abstracts), and another investigated indirect links between the KLF9 literature and neutrophil and sepsis literature by employing, for instance, some KLF9 research themes as "intermediate concepts".

The Google Scholar search "KLF9 AND sepsis" returned several relevant articles. First, a reanalysis of the septic plasma exposure dataset from Khaenam et al. was performed, which was used as a basis for the selection of KLF9 as a candidate (Figure 1, [5]). An increase in the abundance of KLF9 transcripts was also reported in this reanalysis, among other genes, in all three cell populations tested in the study: neutrophils, dendritic cells and PBMCs [80]. In another study, KLF9 was included in several hundred transcripts whose abundance was increased in splenic CD4+ T cells 6 hours following cecal ligation in a murine model of sepsis (KLF9 was increased by more than twofold-fold, with data shown in Supplemental Table 1 provided by the authors) [81].

Next, research themes associated earlier with KLF9 were used as "intermediate concepts" to indirectly link KLF9 with neutrophil immunobiology and sepsis. For example, one of the potentially relevant themes identified in the KLF9 literature was "oxidative stress", with 35 articles, none of which mentioned neutrophils. There are, on the other hand, 4376 articles in the neutrophil literature mentioning the phrase "oxidative stress" in their title or abstract, yet none mention KLF9. The query "neutrophil* AND "oxidative stress" AND sepsis" returned 135 articles. Neutrophils are well-known mediators of oxidative stress under inflammatory conditions. Indeed, after stimulation, neutrophils activate NADPH oxidase complexes in the phagosomal membrane, which catalyze reactive oxygen species (ROS) production and ensure pathogen killing [82]. ROS can also be released extracellularly, where they can induce granule and NET release and therefore promote pathogen elimination [83]. However, excessive production of ROS by neutrophils has been identified as responsible for sepsis-related acute respiratory failure and acute kidney injury and is an important mediator of tissue damage [84].

The possibility that KLF9 plays a role in driving oxidative stress during sepsis has significant potential translational relevance. Additionally, this "angle" was examined further as part of our review of the literature (Figure 6). The role of KLF9 in the regulation of the oxidative stress response has been defined in recent years, first in a bleomycin-induced pulmonary fibrosis murine model [38, 85] and a hepatotoxicity rat model [39], in neuronal cell lines in vitro [40] and two reports published in 2019 in thyroid cancer and melanoma [86, 87]. More recent studies have further implicated KLF9 in driving oxidative stress and apoptosis in various cell types, including cardiomyocytes and retinal pigment epithelial cells [88]. The transcription factor NRF2 (NFEL2) is one of two molecules implicated in this pathway. In murine cell lines and tissues, oxidative stress was shown to induce the expression of NRF2, which plays a key role in promoting the expression of antioxidant factors under low oxidative stress conditions. However, when ROS levels increase above a critical threshold, NRF2 accumulates and drives KLF9 expression,

resulting in a KLF9-dependent increase in the levels of reactive oxygen species and apoptosis. Thus, in the context of sepsis, KLF9 upregulation may indicate that oxidative stress levels have passed a critical threshold beyond which significant tissue damage has occurred. In the dataset used as a starting point for this review, NRF2 transcript abundance was also found to be increased in neutrophils in response to septic plasma exposure (GXB link:[89]), but the abundance levels of NRF2 and KLF9 were not correlated. Thus, whether the increase in KLF9 expression in sepsis is NRF2 dependent remains to be determined. Even if this was the case, the role of KLF9 may not be as straightforward as described in the model described above since additional reports also describe NRF2-induced KLF9 expression as a mediator instead of an inhibitor of oxidative stress and cytoprotection [35, 36]. These observations were made in rat livers and human and murine neuronal cell lines. Therefore, apparent discrepancies may be due to differences between species, cell types and/or tissues or may depend on whether the experimental model operates below or above a critical oxidative stress threshold (mechanisms underlying KLF9 cell-specific translational control described by Imataka et al. in [90]).

Thioredoxin reductase (TXNRD2) is the second molecule linked to the oxidative stress-mediated pro-apoptotic properties of KLF9. Published work has shown that this process is in part affected by the repression of the expression of this antioxidant molecule by KLF9 [91]. A new report published in July 2019 by Yan et al. revealed that KLF9 aggravates ischemic injury in cardiomyocytes by undermining TXNRD2-mediated ROS clearance [88].

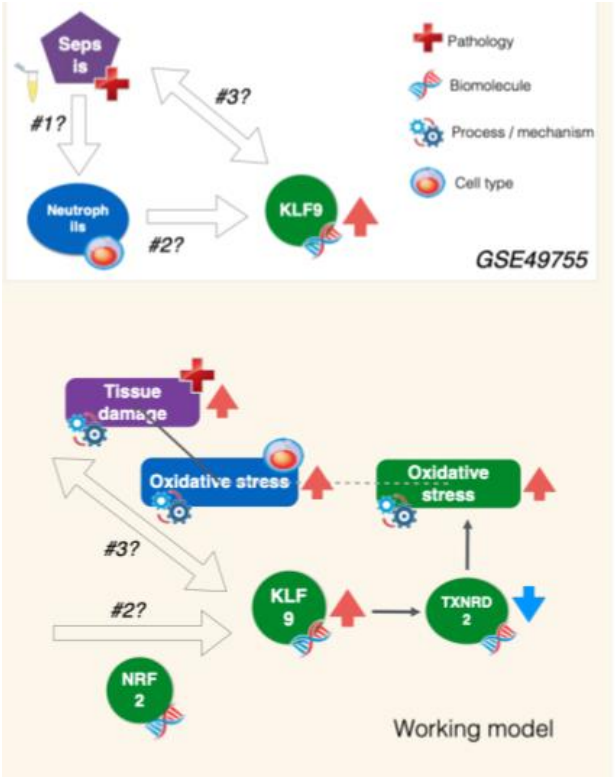

Figure 6. Inferred Role of KLF9 in Sepsis.

The experimental context and relevant questions for the public transcriptome dataset in which an increase in KLF9 expression was initially observed are represented in the panel above (GSE49755).

The involvement of KLF9 in the mediation of oxidative stress responses in neutrophils and sepsis could be relevant clinically. First, the high levels of KLF9 transcripts in the blood could indicate the occurrence of oxidative stress-mediated end-organ damage. Plasma from patients with severe sepsis was much

more potent at inducing KLF9 transcript expression in neutrophils in vitro than was plasma from patients with nonsevere sepsis (as observed in the study by Khaenam et al.) [5]: the third dataset in this study employed equivalent numbers of plasma samples from severe and nonsevere patients (GXB link: [92]). Second, NRF2 activators have shown some promise in mediating oxidative stress resolution and restoring redox balance in neutrophils from healthy human subjects challenged with LPS [93]. However, under conditions of excessive oxidative stress, such as sepsis, NFR2 may lose its antioxidant protective effect by inducing the expression of KLF9, resulting in ROS-mediated apoptosis and tissue damage [81]. Thus, further investigation of the role of KLF9 in this context may also have implications in terms of the design of therapeutic strategies. Identification of the factor(s) present in sepsis plasma that induce neutrophil KLF9 expression in vitro as well as in vivo would also be indicated. Interrogation of reference datasets has shown that KLF9 is one of the few members of this family of transcription factors to be inducible by PMA/ionomycin treatment. However, none of the host-derived or pathogen-derived activators were able to induce KLF9 expression in vitro.

Conclusions

This review provides novel insights into the potential role of KLF9 in the pathogenesis of sepsis by leveraging transcriptomic data and conducting a comprehensive literature review. The findings suggest that KLF9 may contribute to oxidative stress and tissue injury during sepsis, possibly through the regulation of NRF2 and TXNRD2 pathways. However, further experimental validation using different methodologies is necessary to confirm these hypotheses. Future studies should focus on elucidating the precise molecular mechanisms by which KLF9 modulates the immune response and oxidative stress in sepsis, as well as exploring its potential as a biomarker or therapeutic target. Additionally, investigating the conservation of KLF9 function across different biological systems could provide valuable insights into its role in sepsis and inform the development of targeted interventions. Ultimately, a deeper understanding of the complex interplay between transcriptional regulators like KLF9 and the immune system may pave the way for improved diagnosis, prognosis, and treatment of sepsis.

Conflict of Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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