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Review Article

Roles of CD71+ Erythroid Cells in Neonates: A Systematic Review

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Abstract

Purpose: To examine the literature of existing research findings describing the roles, the regulations and the possible factors impairing and circumventing CD71+ erythroid functionsin neonatal baby's immunity, symbiotic colonization and importantly this review may alert the scientific community and national health systems to implement higher attention research wise to such a vital and crucial function.

Methods: The Cochrane Library, Medline\PubMed, Embase, CINAHL and Scopus were searched to September 2017 with no date restriction. As the aim of this review was to obtain every study pertaining to CD71+ erythroid cells and neonates. No restrictions were placed on the study design, methodological quality or year of authorship. Two independent researchers assessed the studies for eligibility. A standardized table was compiled to analyze the available evidence.

Results: Eight full-text articles were analyzed in the quantitative summary. Most studies used a murine model and were lab based. Many of the articles suggested that CD71+ erythroid precursor cells are influenced by the presence of arginase-2.

Conclusion: CD71+ cells establish an immune-regulation post-delivery that do establish in optimal conditions in an immunologically immature baby. Therefore, the role of CD71 induced immune suppression is not aimed at debilitating the defenses of the neonate but to favor the settlement of normal biota. These reviewed research articles raised two fundamental questions for the scientific community: How important are CD71+ erythroid cells in establishing symbiosis with the microbiota? And what are the factors that could impair this "window of opportunity" of life long benefits to human health?

Keywords: CD71+ cells; Neonatal Biota; Immunosuppression; Symbiosis; Commensalism

Introduction

Biological defense against infectious microbial entities is carried out through a complex though organized interplay of immunological responses mediated by the innate and adaptive immunity.

These lines of defense observed in humans result from the gene expression of important and vital cellular compounds, structures and importantly dedicated immunological active and mature cells such as white blood cells. The adaptive immunity is composed of both T cell mediated immunity and B cell mediated humoral immunity [1]. The genesis of this human adaptive immunity, starts from embryogenesis and its ongoing development and maturation is a dynamic process but certainly well controlled so that gaining a functional tolerance of self-antigens and eliciting the specific and adequate response to non-self-antigens is made possible to the 'god' of the organism. Neonatal immunity is immature and while developing is challenging the neonate as it presents fundamental immunocompromised features compared to mature adult immunity. At delivery, when babies are exiting the axenic maternal gestation regarding the protective amniotic sac and placenta, babies are therefore now confronted to a duality or dilemma. This dilemma is associated with the immature but still active immunological capacity and the necessary acquisition of normal biota once exposed at birth. The immature immunological status of neonates is dangerous to the baby as this immunocompromised situation may be disastrous to the baby if infected with a virulent pathogen or even non-virulent microbe. Mother Nature has evolved in time to provide a powerful protection to the neonate by the means of their mothers, a process called Naturally Acquired Passive Immunity (NAPI). NAPI is a highly intertwined regulatory system between the baby and mother during gestation and after delivery. The baby is provided with essential Maternal Immunoglobulin G (mIgG) as such antibodies are able to pass through the placenta during gestation. Such transports are mediated by neonatal Fc gamma receptors at the lining separating the fetus with the mother circulation. Such passage is regulated and starts from the very first weeks of gestation. When gestation is completed, the fetus maternal amount of maternal antibodies exceed the own mother's pool. Immunoglobulins G are specific antibodies as their specificity varies and represents the repertoire of antigenic recognition that the mother holds and shares with her baby. This NAPI mIgG acquisition to the baby is vital therefore to prevent most of viral, bacterial, fungal hematological and organ based infection. However, this NAPI mIgG based protection is ephemeral but though with a half-life of such antibodies enough to protect the baby for a few months post-delivery. In addition, NAPI is made possible naturally by breast feeding starting with the colostrum, a rich nutritional and immunological contribution from the mother to her/his baby with defensins, antimicrobial compounds, immunoglobulins, including IgAs [2]. Therefore, passive immunity transpires prenatally and postnatally through a maternal vital contribution and most importantly is designed naturally to enable a temporal transitional passage from neonate's immature immunological signature to a basic more mature immunological status. Indeed, passive immunity is short-lived after parturition but provide the neonate with two advantages; i) it is protected to the main stream of pathogens that its mother is seropositive to and ii) this NAPI period allows the baby to mount its immunity especially the adaptive arm of such vital process as the baby is expose to pathogens, thus forcing infants to rely on their own immunity to fight pathogens. In summary, the baby as an organism seems to be balanced adequately or at least optimally with a NAPI protection and a less passive advantageous NAPI induce transitional natural development of the neonate immunity when exposed to microbes when born. While this NAPI based balance is functionally vital for the baby, a challenge though faces the newborn in both acquiring and accepting the colonization of the normal biota and in priming its

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own immunity in time both during the NAPI window of protection and beyond such protection when that latter ends. This fundamental process of colonization from the normal biota is called commensalism, a vital lifelong example of symbiosis. Microbiota colonizes the non-axenic sites of the baby's body and includes the skin and external parts of the gastro-intestinal tract where the largest assembly of colonization occurs within the colon [3]. It is noteworthy, that the initial establishment of microbiota is a result of opportunistic colonization by a simple first exposure to bacteria and other microbes after birth [4]. These exposures can vary as such as natural delivery versus cesarean delivery; The type of initial exposure is used to determine the composition of subsequent bacterial species or other microbes that colonize the baby [5]. Thus, it can be inferred that the diversified microbiota composition in an adult, may in part reflects the microbial exposure he or she had in their infant years, however the life style and environment will refine, alter and possibly challenge these initial microbial compositions [6].

Importantly, symbiosis through commensalism or mutualism is necessary to protect and help the physiological requirements of the neonate [7]. A crucial contribution of immunological and physiological benefits includes the normal biota based vitamin K production necessary for the coagulation process within the human body. Among a multitude of physiological functions, coagulation requirements in cases of lesions or impairments/lesions affecting the first line of defense such as the baby's skin are essential in preventing possible entry of pathogens or opportunistic microbes through this impaired structural innate barrier. In addition, the presence of normal biota at the surface of mucosa is providing another example of mutualistic symbiosis with an effective immunological protection known as microbial antagonism. A mechanism in which the simple presence of normal biota prevents the attachment of pathogenic microbes, and diminishes their chance to flourish as the presence of normal biota is a direct microbial competitor to pathogens for nutrients, anchoring opportunities to mucosal sites and unwanted microbial proximity translated by fierce inter microbial 'combats' intolerance. The lack of commensalism presence or establishment endangers the functionality and development of the human immune system. Indeed, absence of commensalism will prevent a much needed and pivotal priming of the baby's immune system. Mode of baby delivery might have consequential significant impacts in babies as disparities of normal biota's composition is observed and therefore differences from caesarian versus Vaginal delivery might be clinically significant as caesarian sections are not physiologically 'programmed' in this overall important first days of a newborn. It is however certain that acquisition of normal flora is a natural requirement for the symbiotic mutualistic lifelong relation of the baby with such biota and its acquisition from diverse modes of delivery is remaining an enigma in science. The absence of such biotic based colonization has impacts in the development of the baby such as the inhibition or impairment of the fundamental development of Peyer's patches, lymphoid tissue of the neonatal GIT with possible irreversible effects on the immune response capacities of the newborn in time in both in antigenic tolerance and allergies(3). The developmental immune components of the neonate's immunity from cells to tissues start early in embryogenesis; embryonic development of blood cells, hematopoiesis, occurs early in gestation and include the yolk within the first three months, followed by the liver and spleen to about seven months, and the adult based biological source of the hematopoietic production, the bone marrow which is starting at about 4 to 5 months during gestation and ongoing to adulthood. Stem cells in the hematopoietic process are regulated and responsible for the production of all blood cells from White Blood Cells (WBCs) to Red Blood Cells (RBCs) and platelets. While WBCs are essential to the overall immune system process and response, RBCs might take some immunological roles especially early in the life of a baby. Erythroid progenitors are responsible for the phenotypic production of erythrocytes or RBC [8]. In the bone marrow, these precursors are nucleated and shift to a maturation process that ultimately undergo a cellular enucleation before being released in the blood circulation. Besides oxygenation, RBCs possess immunological functions such as seen in coagulation and iron recycling and storage abilities. Additionally, during the development of the fetus, fetal production of nucleated splenic erythrocyte precursors is present within the early weeks post egg fertilization and present anti-inflammatory features, an activity that has been described important and abundant immediately post parturition while the neonate being in the process of being exposed to microbes once born [9]. In addition to oxygen transportation, recent studies have demonstrated the crucial link between splenic erythroid cells and their involvement in regulating the innate immunity of neonates [10] and the adaptive immune system [11]. These precursor cells co-express surface transferrin receptor CD71 marker along with other erythroid lineage markers [10]. Analogous manifestation of the presence of CD71 + erythroid precursor cells has been identified in human umbilical cord blood [9]. The CD71+ erythroid cells have interestingly been previously shown to suppress the immune response in neonates postparturition [5]. This immunosuppression seems to be acting and programmed to role play within a short-action period of approximately two weeks post parturition, a process seen as crucial and known as the "window of opportunity". During this phase, infants are highly susceptible to infections such as Listeria monocytogenes and Escherichia coli [4]. However, the apparent benefit of immune suppression activity of these CD71 + cells seems to be protective first against pathogen induced mucosal lining damage to the baby and possibly demonstrated by the reduced production of inflammatory cytokines including Tumor Necrosis Factor-Alpha (TNFα). It is an uttermost importance to preserve the fragile lining of the newborn and to prevent any sepsis if this latter is damaged. Secondly and not least important, the inhibition of the CD71+ cells have not only shown a decrease in TNFα but did show detrimental impacts of the normal biota [9]. This commensalism microbial colonization is therefore precisely regulated by a natural immunosuppression, an active and programmed process mediated by erythroid precursors present the newborn. This active immune suppression mediated by CD71+ cells is now challenging the neonate ability to control and shape his/her relations with the normal flora; a process which is active, regulated, temporal and not simply limited or under a forgoing perception that neonatal immunity is restricted or/and immature. It has rather highlighted that the neonatal innate immune suppression occurs within a key narrow life window and is a post-delivery, highly activated, and regulated important opportunity to allow a healthy life and an optimum immunological based transitional and maturation status from baby to adulthood stage. Therefore, it can be inferred that the neonatal immune system accommodates for optimal colonization of the biota, and that such symbiosis is more mutualistic than indeed commensal as per se. In addition, this window of opportunity is characterized by an unusual immunosuppression within the neonates so that proper normal biota is accommodated. Such window is therefore vital to establish the basis a healthy functional mutualism aimed at lasting as optimal as possible throughout a lifelong symbiosis.

Conditions that influence the concentrations of CD71+ erythroid precursor cells have emerged and some to date have been identified. General pool of Preterm newborns compared to full term pool of neonates were shown to have depleted concentrations of CD71+ erythroid cells [12]. In addition, cesarean sectional procedures as a mode of delivery has been associated with low amounts of CD71+ erythroid cell precursors in neonates. A noteworthy element that seems to affect the expression of the innate immunity in newborns is the lack of the amino acid, arginine. Infants, especially preterm ones, demonstrate an inability to produce or synthesize arginine, thus further contributing to the high mortality rate of newborns [13]. Arginine amino acid is a precursor for Nitric Oxide (NO) and eNOS which is available in RBCs [14]. NO is created from degradation of arginine via the enzymatic activity of Nitric-Oxide-Synthase (NOS) [15]. NOS

enzymes are isoforms present in various immune cells [16]. Within the RBC both eNOS and arginase compete for arginine [14]. Arginine is degraded by arginase-2, an enzyme found in RBCs and erythroid CD71 + cells, thereby reducing the availability for nitric oxide synthesis [7]. Nonetheless, increased concentration of CD71+ erythroid precursor cells have confirmed to be enriched with arginase-2 and affected physiologically by arginine inhibitors and arginine substitutes [17]. The administration effect of various arginase inhibitors such as BEC, ABH, nor-NOVA, or L-NOVA and analogue substitutes (L-arginine) resulted in a reduced elicited immune response as CD71+ erythroid cells were depleted [18]. Arginase-2 seems to disrupt bacterial phagocytic abilities of cells through the depletion of L-arginine [19]. Moreover, the method of birth delivery (cesarean versus vaginal) along with the length of the gestation period, have been shown to influence the natural process of neonatal development of the immune system and its potential response [20, 21].

Similarly, there is a panel of circumstances that influence directly or indirectly the induction and colonization of commensal microbiota with several factors reported and investigated. A recent study in mice demonstrated that maternal exposure to antibiotics during pregnancy was disrupting the quantity and diversity of neonatal commensal bacteria [22]. Interestingly, the caesarean section type of delivery in humans has been associated with diminished commensalism capacities in neonates due to a possible inefficiency of cell-to-cell interactions, a process occurring potentially as optimal in vaginal delivery [6]. Furthermore, several studies have shown that caesarean born babies were consequentially displaying a disrupted commensal biota integrity, a disruption that could span from six months to seven years post-parturition [23, 24]. Preterm newborns were shown to have induced microbiota colonization, this dysbiosis of the gut microbiome likely alters normal development of the infant immune development and gastrointestinal system health [25].

The causality of the infection and the paucity of immune defence or/ and neonatal immunological immaturity [7]. To counteract optimally to such threats, NAPI is passed on from the mother to the baby and eventually enable a progressive and temporal immunological maturation for the neonate's challenge. While this passive maternal immunological protective 'shield' is passed on maternally to the baby, surprisingly a short period, at birth and for few weeks, seems to correlate with an anti-inflammatory based response as a key step to accommodate a microbial colonization to a yet axenic baby. This crucial "window of opportunity" to tolerate normal biota colonization appears to be mediated by CD71+ erythroid precursor cells, an important role within a narrow window that seem to be crucial to a lifelong health benefit. The purpose of this review is to examine the literature of existing research findings describing the roles, the regulations and the possible factors impairing and circumventing CD71+ erythroid functions in neonatal baby's immunity, symbiotic colonization and importantly this review may alert the scientific community and national health systems to implement higher attention research wise to such a vital and crucial function.

Methods

Within this review, animals, humans and laboratory based studies were considered with primary criteria set as about CD71+ erythroid cells and neonates. Due to the diverse and limited nature of the research available, all outcomes were considered.

Electronic databases (Medline, EMBASE, CINAHL, Scopus, Cochrane Library) were searched to September 2017 with no date restriction to identify all studies pertaining to CD71+ erythroid cells and neonates. No language restriction was used. The complete search strategy is outlined as (Neonat* OR Baby OR Babies OR Infant* OR Newborn* OR Toddler*) AND (CD71* OR "transferrin receptor" OR "transferrin-receptor" OR p90 OR TFR1 OR TFRC OR "transferrin receptor protein 1" OR TFR OR IMD46) AND (erythroid* OR Erythropoietic* OR megakaryocyte-erythroid* OR Myeloid* OR progenitor* OR "Stem-cell*" OR "stem cell*" OR hematopoietic* OR Mesenchymal* OR "Bone marrow*" OR bone-marrow* OR "Embryonic Germ*" OR Embryonic-Germ).

We also employed the following other search strategies. Reference lists of included studies were screened for all relevant papers. Scopus was used to identify any articles that cited selected articles. Authors communicated with content experts in the field and with certain authors of selected papers.

Authors of trials were excluded from any decisions regarding inclusion\exclusion criteria, data extraction and risk of bias. Two researchers independently screened the search results by reading titles and abstracts for any study on CD71+ erythroid cells and neonates. Studies were excluded based on a clear indication that CD71+ erythroid cells and neonates was not the primary focus. Potentially relevant studies were obtained in full text and duplicates deleted. Foreign language papers were separated and excluded. The final studies were searched using the SCOPUS database for citations, reference lists were manually searched for missing studies and experts in the field were contacted for additional information (Figure 1). At this stage, research articles were separated into two groups those that merely mentioned CD71+ erythroid cells and neonates and those that had substantial evidence.

Any disagreements were resolved through discussion or the employment of a third author/researcher to cross examine the decision. As the aim of this literature review was to obtain every study on CD71+ erythroid cells and neonates and find information pertaining to update current findings, no restrictions were placed on study design, methodological quality or year of authorship.

Results

Two review authors independently extracted data from the studies using a standardized form and included details about trial design, purpose, and key findings. Table 1 illustrates the aims and key findings of the eight reviewed articles. While majority of the articles suggest that CD71+ erythroid precursor cells are influenced by the presence of arginase-2, a recent article contradicts the aforementioned. Concentrations of CD71+ erythroid cells along with diversity of commensal bacteria were examined in various experiments under numerous conditions.

In 2010, a non-randomized control study examined two neonatal groups: 20 infants born at term and near term (SGA) and 20 neonates born at an Appropriate Gestational Age (AGA) [26]. SGA infants were characterized as parturition that is >35 weeks. Cord blood was extracted from both groups and compared in terms of circulating EPO, prohepcidin (Pro-Hep), and erythroid progenitors. The authors' hypothesis that the SGA group will display a greater number of circulating EPO and erythroid progenitor cells than the AGA was validated. However, their hypothesis that Pro-Hep will be lower in SGA neonates than the AGA group was overturned, as circulating Pro-Hep exhibited in both groups was equal. Some of the notable erythroid progenitor cells that were highly expressed in SGA infants were CD71+, CD45+, and SSC low. Therefore, it can be inferred that SGA infants have high levels of erythropoiesis as they present traces of increased EPO and erythroid progenitor cells circulating in the cord blood. The increased EPO production in the SGA group is likely a result of fetal hypoxia which occurs due to the elevated erythrocyte precursors in Intrauterine Growth Restriction (IUGR). In contrast, the Pro-Hep concentration revealed to have not been influenced by the IUGR. While the reason behind the lack of effect of IUGR on Pro-Hep remains unknown, it can be deduced that the fetal hypoxia only occurred in the kidneys and not in the liver thus allowing for a down regulation of Pro-Hep production. This is assumed to be true, as the liver receives its oxygenated blood directly from the umbilical vein (prior to any exposure to deoxygenated

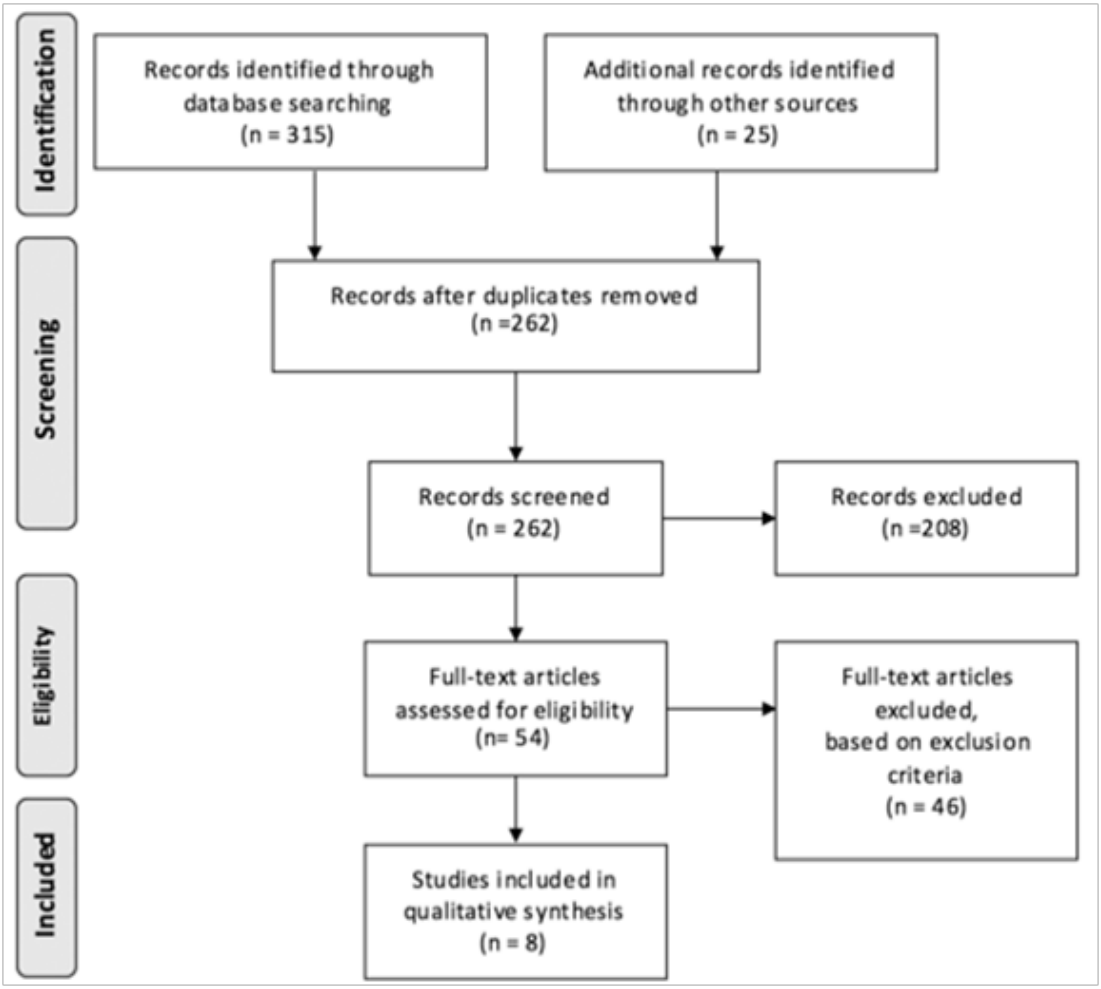

Figure 1: PRISMA 2009 flow diagram.

blood). A crucial limitation addressed in the study was the sample size that may have been too small for any significant differences in Pro-Hep concentration to have been detected.

Three years later, a highly reputable study was done, which investigated the immunosuppressive characteristics of CD71+ erythroid cells in neonatal murine and human cord blood [18]. Elahi et al. defined that parallels existed between human neonates and murine neonates suitability to infection by L. monocytogenes bacteria. Therefore, the effects of adoptive immune cells transfer from adult mice were examined for a thorough analysis of the modulated cellular activity. The authors' first hypothesis was based on previous discoveries that neonates are immunocompromised due to a lack of adequate immune cells. Therefore, they have inferred that the transferring adult cells to neonates will boost the weakened immunity. Nonetheless, this hypothesis was countered as neonates received adult splenocytes, were still highly susceptible to L. monocytogenes infections. Thus, these surprising results focused the authors' attention on further examining properties of protective cytokines such as TNF-alpha. However, when adult splenocytes were transferred to L. monocytogenes infected neonates, the production of protective TNF-alpha was diminished.

While TNF-alpha production is generally low in neonates, following the transition of neonatal splenic cells into adults infected with L. monocyogenes, has led to an increase in TNF-alpha production. Therefore, it can be deduced that the susceptibility of neonates to infection is likely caused by suppression within the neonatal environment rather than a defect in intrinsic immune cells. Consequently, for a thorough analysis of the immunosuppressive properties of neonatal cells, immune cells of adults were co-cultured with neonatal splenocytes to identify the activation and production of cytokines. The results showed, that lower amounts of TNF-alpha and IL-6 were present after being stimulated with heat-killed L-monocytogenes. These findings are further supported with human mononuclear peripheral blood cells and cord blood cells. It is notable, that the mixture of adult and neonatal splenocytes diminished cytokine production, whereas pure adult cultures, demonstrated a greater cytokine production. Furthermore, it has been portrayed that immunosuppression instigated a delay in the upregulation of adult early T-cell markers. Thus, it is concluded that neonatal splenocytes possess suppressive characteristics that halt adult immune cells activation when transferred to infected neonates.

Next, the role of inhibitors and neutralizing antibodies play in autoregulation systems is defined. The impact of arginase's enzymatic activity on adult cells that were co-cultured with neonatal splenocytes was put to the test through the use of inhibitors (BEC, ABH, nor-NOVA, or L-NOVA) and substitutes (L-arginine). The countermanding of arginase resulted in repaired adult responder cell activity, and did not bestow an effect upon the TNF-alpha production in pure adult splenocytes cultures. These findings highlight that neonatal splenocytes share analogous characteristics to suppressor cells that are associated with tumor suppression, as they are in control of active an immune response through the depletion of arginine.

Approximately 65% of all splenocytes expressed CD71+ erythroid cells populations, rather than immune lineage markers. Likewise, human

Table 1: CD71+ Research Analysis.

Authors	Year	Article	Purpose	Key Findings
Amarilyo et al.	2010	"Prohepcidin concentrations and erythroid progenitors in cord blood of appropriate versus small for gestational age neonates"	Cord blood content of, erythropoietin (EPO), prohepcidin (Pro-Hep) and erythroid progenitors were evaluated and compared between two cohorts of neonates (cohort 1: n=20 of neonates born at term and after 35-week gestation; cohort 2: n=20 of neonates born at an appropriate gestational age)	No difference in Pro-Hep concentration between Cohort 1 and Cohort 2. Cohort 1: significantly greater number of circulating EPO and erythroid progenitor cells (CD71+/ CD45+/ SSC_{low}) in cord blood than Cohort 2.
Elahi et al.	2013	"Immunosuppressive CD71+ erythroid cells compromise neonatal host defense against infection"	Assess whether CD71+ erythroid cells have immunosuppressive characteristics in neonatal mice and human cord blood.	The provisional manifestation of CD71+ immunosuppressive cells contributes to neonatal vulnerability to infections. While susceptibility to infection may be unfavorable, it allows for colonization and tolerance of commensal bacteria which provides a greater advantage following this "window of opportunity."
Wynn et al.	2015	"Neonatal CD71+ Erythroid Cells Do Not Modify Murines Sepsis Mortality"	Are CD71+ erythroid cells influencing murine neonatal survival rate following an endotoxin challenge or the induction of a poly-microbial sepsis.	CD71+ erythroid cells do not play a significant role in the survival rate in murine neonates challenged with endo-toxemia or sepsis.
Cui et al.	2016	"Immunoregulatory function of neonatal nucleated red blood cells in humans"	To identify if human cord blood Nucleated Red Blood Cells (NRBCs) play a role in innate immunity regulation and if this has a direct impact on neonates.	NRBCs down regulate LPS- activated monocytic release of TNF-α and IL-1β/Il-19 by mediating an increasing monocyte IL-10 production, a process not mediated by NRBC's arginase activated pathway.
Gomez-Lopez et al.	2016	"Umbilical cord CD71+ erythroid cells are reduced in neonates born to women in spontaneous preterm labor"	To determine if the quantity of CD71+ erythroid cells found in the umbilical cord is altered in spontaneous preterm labor/birth neonates.	Circulating CD71+ erythroid cells greater in cord blood than maternal blood. Comparisons of Circulating CD71+ erythroid cells greater in cord blood: 1) Full term (FT) with/without Laborhave fewer circulating cells than global pre-term (PT) neonates. 2) Labored FT and labored PT show no differences in circulating cells. 3) Labored PT have fewer circulating cells than without laboured PT.
Gonzalez-Perez et al.	2016	"Maternal antibiotic treatment impacts development of the neonatal intestinal microbiome and antiviral immunity"	To examine perinatal maternal antibiotic treatment (MAT) for possible impacts on. 1) Newborn mouse intestinal induction of dysbiosis. 2) Neonatal immunological response to viral challenge.	Perinatal MAT Mouse mother (MMM) have less diversified biota with mainly dominant streptococcus bacteria in stool compared to control mice (Mom and baby). MAT derived neonates (MDNs) have less diversified biota with mainly dominant enterococcus bacteria ($P<0.001$) in stool compared tonon-MAT derived neonates (NMDNs). MDNs challenged with Vaccinia virus (MDNVV) die quicker than NMDNs with the same viral challenge (NMDNVV). CD8+ T cell production of Infγ in MDNs or MDNVVs is suboptimal compared to controls. After 12 days of age, MDNs derived Splenic CD71+ erythroid cells were notably lower than controls.
Namdar et al.	2017	"CD71+ erythroid suppressor cells impair adaptive immunity against Bordetella pertussis"	To show proof of concept that CD71+ cells have a role in suppression of adaptive immunity.	Depletion of CD71+ cells resulted in increased immune cells in lungs of neonatal mice and increased specific T cell responses following B. pertussis challenge. CD71+ cells impaired humoral immunity by suppressing B cell activation and IgG antibody formation. CD71+ depletion prior to immunization enhanced production of IgG and IgA antibodies specific to B. pertussis, which further protected mice against infection.

Dunsmore et al.	2017	"Erythroid Suppressor Cells Compromise Neonatal Immune Response against Bordetella pertussis"	To investigate the role of CD71+ cells and their immunosuppressive properties in response to B. pertussis infection in neonates.	Depletion of CD71+ cells in neonatal mice resulted in reduced susceptibility to B. pertussis infection and increased survival at 2 weeks post-infection. The proposed mechanism of increased resistance against B. pertussis following CD71+ depletion was found to be due to upregulation of costimulatory molecules CD40, CD80 and CD86 along with increased levels of protective cytokines IFN-γ, TNF-α, and IL-12.L-arginine depletion via the arginase-2 activity of CD71+ cells impaired bacterial phagocytosis of B. pertussis.

cord blood was shown to be highly enriched with CD71+ erythroid cells that co-express erythroid markers, whereas the peripheral blood presented with high concentrations of mononuclear cells. Therefore, to establish a definitive suppressor element, the neonatal splenocytes were allocated various concentrations of anti-CD71 antibodies. The suppressor activity of the assorted co-cultures was evaluated. The essential outcome revealed that no suppression effect had occurred, as the amount of CD71+ erythroid cells was depleted. Conversely, the inhibition of immune lineage markers has induced CD71+ erythroid cells expression. Furthermore, murine splenocytes and human cord blood cells portrayed that a depletion in CD71+ erythroid cells induced cytokine production, thereby indicating that CD71+ erythroid cells impair the cell activation of systemic neonatal cells.

Fewer convalesce L. monocytogenes bacteria concentrations were found, following the anti-CD71 antibody treatment. The beneficial bacteria clearance effect was similarly illustrated with E. coli infection. Elahi et al. (2013) demonstrated that as murine neonates became older, the CD71+ erythroid cell concentration reduced and the pathogen clearance increased. The succeeding objective defined by this study illustrated whether the immunosuppression by CD71+ erythroid cells was evident beyond neonatal age. Concurrent with the reduced levels of arginase-2, CD71+ erythroid cell concentration was depleted and thereby did not illicit immune suppression in adults. These findings preceded to investigate the reasoning behind short-lived activity of CD71+ erythroid cells. The authors deduced, that CD71+ erythroid cells are likely activated during the transitional phase from in utero to the colonization of microbes. This proposed reasoning is supported, as commensal microbes rapidly colonize the intestine with in the first week of life.

To further investigate the correlation between CD71+ erythroid cells and commensal bacteria in suppressing intestinal immune cell activation, pregnant murine mothers were evaluated under various conditions. Antibiotic combination was administered to the water of murine mother to halt the colonization of microbes in neonates. By eradicating the commensal bacteria colonization, TNF-alpha production was reduced and the depletion of CD71+ erythroid cells resulted in an increase of signaling molecule expression. For further analysis, germ-free murine were used for the evaluation of intestinal cell activation. Although the gnotobiotic murine displayed similar levels of CD71+ erythroid cells, the reduction in these cells did not induce intestinal cell activation. Therefore, these findings highlight, that neonatal CD71+ erythroid cells protect against intestinal inflammation which is caused by commensal microbes, while the depletion caused through the use of antimicrobials and germ-free conditions hinder the protective benefits of CD71+ erythroid cells.

Collectively, the provisional manifestation of CD71+ immunosuppressive cells causes the vulnerability of neonates to infections. While susceptibility to pathogens may be unfavorable, it allows for colonization and protective benefits of commensal bacteria, which provide a greater advantage following this "window of opportunity".

In the subsequent two years, a non-randomized control study was conducted to illustrate that neonatal CD71+ erythroid cells were not a contributing factor in the neonatal survival to endotoxin challenge and polymicrobial sepsis. It has been previously shown, that murine spleens are enriched with CD71+ erythroid cells following microbial colonization [27]. This study supports the aforementioned, as post Ab-mediated CD71+ erythroid cells reduction in the intestine, microbiota-dependent immune cells were activated. In addition, the anti-CD71 treatment was shown to have a high beneficial effect of pathogen clearance. Therefore, the suppressed immune response has revealed to not be correlated, as pathogen clearance was initially unaffected by the presence of CD71+ erythroid cells through adoptive transfer. Moreover, the enhanced peritoneum immune cells activity is likely triggered by the anti-CD71 treatment which replenished the peritoneum microbiota. This stimulation of local immune cells has previously been linked to a positive effect on pathogen resistance and survival.

Remarkably, the hypothesis that murine spleen enduresCD71+ erythroid cells for approximately 2-3 weeks following microbial colonization is over turned. This opposition is further supported, as previous studies have shown that the microbiota colonization of human neonates begins during the delivery process and persists for the first several years of life.

The impact of CD71+ erythroid cells may be more miniscule than previously established, as a lack of effect on neonatal murine survival to septic challenge or to noninfectious inflammatory challenge such as LPS, was portrayed following either the depletion or adoptive transfer of CD71+ erythroid cells. Further supportive evidence was put forth by the clearance of bacteria following anti-CD71 treatment, thus suggesting that immune priming was taking place rather than immunosuppression. Despite the proposed limitation of inadequate comparison of various inflammatory and pathogenic challenges, a conclusion was presented which identified that CD71+ erythroid cells do not play a role in the survival of murine neonates with endotoxemia or sepsis.

A year later, three studies were conducted, the first of which was a cohort study that explored whether human NRBCs (Nucleated Red Blood Cells) contributed to an innate immune reaction, as well as the reaction of monocytes to LPS-stimulation [28]. For the purposes of this research, CD36+, CD71+, and GPA+ cells were used as NRBCs. Blood samples from the umbilical cord of healthy mothers were freshly acquired, along with human peripheral blood from healthy volunteers. These samples were manipulated and analyzed in a series of experiments, one of which investigated the gene expression of arginase. To the authors' surprise, the gene expression identified in the cord blood extracted NRBCs was arginase-1 mRNA, rather than arginase-2 mRNA as previously concluded by Elahi et al. (2013). However, while the lack of arginase-1 and arginase-2 was portrayed in the monocytes, the naïve T-cells such as CD4+ and CD45RA+, expressed arginase-2.

Nonetheless, the pretreatment of NRBCs with arginase inhibitors (ABH, BEC, or L-HOArg.AcOH), followed by the incubation of the monocytes with LPS, allowed arginase to be examined in relation to its potential suppressor effect on LPS-stimulated monocytes activity in producing inflammatory cytokines. The aforementioned arginase inhibitors, demonstrated no regulatory effect on the monocytes' NRBCs. Thus, contrary to popular belief, arginase does not play a role in the suppressing the activity of human monocytes by the NRBCs.

Interestingly, the Cui et al. found that the NRBCs' suppressive function seems to be carried out by some unidentified soluble factor, as this factor is likely responsible for the characteristic change in monocytes. The elevation in IL-10 production from LPS-stimulated monocytes in the presence of NRBCs thus led the authors to believe that IL-10 is a key molecule that is responsible for the distinguishing effects of NRBCs. Furthermore, in the presence of anti-IL-10R antibody during LPS-stimulation, the suppressive effect of NRBCs was reduced. Moreover, it has been previously suggested, that IL-10 is prone to having an anti-inflammatory role by overturning production of inflammatory cytokines. However, the IL-10 production is suggested to be regulated by cell-to-cell contact between the monocytes and NRBCs. The authors of this study also considered the role of arginase which has been previously considered as playing a role in immune system suppression, however they found no traces of arginase-2 mRNA were present in human NRBCs.

This paper also highlights, that previous studies have proposed that the IL-10 super family cytokine, IL-19, plays a significant role in the increased production of IL-10 from the monocytes. However, for unknown reasons, the authors of this study did not replicate these findings and rather showed that IL-19 did not halt production of inflammatory cytokines from the LPS-stimulated monocytes.

In conclusion, it has been suggested in this study, that adult innate immunity is not superior to that of neonates. While NRBCs have a role as regulatory cells in the innate immunity, the inflammatory cytokine production seems to be more suppressed in the adult peripheral blood than from cord blood monocytes. This is likely a result of reduced exposure of cord blood monocytes to the unidentified soluble factor or to IL-10. Although, the limitations of this study highlight that further research is needed to challenge the influence of various other cells and the resulting effects on other immunity ligands, this study clearly emphasized that human NRBCs are not suppressed by arginase similar to murine NRBCs.

The second noteworthy study of the same year was anon-randomized, blinded, control study that aimed at determining whether neonates born during spontaneous preterm labor or birth, displayed reduced quantities of CD71+ erythroid cells in the umbilical cord [12]. A total of 155cord blood samples were collected from neonates born to women in four different labor groups: TIL-at term spontaneous labor (38.3-40.3 weeks) n=82; TNL - at term without spontaneous labor (38.8-39.1 weeks) n=22; PTL- preterm with spontaneous labor (33.8-36.3 weeks) n=39; PTNL- preterm without spontaneous labor (30.4-35.8 weeks) n=12.

The findings challenged the authors' initial hypothesis, as the pathological course of labor may play a role in reducing neonate's immunosuppressive response. That interpretation was supported as reduced frequency of CD71+ erythroid cells were present in the umbilical cord of neonates born during PTL when compared to infants born in PTNL. Thus, it can be inferred, that a significant reduction in the number of CD71+ erythroid cells is correlated with the type of preterm labor. Furthermore, this suggests that during the preterm gestation period, an abundance of CD71+ erythroid cells exist in the cord blood. Gomez-Lopez et al. found that a greater amount of CD71+ erythroid cells appear in the cord blood of women who underwent PTNL than TIL and TNL. This further reinforces, that the process of premature labor likely influences the frequency of CD71+ erythroid cells, as no significant difference was identified in the cord blood of neonates born at term, regardless of the method of labor. Furthermore, no difference was detected in the frequency and number of CD71+ erythroid cells in the cord blood of neonates born to women during PTL and TIL or TNL.

Further research is recommended by the authors, to define the operative characteristics and the timely detection of CD71+ erythroid cells in the umbilical cord during preterm gestations. This study concludes, that umbilical cord blood was enriched with CD71+ erythroid cells, while maternal blood did not portray a difference in the presence the cells across the 155 samples. Nonetheless, evidence of weakened immune neonatal system in premature neonates is reported for such infants and is linked to increased susceptibility to infection.

Further investigation within this recent non-randomized control study was carried out to explore potential of neonatal mouse gut microbiotal dysbiosis following maternal injection of perinatal antibiotics [22]. Additionally, effects of the vaccinia virus infection on the neonatal immunity capacity and response of such neonates born from maternally antibiotic injected mothers were examined. The murine subjects were purchased, maintained, and manipulated in various settings. The studied groups consisted of a control group of mothers (n=4) and their infants (n=3), while the Maternal Antibiotic Treated (MAT) group consisted of MAT mothers (n=4) and their MAT infants (n=3). Antibiotics such as ampicillin, streptomycin, and clindamycin were administered to the water of MAT pregnant mothers, in order to manipulate the fecal composition of MAT murine subjects. A stool sample was collected from all subjects (control and study) following the delivery of murine infants, for DNA extraction and analysis of bacterial diversity composition. The GIT microbiota of MAT mothers was shown to have been influenced by the broad-spectrum antibiotics combination, as the presence of aerobic and anaerobic Gram-positive and Gram-negative microbes declined. Consequently, the MAT infants displayed a noteworthy decrease in total bacteria. In comparison to control mothers, MAT mothers displayed a significant reduction in bacterial diversity ($P<0.001$) and were nearly fully dominated by Streptococcus spp. bacteria. While the control murine neonates' bacterial diversity was lower than that of their mothers', the MAT mothers' microbiota diversity was further reduced than that of control infants ($P<0.01$). To the authors' surprise, the fecal pellets composition of MAT infants was shown to contain the least diversified amount microbiota in comparison to control infants and MAT mothers ($P<0.01$ respectively). Interestingly, the dominated microbe strain that was found in MAT infant stool sample was Enterococcus spp.

The second part of the hypothesis was then addressed, analyzing the potential effects of vaccinia virus infection on the neonatal immune system. To ensure validity of results, this experiment was conducted three separate times. Control murine infant (n=15) and MAT infants (n=16) were infected with vaccinia infection and observed. The overarching findings from these tests, illustrated that MAT infants disrupted colonization lead to a lower percentage frequency of CD71+ erythroid cells, and to a less suppressed immune response than that of the control infants. However, MAT infants were shown to have a lower survival rate and a higher susceptibility to the vaccinia infection. This is likely attributed to the observed reduction in Ag-specific IFN-Y-producing systemic CD8+ T-effector cells of MAT infants. This notable defective response of MAT murine infants to systemic infection is associated with the significant reduction in quantity, diversity, and composition of the GIT microbiota.

The most recent additions to the body of research regarding CD71+ cells looked at responses following challenge against Bordetella pertussis (B. pertussis) [11,19]. B. pertussis is a contagious respiratory infection causing whooping cough. In recent years, B. pertussis has reappeared worldwide causing serious complications and mortality in affected

neonates. Vaccination to B. pertussis is highly effective, however, in young children it is associated with decreased protection to infection, antibody production and antibody memory [29, 30].

Developing from the earlier study [18], Dunsmore et al. (2017) sought to continue to challenge the idea that active immune suppression was responsible for the susceptibility to infection during the neonatal period rather than intrinsic deficits in immune function in neonates. Neonatal mice were used as subjects due to their similar susceptibility to human neonates to B. pertussis and CD71+ cell presence. The findings of this study showed that depletion of CD71+ cells is associated with reduced susceptibility to B. pertussis infection. This was exhibited by infecting control adult and neonatal mice with B. pertussis. All neonatal mice died by day 8, whereas, all adult mice survived at 2 weeks post infection. In comparison, when neonatal mice were depleted of CD71+ cells, significant reduction in B. pertussis bacterial loads and ~90% survival to 2 weeks post infection were revealed. The effects of CD71+ cells on adult mice following infection with B. pertussis was tested by CD71+ cell infusion. This demonstrated a greater bacterial load compared to the control adult mice, further illustrating the immunosuppressive capabilities of these cells. The study proposed that the mechanism by which CD71+ depletion aids the immune system is via upregulation of costimulatory molecules CD40, CD80, and CD86 in CD11b+ granulocytes/macrophages and CD11c+ DCs, and an increase in protective cytokines such as IFN-γ, TNF-α, and IL-12. Arginase-2 was also investigated in this study. It concluded that arginase-2 expression by CD71+ cells depleted L-arginine, which has a direct effect on bacterial phagocytosis in the lungs of neonatal mice following the B. pertussis challenge. This was assessed by comparison of neonatal CD11b+ and adult CD11b+ cells in their ability to engulf live B. pertussis in vitro. The findings were that neonatal cells were impaired in their ability to phagocytose. Additionally, when neonatal cells were added to adult cells, the neonatal cells impaired adult cell function. It was found that this impaired function was reversible with L-arginine supplementation by outcompeting arginase activity.

Previous studies considered immunosuppression from the innate immune system perspective however, the study by Namdar et al. (2017) looked at CD71+ immunosuppression and its effect on adaptive immunity [11]. Where previously it has been thought that immune system immaturity was responsible for a neonate not responding as robustly to vaccination, an argument can be made that neonates have a functional immune system but under certain circumstances these functions are supressed. This study provided a concept as to how CD71+ cells supress the adaptive immune system. The study used mice as subjects and challenge to B. pertussis infection. Similarly, to the previous study, it was found that depletion of CD71+ cells resulted in increased immune cells in the lungs of neonatal mice after B. pertussis infection. In addition, a mechanistic role of increased costimulatory molecules CD40, CD80, and CD86 was established. The number of CD4+ cells was increased, however CD8+ T cells did not change. Depletion of CD71+ cells resulted in more IFN-γ and IL-17, which demonstrated that the B. pertussis specific T cell response was enhanced following the depletion of CD71+ cells. Furthermore, upregulation of the costimulatory molecules was shown in CD71+ depleted mice following B. pertussis challenge and resulted in greater B cell numbers and enhanced pertussis-specific IgG antibody but not pertussis-specific IgA antibody. Most previous studies looked at primary infection and not reinfection. To assess reinfection, CD71+ depleted mice 2 weeks post primary infection, were re-infected with B. pertussis. These mice were found to have a significantly reduced bacterial load in their lungs compared with control mice. The mechanism by which this is proposed is via enhancement of the adaptive immune system through greater levels of protective cytokines and a stronger antibody response during primary infection. Following this, vaccination and depletion of CD71+ cell was examined. It was found that CD71+ depleted mice have the presence of B. pertussis-specific antibodies of both IgG and IgA-isotypes compared to control vaccinated mice. This was further investigated by challenging both cohorts to B. pertussis infection, which showed that the vaccinated depleted group had a significantly less bacterial load of B. pertussis in their lungs, indicating that vaccination in the presence of CD71+ cells provides less protection.

Conclusion

The immune response capacities of human and murine adults are superior in adaptability, response time and maturation state to that of their respective neonates. Dysbiosis occurring in humans is often associated with improper immune capacities in adults such as seen in diabetes, obesity, irritable Bowel disease [3].

In neonates, the good settling of biota colonization in the GIT is primordial for the symbiotic benefits for the host. CD71+ cells establish an immune-regulation post-delivery that do establish in optimal conditions in an immunologically immature baby. Therefore, the role of CD71 induced immune suppression is notaimed at debilitating the defenses of the neonate but to favor the settlement of normal biota. Optimal biota colonization will favor in time the priming of the immune system during maturation. Such a concept was demonstrated by the team of Wynn et al. [27], here they sought to differentiate between immune priming and the absence of immunosuppression by a nonlethal septic challenge in two groups of anti-CD71-treated neonatal mice.

The use of antibiotic treatment was demonstrated in two of the articles, signifying that if the murine mother exhibits reduced bacterial composition while pregnant, she trans-placentally exposed the fetus to the limited microbe diversity [18, 22]. Therefore, when murine neonates were born, a downregulation of immune suppression occurred as depleted amounts of CD71+ erythroid cells were revealed. Nonetheless, neonates were still vulnerable to infections. It is therefore hypothesized that while low expression of CD71+ erythroid cells are normally associated with a mature immune response, the antibiotic treatment given to the mother perinatally and postnatally, inhibited the activation of certain signaling molecules that are expected to trigger the activation of CD71+ erythroid cells, thereby resulting in a dysregulation of the immune suppression. Current perspectives [11], delve into how manipulation of CD71+ cells could be used to further our knowledge in vaccination of infants. However, apart from one study by Gomez-Lopez et al. [12], all other aforementioned studies produced their results with a relatively small sample size thus questioning the significance of their results and the reproducibility of their findings. In addition, while some experiments of the reviewed studies were conducted on human cord blood [11, 12, 18, 19, 26, 28], inconsistency existed as majority of the substantial findings were extracted from murine tissue. Nonetheless, all papers referenced Elahi et al.'s ground breaking research [18], thereby illustrating that the scope of research was limited. Elahi was involved in both 2017 studies [11, 19] building further on our understanding of CD71+ cells. Moreover, this review highlights the faced limitations of either having too narrow sample sizes or lack of research that exists regarding CD71+ erythroid cell's role as part of the big picture of neonatal immunity. Taken together, these reviewed research articles raised two fundamental questions for the scientific community: How important are CD71+ erythroid cells in establishing symbiosis with the microbiota? And what are the factors that could impair this "window of opportunity" of lifelong benefits to human health?

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References

1. Janeway CA, Medzhitov R. (2002) Innate Immune Recognition. Annual Review of Immunology. 20: 197-216.

2. Maynard CL, Elson CO, Hatton RD, Weaver CT. (2012) Reciprocal interactions of the intestinal microbiota and immune system. Nature. 489: 231-241.

3. Belkaid Y, Hand TW. (2014) Role of the microbiota in immunity and inflammation. Cell. 157: 121-141.

4. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. (2016) How colonization by microbiota in early life shapes the immune system. Science. 352: 539-544.

5. Goenka A, Kollmann TR. (2015) Development of immunity in early life. J Infect. 71: S112-S120.

6. Neu J, Rushing J. (2011) Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol. 38: 321-331.

7. Kan B, Razzaghian HR, Lavoie PM. (2016) An Immunological Perspective on Neonatal Sepsis. Trends Mol Med. 22: 290-302.

8. Liang R, Ghaffari S. (2016) Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. Br J Haematol. 174: 661-673.

9. Badurdeen S, Mulongo M, Berkley JA. (2015) Arginine depletion increases susceptibility to serious infections in preterm newborns. Pediatr Res. 77: 290-297.

10. Elahi S. (2014) New insight into an old concept: role of immature erythroid cells in immune pathogenesis of neonatal infection. Front Immunol. 5: 376.

11. Namdar A, Koleva P, Shahbaz S, Strom S, Gerdts V, et al. (2017) CD71+ erythroid suppressor cells impair adaptive immunity against Bordetella pertussis. Sci Rep. 7: 7728.

12. Gomez-Lopez N, Romero R, Xu Y, Miller D, Unkel R, et al. (2016) Umbilical cord CD71+ erythroid cells are reduced in neonates born to women in spontaneous preterm labor. Am J Reprod Immunol. 76: 280-284.

13. Wu G, Jaeger LA, Bazer FW, Rhoads JM. (2004) Arginine deficiency in preterm infants: biochemical mechanisms and nutritional implications. J Nutr Biochem. 15: 442-451.

14. Sessa WC. (2004) eNOS at a glance. J Cell Sci. 117: 2427-2429.

15. Ostrand-Rosenberg S. (2016) Tolerance and immune suppression in the tumor microenvironment. Cell Immunol. 299: 23-29.

16. Bronte V, Zanovello P. (2005) Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol. 5: 641-654.

17. Cortese-Krott MM, Kelm M. (2014) Endothelial nitric oxide synthase in red blood cells: Key to a new erythrocrine function? Redox Biol. 2: 251-258.

18. Elahi S, Ertelt JM, Kinder JM, Jiang TT, Zhang X, et al. (2013) Immunosuppressive CD71+ erythroid cells compromise neonatal host defence against infection. Nature. 504: 158-162.

19. Dunsmore G, Bozorgmehr N, Delyea C, Koleva P, Namdar A, et al. (2017) Erythroid Suppressor Cells Compromise Neonatal Immune Response against Bordetella pertussis. J Immunol. 199: 2081-2095.

20. Lawn JE, Cousens S, Zupan J. (2005) 4 million neonatal deaths: when? Where? Why? Lancet. 365: 891-900.

21. Unger S, Stintzi A, Shah P, Mack D, O'Connor DL. (2015) Gut microbiota of the very-low-birth-weight infant. Pediatr Res. 77: 205-213.

22. Gonzalez-Perez G, Hicks AL, Tekieli TM, Radens CM, Williams BL, et al. (2016) Maternal antibiotic treatment impacts development of the neonatal intestinal microbiome and antiviral immunity. J Immunol. 196: 3768-3779.

23. Gronlund MM, Lehtonen OP, Eerola E, Kero P. (1999) Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. J Pediatr Gastroenterol Nutr. 28: 19-25.

24. Salminen S, Gibson GR, McCartney AL, Isolauri E. (2004) Influence of mode of delivery on gut microbiota composition in seven year old children. Gut. 53: 1388-1389.

25. Groer MW, Luciano AA, Dishaw LJ, Ashmeade TL, Miller E, et al. (2014) Development of the preterm infant gut microbiome: a research priority. Microbiome. 2: 38.

26. Amarilyo G, Mimouni FB, Oren A, Ochshorn Y, Ballin A, et al. (2010) Prohepcidin concentrations and erythroid progenitors in cord blood of appropriate versus small for gestational age neonates. J Perinatol. 30: 396-398.

27. Wynn JL, Scumpia PO, Stocks BT, Romano-Keeler J, Alrifai MW, et al. (2015) Neonatal CD71+ Erythroid Cells Do Not Modify Murine Sepsis Mortality. J Immunol. 195: 1064-1070.

28. Cui L, Takada H, Takimoto T, Fujiyoshi J, Ishimura M, et al. (2016) Immunoregulatory function of neonatal nucleated red blood cells in humans. Immunobiology. 221: 853-861.

29. Healy CM, Munoz FM, Rench MA, Halasa NB, Edwards KM, et al. (2004) Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis. 190: 335-340.

30. Mahon BP, Brady MT, Mills KH. (2000) Protection against Bordetella pertussis in mice in the absence of detectable circulating antibody: implications for long-term immunity in children. J Infect Dis. 181: 2087-2091.

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