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Immune responses in perinatal brain injury

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ABSTRACT

The perinatal period has often been described as immune deficient. However, it has become clear that immune responses in the neonate following exposure to microbes or as a result of tissue injury may be substantial and play a role in perinatal brain injury. In this article we will review the immune cell composition under normal physiological conditions in the perinatal period, both in the human and rodent. We will summarize evidence of the inflammatory responses to stimuli and discuss how neonatal immune activation, both in the central nervous system and in the periphery, may contribute to perinatal hypoxic-ischemic brain injury.

1. Introduction

The immune system can be broadly divided into the innate and the adaptive branch. Traditionally, the innate immune system is defined as fast acting and responds to a broad array of pathogens, whereas the adaptive immune system is tailored towards specific pathogens and has memory. However, there is immense cross-talk between the two branches of the immune system and between different immune organs (Gensollen et al., 2016; Tamburini et al., 2016), and emerging evidence suggest that even innate immune cells have memory (Netea et al., 2016).

The immune system is comprised of circulating blood cells, cells in secondary lymphoid organs (e.g. lymph nodes, tonsils, spleen) and cells resident in specific tissues (such as the skin, gut and the brain). Under pathological conditions, such as multiple sclerosis, peripheral cells are also found in tertiary lymphoid structures, such as the brain (Kuerten et al., 2012). Immune cell types are extremely heterogeneous and the phenotype and functional properties of each subset depends on the microenvironment, and hence the tissue that the cells reside in. All mature cells are derived from pluripotent hematopoietic stem cells, which in early development, can emerge from the yolk sac, chorioallantoic placenta and aorta-gonad-mesonephros region (Dzierzak and Speck, 2008). These progenitor cells give rise to both lymphoid and myeloid progenitor cells that sequentially seed the liver, thymus, spleen and finally the bone marrow where hematopoiesis takes place throughout life (Boiers et al., 2013; Migliaccio et al., 1986). Microglia, the brain macrophage, originate from precursor cells in the yolk sac and invade the brain in early embryonic life, where they are long-lived (Ginhoux et al., 2010).

2. Circulating immune cells in the human newborn

Upon birth, the immune system changes rapidly within hours to adapt to the *ex utero* milieu and then slowly matures over the following weeks to months (Christensen et al., 2012; Dowling and Levy, 2014; Xanthou, 1970). In general, infants have higher absolute white cell (leukocytes) counts in the blood than adults and their numbers slowly decline until early childhood to teenage years when they reach adult levels (Quinello et al., 2014; Schmutz et al., 2008) (Table 1, Fig. 1). Neutrophil numbers sharply increase during the first 3 days of life and then gradually decrease. Circulating monocytes show a similar trend, but the initial fluctuations are less dramatic and it is mostly the rise in neutrophils that accounts for the high leukocyte counts observed in the first days of life. Both neonatal neutrophils and monocytes demonstrate functional impairments, such as reduced chemotaxis, rolling/adhesion and antigen presentation (Perez et al., 2010). Also, the number of lymphocytes increases immediately after birth and then remains stable until about 2 years of age, reaching adult levels by early

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Table 1
Human leukocyte composition in blood at various developmental stages.

Cell type	Preterm		Term		Neonate		Adult		Comments	References
	#/ul	%	#/ul	%	#/ul	%	#/ul	%		
Leukocytes	8700								Preterms ⩽ 32 wks, n = 51	Ma et al. (2014)
							6700		Age 21–67 yrs, n = 100, mean values	Valiathan et al. (2014)
Lymphocytes (% of total leukocytes)							2134	32	Age 21–67 yrs, n = 100, mean values	Valiathan et al. (2014)
							2302		Age 16–65 yrs, n = 232	Chng et al. (2004)
			4900				2100		Term GA 37–41 wks, n = 15; Adult 20–40 yrs, n = 9	de Vries et al. (2000)
	4002	53	4100	31			2162	33	Preterm GA 30–33 wks n = 13; Term GA 37–41 wks n = 22; Adults n = 39. Not gated for CD45	Quinello et al. (2014)
			5400		5700		2300		Term GA 35+ wks, n = 18; Neonate 1 wk to 2 months, n = 11; Adult 16–77 yrs, n = 21. Not gated for CD45	Schatorje et al. (2012)
					5902				Neonates 6–8 wks	Berrington et al. (2005)
			4800		6700		1800		Term, GA not noted, n = 20; Neonates 1 wk to 2 months, n = 13; Adults n = 51	Comans-Bitter et al. (1997)
	3252	38							Preterm GA ⩽32 wks n = 51	Ma et al. (2014)
	3621		4267						Preterm GA 32 wks n = 10; Term GA 41 wks n = 18	Perez et al. (2007)
	4600		4100						Preterm GA <32 wks, n = 10; Term n = 21; Adults n = 23. Two-color FACS, not gated for CD45, mean values	Juretic et al. (2000)
	3500		5600						Preterm GA <33 wks n = 2; Term n = 19, two-color FACS, mean values	Chabra et al. (1998)
	3372	46	4378	31					Preterm GA 33 wks n = 117; Term GA 39.6 wks, n = 94	Correa-Rocha et al. (2012)
T cells, $CD3^+$ (% of lymphocytes)							1075	73	Age 50 yrs, n = 70	Bisset et al. (2004)
							1593	78	Age 21–67 yrs, n = 100, mean values	Valiathan et al. (2014)
							1550	68	Age 16–65 yrs, n = 232	Chng et al. (2004)
			3300	64			1500	72	Term GA 37–41 wks, n = 15; Adult 20–40 yrs, n = 9	de Vries et al. (2000)
			3100	58	4000	70	1500	67	Term GA 35+ wks, n = 18; Neonate 1 wk to 2 months, n = 11; Adult 16–77 yrs, n = 21. Not gated for CD45	Schatorje et al. (2012)
					4098	69			Neonates 6–8 wks	Berrington et al. (2005)
			2800	62	4600	72	1200	72	Term, GA not noted, n = 20; Neonates 1 wk to 2 months, n = 13; Adults n = 51	Comans-Bitter et al. (1997)
	2111	76							Preterm GA ⩽32 wks n = 51	Ma et al. (2014)
	2719	67	2418	58					Preterm GA 32 wks n = 10; Term GA 41 wks n = 18	Perez et al. (2007)
				66					Preterm GA <32 wks, n = 10; Term n = 21; Adults n = 23. Two-color FACS, not gated for CD45, mean values	Juretic et al. (2000)
Helper T cells, $CD4^+$							691	48[a]	Age 50 yrs, n = 70	Bisset et al. (2004)
							931	46[a]	Age 21–67 yrs, n = 100, mean values	Valiathan et al. (2014)
							814	35[a]	Age 16–65 yrs, n = 232	Chng et al. (2004)
			2300	73[b]			1000	58[a]	Term GA 37–41 wks, n = 15; Adult 20–40 yrs, n = 9	de Vries et al. (2000)
	1606	43[b]	1502	37[b]			904	42[b]	Preterm GA 30–33 wks n = 13; Term GA 37–41 wks n = 22; Adults n = 39. Not gated for CD45	Quinello et al. (2014)
			2200		3000		1000	50	Term GA 35+ wks, n = 18; Neonate 1 wk to 2 months, n = 11; Adult 16–77 yrs, n = 21. Not gated for CD45	Schatorje et al. (2012)
					2946	50[a]			Neonates 6–8 wks	Berrington et al. (2005)
			1900	41[a]	3500	55[a]	700	44[a]	Term, GA not noted, n = 20; Neonates 1 wk to 2 months, n = 13; Adults n = 51	Comans-Bitter et al. (1997)
	1501	52[b]							Preterm GA ⩽32 wks n = 51	Ma et al. (2014)
	1764	48[a]	1775	43					Preterm GA 32 wks n = 10; Term GA 41 wks n = 18	Perez et al. (2007)
		35[a]		49[a]				44[a]	Preterm GA <32 wks, n = 10; Term n = 21; Adults n = 23. Two-color FACS, not gated for CD45, mean values	Juretic et al. (2000)
	1600		2700						Preterm GA <33 wks n = 2; Term n = 19, two-color FACS, mean values	Chabra et al. (1998)
	1605	48[a]	1942	44[a]					Preterm GA <33 wks n = 2; Term n = 19, two-color FACS, mean values	Correa-Rocha et al. (2012)
Cytotoxic T cells $CD8^+$							347	23[a]	Age 50 yrs, n = 70	Bisset et al. (2004)
							522	27[a]	Age 21–67 yrs, n = 100, mean values	Valiathan et al. (2014)
			700	27[a]			616	27[a]	Age 16–65 yrs, n = 232	Chng et al. (2004)
			800				500	33[b]	Term GA 37–41 wks, n = 15; Adult 20–40 yrs, n = 9	de Vries et al. (2000)
			800	14[a]	900		500	24[a]	Term GA 35+ wks, n = 18; Neonate 1 wk to 2 months, n = 11; Adult 16–77 yrs, n = 21. Not gated for CD45	Schatorje et al. (2012)
			1100	24[a]	1000	16[a]	400		Term, GA not noted, n = 20; Neonates 1 wk to 2 months, n = 13; Adults n = 51	Comans-Bitter et al.

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