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Review

Development of immune organs and functioning in humans and test animals: Implications for immune intervention studies

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ABSTRACT

A healthy immune status is mostly determined during early life stages and many immune-related diseases may find their origin in utero and the first years of life. Therefore, immune health optimization may be most effective during early life. This review is an inventory of immune organ maturation events in relation to developmental timeframes in minipig, rat, mouse and human. It is concluded that time windows of immune organ development in rodents can be translated to human, but minipig reflects the human timeframes better; however the lack of prenatal maternal-fetal immune interaction in minipig may cause less responsiveness to prenatal intervention. It is too early to conclude which immune parameters are most appropriate, because there are not enough comparative immune parameters. Filling these gaps will increase the predictability of results observed in experimental animals, and guide future intervention studies by assessing relevant parameters in the right corresponding developmental time frames.

Contents

Abbreviations: AGM, aorta-gonad-mesonephros; BALT, bronchus-associated lymphoid tissue; E, embryonic day; FSC, first stem cells; GC, germinal centers; GD, gestational day; GI, gastrointestinal tract; GW, gestational week; H&E, haematoxylin and eosin; HEV, high endothelial venule(s); HSC, hematopoietic stem cells; IDCs, interdigitating cells; IEL, Intraepithelial lymphocytes; ILN, inguinal lymph node; LN, lymph node(s); LPL, lamina propria lymphocytes; LTi cells, lymphoid tissue inducer cells; LTo cells, lymphoid tissue organizer cells; MALT, mucosa-associated lymphoid tissue; MLN, mesenteric lymph node; MZ, marginal zone; NALT, nasal-associated lymphoid tissue; NK cells, natural killer cells; PALS, periarteriolar lymphocyte sheet; PLN, popliteal lymph node; PND, postnatal day.

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1. Introduction

The immune system plays a crucial role in maintaining health, and a healthy immune status is strongly determined during early life stages (reviewed e.g. by [1–3]). Many immune-related diseases including atopy and certain autoimmune diseases are thought to find their origin in adverse shifts in immune balances during pregnancy or the first 2–3 years of life [4–8]. Therefore, risk reduction measures or immune health optimization during these early stages of life may be most effective and efficient in reducing the loss of health, loss of quality of life and costs to society due to immune-related diseases and disorders at an older age. In addition to growing awareness of the long lasting effects on the immune system of environmental exposure to chemicals in early life, a clear trend towards immune targeted nutrition introduced on the market is ongoing. Securing the safety and efficacy thereof is also of great importance. This is especially relevant for very early life interventions, because the acceptable daily intake (ADI) concept is only applicable from the age of 12 weeks onwards and applications in younger infants, including at embryonic and fetal life, should be addressed on a case by case base using relevant models/approaches [9–11]. Several starting points for immune health interventions have been identified and are being developed into prophylactic or therapeutic approaches, particularly targeted at the early life stages, but there is no consensus on which parameters should be addressed to assess the safety and/or efficacy of the early life interventions and how all the available data should be interpreted eventually.

There are five critical windows in immune development defined by [5] and [12] (Table 1). The critical windows represent a one-time-only event or a necessary building block for later immune maturation. Thus intervention or unintended toxic provocations during these critical windows are expected to have a high impact on immune functioning later on in life. The five windows relate to five major maturational events occurring in immune system development: (1) Initiation of hematopoiesis or the initial organogenesis of the hemato-lymphoid system from undifferentiated mesenchymal

Table 1
Developmental stages in human, minipig, rat and mouse.

Prenatal milestones

		Human	Minipig	Rat	Mouse
Gestational period	1. Early	GD0[a]–GW12	GD0[a]–GD37	GD0[a]–6	GD0[a]–6
	2. Mid	GW13–28[b]	GD38–75	GD7–13	GD7–13
	3. Late	GW29–40[b]	GD76–113	GD14–21	GD14–21
Blastocyst		GD 4–6.5	GD5–6	GD3.5–5.5	GD3–6
Implantation		GD 6–7	GD11–13	GD 5–6	GD 5
Primitive streak/primitive hematopoiesis		GD 13	GD8–12	GD 8.5	GD 6.5
Placental completion:					
1. Inverted yolk sac placenta		–		GD 9.5	GD 7.2
2. Chorioallantoic placenta:					
– Diffuse epitheliochorial type		–	?/GD18[c]	–	–
– Discoid hemochorial type		GD 27		GD 11.5	GD 9.1
First heartbeat		GD 19	?	GD 9.5	GD8+
Circulation begins		GD 26	?	GD 10	GD 7/9
Transition embryo-foetus		GD 72/GW 8	GD35–36	GD 15–17	GD15
End of organogenesis[d]		GD 50–56	GD35	GD 15–17	GD15
Critical windows for toxicity/intervention[e]					
1. initiation hematopoiesis		GW8–10	?/DG16–?[c]		GD7–9[f]
2. migration stem cells + expansion progenitor cells		GW10–16	?		GD9–16
3. colonization bone marrow, thymus		GW16-birth	?		GD13-birth
4. Maturation of immune competence		Birth-year 1	?		Birth-day 30
5. Establishment of immune memory (ends at sexual maturity)		Years 1–18	Months?–5/6		Day 30–60

Postnatal key age classes

	Duration of gestation from fertilization-birth		Newborn	Infant		Child/Juvenile	Adolescent
Human	252–280 days	Birth	0–28 days	1–23 months	Weaning	2–12 years	12–16 years
Minipig	112–115 days		0–15 days	2–4 weeks		4–14 weeks	4–6 months
Rat	20–21 days		0–7/10 days	1/1.5–3 weeks		3–4.5/6 weeks	5/7–10/11 weeks
Mouse	20–21 days		0–7/10 days	1/1.5–3 weeks		3–5 weeks	5–7 weeks

– not present, ? no information found; + DeSesso 2006.
[a] Starts at fertilization/conception.
[b] The second and third trimesters have been defined also as 13-24 and 25-36 gestational weeks, respectively.
[c] Unknown for minipig/porcine data.
[d] The end of organogenesis is defined more or less as the transition from embryo to fetus.
[e] For definition see text.
[f] Applicable to both rat and mouse.