Pathology of Minipigs

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Similar physiology, metabolism and anatomy
- Skin
- GI tract
- Heart
- Brain
- Kidney
- Metabolism
- Teratogenic sensitivity

Conventional swine:
- Long history in pharmacology, surgical research
- Limited use in toxicology due to size

Swine as Lab Animals

Swine vs Dogs

- Ethics
- Not prone to vomiting
- Better NSAID tolerance
- Tolerate sympathomimetic drugs better, no cardiotoxicity
- Physiologically more similar to man
Swine vs Primates

- Ethics
- Lower costs
- Early sexual maturity (3-6 months)
- High reproduction rate
- No supply or conservation concern
- Easier to handle, transport, and house
- Fewer zoonotic diseases

Miniature Pigs

- *Sus scrofa domestica*
- Smaller than 75 kg adult weight, easy to handle
- Require less food, less test material
- Controlled geno- and phenotype
- Regulatory acceptability (US, Japan, EU)

Miniature Pigs

- Common miniature pig breeds used in research: Goettingen, Hanford, Sinclair S-1, Yucatan
- Available as SPF barrier-bred; some are also available as germ-free
- Low background lesion incidence in most breeds
Resources

- Bollen et al, The Laboratory Swine
- Svenson, The Minipig in Toxicology
- Swindle, Swine in the Laboratory
- Gad, Animal Models in Toxicology
- Hau & Van Hoosier, Handbook of Laboratory Animal Science, Vol. 3

Goettingen

- Supplied by Marshall or Ellegaard
- Used extensively in Europe
- White-skinned, short snout, pot belly
- 6-mo weight ~20 kg

Hanford

- Supplied by Sinclair Bio-resources
- Looks like a conventional pig
- White-skinned
- 6-mo weight ~40 kg
- Surgical and cardiovascular research
  - Heart size, weight similar to humans
  - Less subcutaneous fat than other breeds
**Sinclair S-1**
- Supplied by Sinclair Bio-resources
- 6-mo weight ~25 kg
- Different colors; easy identification
- Used for cardiovascular, osteoporosis, diabetes, and fetal alcohol syndrome research
- Melanoma model line

**Yucatan**
- Supplied by Sinclair Bio-resources
- Only naturally occurring miniature pig; native to Southern Mexico & Costa Rica
- Two distinct sizes available
  - Minipig: 6-mo weight ~30 kg
  - Micropig: 6-mo weight ~20 kg
- Darkly pigmented skin with little or no hair
- White skin line for dermal studies
- Spontaneous ventricular septal defect line
- Docile, easy to handle

**Yucatan Minipig**

**Yucatan Micropig**
Housing

- US regulatory guidelines:
  - Biomedical Research - Guide for Care and Use of Animals, 1996
  - Agricultural Research - Guide for the Care and Use of Animals in Agricultural Research and Teaching, 1999
- No consensus on cage sizes or types
- Often no dedicated facilities (flexibility!)

Guide for Care and Use of Animals, National Academy of Science, 1996

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Guide for Care and Use of Agricultural Animals in Agricultural Research, 1999

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<td>Litter and lactating sow, sow portion</td>
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<td>Nursery (3-27 kg of weight)</td>
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<td>Growing (27-57 kg of weight)</td>
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<td>Finishing (57-104 kg of weight)</td>
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<td>Late finishing (105-125 kg of weight)</td>
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<td>Mature adults</td>
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Systemic Pathology

Findings

Melanosis
- Pigmentation in internal organs – Normal in pigmented swine
- Meninges, lungs, spleen, heart valves, liver, lymph nodes

Necrotizing Myositis
- Goettingen
- Multifocal skeletal muscle degeneration and necrosis
- Mononuclear cell infiltrates
- May see myocyte regeneration
Mononuclear Cell Infiltrates

- Normal background finding
- Seen in many different organs:
  - Liver
  - Adrenal cortex
  - GI tract
  - Lung
  - Heart
- May indicate normal immune function

Integumentary System

- Lightly-pigmented, sparse hair
- Thick epidermis
  - Pig: 70-140 µm
  - Human: 50-120 µm
  - Rat: 10-20 µm
- Epidermal morphology and cell turnover
- Immunologic reactivity
- Dermal penetration of compounds

Similarities to Humans

- Lightly-pigmented, sparse hair
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Differences from Humans

- Ichthyiform; thick stratum corneum
- Eccrine sweat glands limited to snout and carpal areas (not involved in thermoregulation)
- Extensive subcuticular adipose
- Skin pH of 6-7 compared to 5 in man

Porcine juvenile pustular psoriasiform dermatitis (Pityriasis rosea)

- Young, white-skinned breeds
- Circular to serpiginous, erythematous lesions with crusts, usually on ventral abdomen & inner thighs
- Etiology unknown
- Transient anorexia and diarrhea reported
- Spontaneous resolution in 6-8 weeks

Microscopic lesions
- Early: perivascular eosinophilic and lymphoplasmacytic inflammation, spongiform pustules, & psoriasiform hyperplasia
- Later: Hyperplastic plaques with little inflammation, ultimately resolve completely, leaving normal skin
**Cutaneous Melanoma**

- Specific line of Sinclair S-1 pigs is a model for malignant melanoma
- ~50% of piglets have tumors at birth, 85% by 6 weeks of age
- Hereditary, not related to sun exposure
- Microscopic features, pattern of metastasis very similar to humans
- Spontaneous depigmentation and regression between 6-12 months of age

**Thrombocytopenic Purpura Syndrome**

- Goettingen piglets
- Immune-mediated thrombocytopenia (platelets <20,000/ul) and anemia
- Cutaneous purpura
- Disseminated visceral hemorrhages

**Others ??**

- Other cutaneous pig diseases are seen rarely if ever in laboratory minipigs
  - *Staphylococcus* (greasy pig disease)
  - *Erysipelothrix rhusiopathiae* (diamond skin disease)
  - Parakeratosis (zinc-responsive dermatosis)
  - Ringworm
  - Dermatosis vegetans
Respiratory System

Respiratory Diseases
- Minipigs are genetically susceptible to all porcine respiratory diseases
- Actual disease rare in the lab setting
  - SPF / barrier-raised pigs
  - Vaccination
  - Husbandry
- Should always perform complete necropsy on acute pigs to protect herd health

Porcine Respiratory Disease Complex
- Primary pathogens
  - M. hyopneumoniae
  - A. pleuropneumoniae
  - SIV
  - PRRSV
  - PRV
  - PRCV
  - PCV
- Secondary pathogens
  - P. multocida
  - S. suis
  - H. parasuis
  - B. bronchiseptica
  - A. pyogenes
  - **A. pleuropneumoniae
Laryngeal trauma

- Long soft palate and laryngeal diverticulum make intubation or gavage difficult
- Traumatic procedures can cause edema / acute inflammation in the pharynx, larynx, and cervical region

Alveolar Histiocytosis

- Increased numbers of foamy macrophages in alveoli
- May be grossly visible as white areas in lung
- Can be increased in gavage studies or studies with amphiphilic compounds, but also occur as a normal background finding in control pigs

Pulmonary Intravascular Macrophages (PIMs)

- Primary site of removal of blood-borne particulates in pigs and ruminants
- Similar function to the hepatic Kupffer cell in dogs, rodents and primates
- PIMs are resident cells, junctionally adherent to pulmonary capillary endothelium
- Be cautious using pigs for studies with injectable microencapsulated compounds
Digestive System

Similarities to Humans
- Omnivorous
- Large stomach, long small & large intestine
- Gastric cell types and secretions
- Small intestinal transit time
- Digestion, absorption, pH changes
- Tooth development

Gastric ulcer syndrome
- Begins with hyperkeratosis of the esophagus and/or pars esophagea
- Related to anorexia or finely ground, pelleted feed – decreased gastric emptying
- Stomach acid damages the squamous epithelium
- Exacerbated by stress
Cardiovascular System

Similarities to Humans

- Cardiovascular physiology, especially stress-related responses
- Similar heart and great vessels
- Coronary arterial blood supply
  - No collateral vessels in myocardium
  - Coronary artery can be clamped to induce myocardial infarct
- Postprandial lipemia

Arteritis

- Goettingen minipigs
- Degenerative vascular lesions in small- to medium-sized muscular arteries
- Coronary arteries and vessels of the renal pelvis are most consistently involved
- Intimal proliferation, medial thickening +/- necrosis, endothelial proliferation, luminal stenosis, thrombosis, disruption and fragmentation of the internal elastic lamina
Ventricular Septal Defect (VSD)

- Specific Yucatan mini- and micropig lines are models for VSD
- Occurs in about 20% of fetuses
- 65% are high membranous defects
- Polygenic defect

VSD

- Small defects may close spontaneously
- Large defects create L to R shunts leading to pulmonary hypertension and respiratory distress
- May also cause a "failure-to-thrive" syndrome
- Excellent model for human disease

Urinary System
Interstitial Nephritis
- Goettingen and Sinclair S-1
- Interstitial mononuclear cell infiltrates
- Tubular degeneration and loss
- Tubular ectasia and proteinosis
- Basement membrane thickening
- Glomerulosclerosis
- Fibrosis

Nervous System

Similarities to Humans
- CNS development; brain growth spurt before birth
- Majority of CNS cell division before birth
- Myelination largely postnatal
- Blood-brain barrier relatively immature at birth
- Highly developed eye
- Ideal for teratology studies
Retinal Dysplasia

- Goettingen
- Folds or "rosettes" in retina
- Congenital background lesion