Pathology of Human Disease Models
Genomic Medicine: Implications and Opportunities for Pathology

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Gene-Specific Tumor Phenotypes

1988
1991
2002

Gene-Specific Tumor Phenotypes
HUMANS have known for millennia that heredity affects health. However, Mendel’s seminal contribution to the elucidation of the mechanisms by which heredity affects phenotype occurred less than 150 years ago, and Garrod began ap-Genomics has a broader and more ambitious reach than does genetics. The science of genomics rests on direct experimental access to the entire genome and applies to common conditions, such as breast cancer and colorectal cancer, human immunodeficiency virus (HIV) infection, tuberculosis, Parkinson’s disease, and Alzheimer’s disease. These common disorders are also all due to the interactions of multiple genes and environmental factors. They are thus known as multifactorial disorders. Genetic variations in these disorders may have a protective or a pathologic role in the expression of diseases.

The role of genomics in health care is in part highlighted by the decreasing effect of certain environmental factors, such as infectious agents, on the burden of disease. Genomics also contributes to the understanding of such important infectious diseases as the acquired immunodeficiency syndrome (AIDS) and
GENOMIC MEDICINE

What is the Mouse Trying to Tell Us?

Gene function will be understood via phenotyping.
Phenotyping will be done in the mouse.
Disease phenotyping IS Pathology.
What is the Mouse Trying to Tell Us?

Lessons from the mouse:

* Tumor Biology
* Verification vs Validation
* Diagnosis
* Discovery
What is the Mouse Trying to Tell Us?

Gene-Specific Tumor Phenotypes

Ras  Myc  Neu
Genomic Pathology: DOES THE MOUSE “LOOK LIKE” HUMAN?

Spontaneous Lobular Breast Carcinoma
LOH: CDH1
Human

Spontaneous Lobular Mammary Cancer
Tm(p53XCDH1)
Mouse
GEM PROSTATE TUMORS
That Mimic Human

WHICH IS HUMAN?
A or B?

Phenocopies!!
Elwood-Yen PMID 14522256
GEM PROSTATE TUMORS
That Mimic Human
Full Disclosure!

GEM cMyc

Elwood-Yen PMID 14522256

Human

Shappell PMID 15026373
GEM PROSTATE TUMORS
That Mimic Human

Induced by MYC

SPONTANEOUS HUMAN

WHICH IS HUMAN?
A or B?

Elwood-Yen PMID 14522256
Too Many Mice, Too Few Pathologists

Without Proper Training and Organization, Research Dollars Will Be Wasted

Robert D. Cardiff, M.D., Ph.D., and Bruce W. Altrock, Ph.D.

The biotechnology industry faces a major problem, too many genetically modified mice and too few comparative pathologists. National and international programs aimed at unraveling the mysteries of the genome will produce a flood of transgenic and knockout mice, but not the resources for their characterization.

For example, there are already over 10,000 mouse strains available at The Jackson Laboratory and thousands more in the Laboratory of Comparative Medicine at Harvard University. Many of these mouse strains have not been pathologically evaluated due to limited resources.

Anecdotal accounts from the Jackson Laboratory indicate that some of their knockout mice have been misdiagnosed due to under-trained individuals.

Examples are numerous, including published accounts of normal mouse organs misdiagnosed as tumors, neuroendocrine tumors misdiagnosed as adenocarcinomas, periodontal abscesses misdiagnosed as lymphoma, dysplasias of repair misdiagnosed as cancers, and parasitic infestations called tumors. Results of such misdiagnoses are far-reaching and can result in years of research and millions of dollars in lost opportunity costs. Clearly, industry experts agree that proper training is essential.

Expert comparative pathologists with experience in both mouse and human histopathology. Comparative mouse pathology requires a unique set of skills and a knowledge base not possessed by most investigators, or, for that matter, the standard pathologist. Validation requires familiarity with the nuances of the mouse, and the knowledge of the human condition to be emulated by the mouse model.

The NIH is investing significantly in mouse-related research, but the investment will be all for naught without the validation, effective application, and translation toward the advancement of human health that is provided by comparative pathologists. NIH funding should reflect this by increased support for well-trained and experienced comparative pathologists.

Only 20% of knock out mice have been evaluated by a pathologist

14,000 new strains are expected by 2010 (US KOMP)
Documenting the critical shortage

The PRIME and ACVP reports

Few experimental mouse pathologists (250 jobs open)

- Few experienced with multiple mouse lines. (Ave=4.5/year)

- Necropsies often done without benefit of trained pathologists.

- Workers often lack appropriate qualifications.

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10 The Netherlands Cancer Institute, Plesmanlaan 121, NL 1066 CX Amsterdam, The Netherlands
11 University of Cambridge, Department of Physiology, Development and Neuroscience, Downing Street, Cambridge CB2 3DY, UK
Do-it-Yourself (DIY) Pathology

What type of tumor?

- Papilloma?
- Teratoma?

From J. Ward Archives
PERSPECTIVE

‘One medicine—one pathology’: are veterinary and human pathology prepared?

Robert D Cardiff¹,², Jerrold M Ward³ and Stephen W Barthold¹,²,⁴

The American Medical Association and the American Veterinary Medical Association have recently approved resolutions supporting ‘One Medicine’ or ‘One Health’ that bridge the two professions. The concept is far from novel. Rudolf Virchow, the Father of Modern Pathology, and Sir William Osler, the Father of Modern Medicine, were outspoken advocates of the concept. The concept in its modern iteration was re-articulated in the 1984 edition of Calvin Schwabe’s ‘Veterinary Medicine and Human Health.’ The veterinary and medical pathology professions are steeped in a rich history of ‘One Medicine’ but they have paradoxically parted ways, leaving the discipline of pathology only partially represented in veterinary medical curricula. The time has come for one profession to embrace the discipline of pathology, one that could only contribute to the medical care of our patients.
ENABLING TECHNOLOGY

1. Ontologies that work
2. Workflow Modeling
3. Electronic Media
   - Relational Databases
   - Digital imaging
   - Interconnectivity
INTRODUCTION TO PATHOLOGY

An organism is a physical entity that has structure and function.

Structure is a physical entity that is a part of an organism.

Function is the changes of relations between various structural entities.

A functional organism is a physical entity that is able to maintain homeostasis between structure, function, and the environment.

Data Flow
Related
Ontology
Where are the gaps?

BETWEEN
MOLECULAR CLASSIFICATIONS AND REALITY
Classification of NST Breast Cancer
# Classification of NST Breast Cancer

## Table 1. Breast cancer subtypes

<table>
<thead>
<tr>
<th>Characteristic genes</th>
<th>IHC markers</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like</td>
<td>ER-negative</td>
<td>High grade</td>
</tr>
<tr>
<td>Keratin 5 and 17</td>
<td>PgR-negative</td>
<td>More common among pre-menopausal African American women</td>
</tr>
<tr>
<td>Laminin</td>
<td>HER2-negative</td>
<td>Strong association with BRCA1 mutation carriers</td>
</tr>
<tr>
<td>Fatty acid binding protein 7</td>
<td>CK5/6-positive</td>
<td>Higher risk of recurrence</td>
</tr>
<tr>
<td>P-Cadherin</td>
<td>Often EGFR-positive</td>
<td>Responsive to chemotherapy</td>
</tr>
<tr>
<td>TRIM29</td>
<td>Ki-67 high</td>
<td>No known targeted treatment</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td>ER-negative</td>
<td>Usually high grade</td>
</tr>
<tr>
<td>HER2/c-erb B2</td>
<td>PgR-negative</td>
<td>More likely to have involved axillary lymph nodes at presentation</td>
</tr>
<tr>
<td>GRB7</td>
<td>HER2-positive</td>
<td>Higher risk of recurrence</td>
</tr>
<tr>
<td></td>
<td>Ki-67 usually high</td>
<td>Responsive to chemotherapy</td>
</tr>
<tr>
<td>Adipose tissue enriched</td>
<td></td>
<td>Responsive to anti-HER2 antibody trastuzumab and EGFR/HER2 tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>pattern</td>
<td></td>
<td>Ipatinib</td>
</tr>
<tr>
<td>Normal breast-like</td>
<td></td>
<td>Potentially due to normal tissue contamination</td>
</tr>
<tr>
<td>Adipose tissue enriched</td>
<td></td>
<td>Variable grade</td>
</tr>
<tr>
<td>Luminal A</td>
<td>ER-positive and/or PgR-positive</td>
<td>Usually responsive to endocrine therapy including selective estrogen receptor modulators and aromatase inhibition</td>
</tr>
<tr>
<td>ER cluster</td>
<td>Sometimes HER2-positive</td>
<td>If HER2+, responsive to anti-HER2 strategies</td>
</tr>
<tr>
<td>Adipose tissue enriched</td>
<td>Ki-67 high compared to luminal A</td>
<td>Most common form of breast cancer</td>
</tr>
<tr>
<td>Proliferation genes</td>
<td></td>
<td>Usually low grade</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower risk of recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Responsive to endocrine therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often less responsive to chemotherapy</td>
</tr>
</tbody>
</table>

**Abbreviations:** ER, estrogen receptor; PgR, progesterone receptor. **Source:** From Ref. 7.
Mouse Models of Basal BrCa?

- All spontaneous mouse tumors are Basal!
- Most GEM models of human Breast Cancer are Basal!
- Are Wnt-based models Basal?
- Muller PTENxERB-B2 Model Basal?
Tg(PTENXERB-B2) CK5
ONCOGENE ADDICTION

Gene-Specific Tumor Phenotypes

Ras   Myc   Neu
ONCOGENE ADDICTION

RECURRENT AND PERSISTENT TUMORS

Mutation (Gleevec)

Complementary Oncogene (K-Ras)

Epithelial-Mesenchymal-Transition (EMT) Tumors

ESCAPE FROM ONCOGENE ADDICTION
(Lessons from GEM)
EMT TUMORS HAVE *SPINDLE CELL* PHENOTYPE
and Loss of Initiating Oncogene

Adenocarcinoma → Spindle cell tumor

Epithelial tumors excluding stroma

Spindle cells infiltrate stroma

Oncogene expression is lost. 
AND
A *NEW* tumor type emerges.
EMT Tumors are Dual Staining For Epithelial and Mesenchymal Biomarkers

Epithelial IHC Stains

Mesenchymal IHC Stains

Does it Happen in Humans?
EMT in HUMAN BREAST CANCER

37 year old woman

REVERSE MODELING!!
EMT in HUMAN BREAST CANCER
37 year old woman

REVERSE MODELING!!
Genomic Medicine Creates A Problem And An Opportunity

Mission

The Center for Genomic Pathology (CGP) is a not-for-profit educational foundation whose goal is to collect, integrate and disseminate knowledge about Genomic Pathology. The CGP is designed to support educational activities of the Academy of Genomic Pathology (AGP). CGP will provide training and expertise in comparative pathology with an emphasis on the pathobiology of the genetically manipulated laboratory mouse as applied to human disease. Our objective is to train the next generation of comparative pathologists, their students and staff helping them meet the needs of the scientific community with accurate interpretation of the diseases produced in mice through experimental and genetic manipulation. This objective is being realized using remote and on-site training based on our annotated, digitized images and databases coupled with modern telepathology and Distance Learning systems. A network of international expert comparative mouse pathologists (AGP) provides interactive training and consultation.

Background

Genetically engineered mouse (GEM) mutants are rising substantially in number and complexity. However, the scientific community lacks a sufficient workforce with expertise in comparative pathology to effectively characterize and validate these model animals.

Following large-scale mouse mutagenesis programs and expansion of Genetically Engineered Mice created by individual scientists, the National Institutes of Health (NIH) is embarking on the
Industry, NIH and other international agencies are generating huge numbers of genetically modified mice. (20,000 new strains)

Such mouse mutant phenotypes are often inadequately characterized or misinterpreted.

Not enough existing comparative pathologists to meet this need.
SOLUTIONS

1. Enabling technology:
   - Whole Slide Imaging
   - Organized, Integrated Knowledge Base: NCI-caELMIR/Aperio-Spectrum/CASIMIR
   - Pathbase

2. Education:
   - Dedicated Faculty: Center for Genomic Pathology (CGP)
   - Distance Education: CGP/UCD Extension
SOLUTIONS

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caELMIR is a pre-clinical experimental data management system

The intent of caELMIR is to provide the pre-clinical scientist with a data management system to record experimental data. caELMIR provides the pre-clinical scientist with the following benefits:

- Secure web based application, allowing users to simply use the application without the need to install anything
- Built with industry standard components
  - Java (JBoss) server architecture
  - caBIG user interface standards
  - Support for multiple database back ends
    - Oracle®
    - PostgreSQL
- Assists in experimental design and management
  - caELMIR enforces the concept of studies, experiments, and experimental groups
Integrated DataBases

Experiment Specimens

Add New Specimens | Remove Specimen

Open Specimen
Specimen ID: 20728
Accession Number: TG06-0686MU
Gender: f
Cohort: Wild Type
Tumor Seen Date: 2006-12-06 00:00
DOB:
Gross Description: H&E stained paraffin section of erb2 derived MINO passage 7. Preneoplastic lesion derived from native erb2 knock in mouse donor #6536. A piece of this lesion was transplanted into cleared fat pad of an FVB mouse (passage 1). After two month a pi
Microscopic Description: None
Diagnosis: MINO WITH PARTIALLY NECROTIC ADENOCARCINOMA WITH CRIBRIFORM PATTERN(TRANSPLANT)
Comment: None
DOD: 2006-08-30 00:00:00
Gravid: 0.0
External Specimen Id: 4719
Species: mus
Genes
Endogenous - NeuIT - +/la
Engineered #1: NONE - --- - NONE
Engineered #2: NONE - --- - NONE
Fixative: Formalin - Alcohol
Fixation: on
Strain: FVB

SS134 7 3 Success 99
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CGP Faculty

- **James M. Crawford**, M.D., Ph.D. Chairman of Pathology and Editor in Chief Lab Investigation (229 PubMed publications)
- **Stephen W. Barthold**, D.V.M., Ph.D. Professor and Director, Member NAS (211 PubMed publications), Co-author Percy and Barthold “Rodent Pathology”.
- **Claudio Conti**, D.V.M, Ph.D., MD Anderson-Smithville (234 PubMed publications)
- **Murray B. Gardner**, M.D., Professor Emeritus, Former Chair UCD Pathology. AAAS Fellow (245 PubMed publications)
- **VE Ted Valli**, D.V.M., M.Sc., Ph.D. Former Chair of Pathology, Guelph, Former Dean Illinois College of Veterinary Medicine (225 PubMed publications)
- **Cory Brayton**, D.V.M. (World Traveler)
- See [http://ctrgenpath.net](http://ctrgenpath.net) for all CGP members
“GENOMIC PATHOLOGY”
Divisions of Course Work
offered over the Internet

◆ TIER ONE: BIOLOGY OF LABORATORY MICE
  - DESIGNED For graduate students, fellows and technical staff
  - GOAL: To train the student to more effectively and accurately perform studies using a mouse model. Emphasis on identification of gross and microscopic features of the healthy and diseased animals

◆ TIER TWO: PATHOLOGY OF GENETIC ENGINEERED MICE (GEM)
  - DESIGNED For persons with advanced degrees and Level I graduates
  - GOAL: To provide training in the biology and pathology of GEM for PIs.

◆ TIER THREE: GENOMIC PATHOLOGY
  - DESIGNED For certified veterinary and medical pathologists who desire advanced study on GEM
  - GOAL: To provide graduate information on specific pathologic changes seen in many GEM strains. To prepare the pathologist to become competent in evaluating these unique changes both gross and microscopically.
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Following large-scale mouse mutagenesis programs and expansion of Genetically Engineered Mice created by individual scientists, the National Institutes of Health (NIH) is embarking on the “knock out mouse project” (KOMP), aiming to knock out all functional mouse genes. Similar large-scale efforts are underway in Canada (NorCOMM, North American Conditional Mouse Mutagenesis Project), Europe (EUCOMM, European Conditional Mouse Mutagenesis Programme) and Asia. These programs, now amalgamated as the "International Mouse Knockout Consortium", are creating a critical, but unmet, need for expert comparative pathologists who are knowledgeable in mouse biology and human disease.

Comparative pathologists are the gatekeepers of translational research. Effective mouse pathology provides a global understanding of normal biology. Comparative mouse pathology
What is this mouse trying to tell us?

ONE GENE, ONE DISEASE, ONE MEDICINE

Lessons from the mouse:

*Those who understand the mouse will lead the post-genomic world.*
Thank you
CASIMIR

“...it all started with a mouse.”
W. Disney

This is the end!!

Thank you for your kind attention.