Molecular Advances in MDS

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Learning Objectives

- Next Generation Sequencing
- MDS Genomics
- Hereditary MDS
- Future Directions
Genes, Genomes, Mutations

Normal: ATCCCGA\textcolor{red}{C}CTTGCCCTGTA\textcolor{red}{A}ATCC\textcolor{red}{C}AA

Mutation: ATCCCGAC\textcolor{red}{T}TTGCCC\textcolor{red}{C}GT\textcolor{red}{A}AATCC\textcolor{red}{C}AA
Sequencing: Disruptive Technology

Main Frame

Mini Computer

Personal Computer

Gel Based Sequencing

Sanger Sequencing

Next Generation Sequencing
Sequencing Costs Have Plummeted
An Explosion in Genetic Knowledge

Massive Genomics Research

Thousands of genomic associations, many with clinical implications
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Hematology / Oncology: An Imperfect Art

Given limited ability to predict responders, doctors today practice trial-and-error medicine

Adapted from: Spear et al. TRENDS in Molecular Medicine Vol.7 No.5 May 2001; PMC Nov 2006
“Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient …[by the] ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.

Adapted from: Aleshin A et al. Neoplasia. 2010
Two Sides of Mutations

**Somatic mutations**
- Occur in *nongermline* tissues
- Cannot be inherited

**Germline mutations**
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Mutation in tumor only

Mutation in egg or sperm

All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
Two Sides of Mutations

Somatic mutations
- Occur in *nongermline* tissues
- Cannot be inherited

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Parent

Nonheritable

Mutation in tumor only

Heritable

Mutation in egg or sperm

All cells affected in offspring

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
MDS is Genetically Not One Disease...
Mutations Cluster with MDS Subtype

Adapted from: Cazzola et al, Blood 2013
How Do We Identify These Mutations?

Panels vs Single Gene

1. Test for Known Mutations
   - Mutations discovered through GWAS, exome, WGS studies
2. Fast turn around time
Molecular Diagnostics in MDS – Possible Uses

- **Support / Refine Diagnosis**
  - MDS with ring sideroblasts when number of ring sideroblasts < 15%

- **Risk Stratification**
  - Better refine risk for progression to AML or higher risk MDS

- **Identify Potential Therapeutic Targets**
  - IDH2 mutations -> enasidenib (Idhifa)

- **Monitor Disease over Time**
  - Identify evidence of clonal evolution
  - Detect emergence of high risk clones
Support / Refine Diagnosis

Adapted from: Kwok et al, Blood 2015
Risk Stratification
(Different from Treatment Selection)

- Many mutations are PROGNOSTIC

- So far ONLY FEW are PREDICTIVE of treatment response

Risk Stratification

SF3B1 Mutation and Favorable Prognosis

Risk Stratification

ASXL1 Mutation and Worse Prognosis

Thol et al, JCO 2011
Disease Monitoring

Adapted from: Da Silva-Coelho et al, Nature Communications. 2017
Treatment Selection

- Splicesome mutation -> H3B-8800 splicesome inhibitor
- SF3B1 -> trial of luspatercept
- del 5q -> lenalidomide

Adapted from: Coombs et al, Nat Rev Clin Oncol. 2016
Learning Objectives

- Next Generation Sequencing
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Two Sides of Genetics ... Hereditary

Somatic mutations
- Occur in _non-germline_ tissues
- Cannot be inherited

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Mutation in tumor only
Nonheritable

Mutation in egg or sperm
Heritable

All cells affected in offspring
Child

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
All Cancer is Genetic...

...But only 10% is inherited
Hereditary Syndromes w/ Predisposition to MDS

- Familial MDS/AML syndromes
- Inherited Bone Marrow Failure Syndromes
- Familial cancer predisposition syndromes with increased risk for MDS/AML (BRCA1/2, TP53, etc)

Disorders rare, but increasingly being recognized and tested for in clinic

Adapted from: NCCN, V 1.2018
Benefits of Testing

- Modify cancer surveillance options and age of initial screening
- Suggest specific risk-reduction measures (e.g. considering early bone marrow transplant)
- Clarify and stratify familial cancer risks, based on gene-specific cancer associations, such as risk for colon cancer and sarcomas in Li-Fraumeni syndrome associated with TP53 mutations
- Offer treatment guidance (e.g. avoidance of radiation-based treatment methods for individuals with a TP53 mutation)
- Identify other at-risk family members
- Provide guidance with new gene-specific treatment options and risk reduction measures as they emerge
Red Flags: If you or family member have one of these ...

- Pulmonary alveolar proteinosis
- Congenital deafness
- Hereditary lymphedema
- Skin and nail changes
- Sensorineural deafness
- Pulmonary fibrosis

- Neurofibromatosis
- Predisposition to opportunistic infections
- Multiple family members with MDS or AML
- Premature hair graying
- Thumb hypoplasia
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From Bench to Bedside: New Clinical Workflow

- Patient Presents
- Tests
- Interpretation
- Treatment & Clinical Trial Options
- Personalized Treatment & Monitoring Plans

Genetic testing fits seamlessly into current clinical workflow.