New Directions in Aplastic Anemia Treatment: What's on the Horizon?

AA&MDS International Foundation

Living with Aplastic Anemia, MDS, or PNH Patient and Family Conferences in 2015

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NEW ASPECTS AND TRENDS IN AA

- New concepts in understanding of disease mechanisms
- Biomarkers/new diagnostics
- Management issues
- New potential therapies

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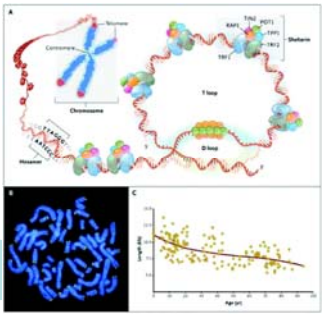
MUTATIONS

- Germ line mutations: from both or one of the parents “gene variants which run in the family”
- Somatic acquired in some, but not in all cells in the body: e.g., leukemic and MDS hematopoietic stem cells

Somatic mutations are present in all cells of the body and are easy to detect.

IMPORTANCE OF TELOMERES IN AA: TELOMERASE MUTATIONS AS EXEMPLARY GERM LINE MUTATIONS

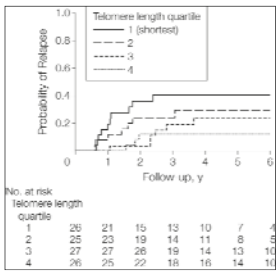
- Telomeres are DNA caps which protect ends of chromosomes
- Telomeres shorten with each cell division and thus with age
- Telomerase is needed to prevent telomeres from shortening



Germ line mutations in telomerase cause rare familiar aplastic anemia

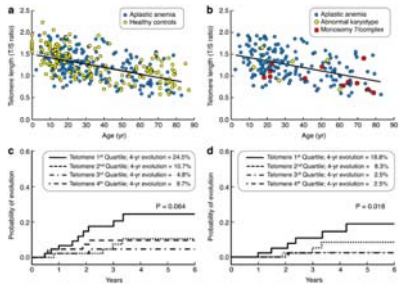
IMPORTANCE OF TELOMERE LENGTHT IN AA

Telomere Length and Disease Relapse



IMPORTANCE OF TELOMERES IN AA

Telomere Length as a predictor for clonal evolution in AA



NEW GENERATION SEQUENCING

- We can now screen all the cell in the body for the presence of mutations.
- Till recently if mutation was present in only a few cells, detection was not possible
- Now it is possible to find mutations in a few cells and screen for the presence of mutations in many genes at once
- What would take 5 years ago 10 years for 100 technicians, can be done now in 2 days by 1 person: genomic revolution!

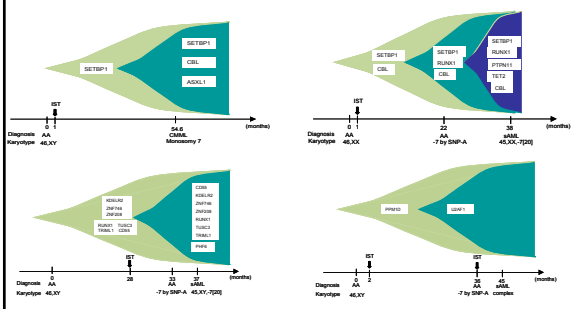
WITH NEW GENERATION SEQUENCING IS IT POSSIBLE TO IDENTIFY OTHER (than telomerase) GERM LINE MUTATIONS PREDISPOSING TO AA?

Preliminary data suggests that other mutations involved may be also present in AA.

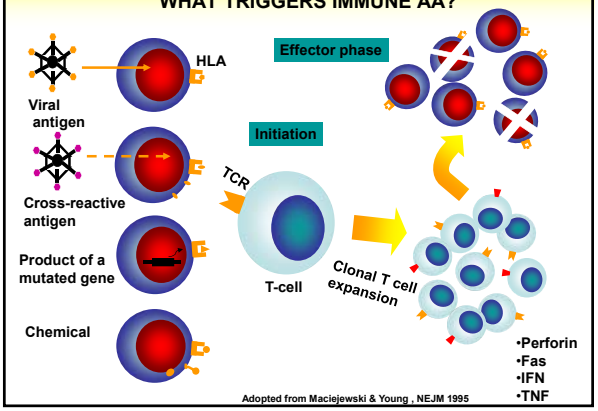
Heterozygous Fanconi Anemia gene mutations, DNA repair genes and other genes

Concepts of incomplete penetrance or disease anticipation… weak mutations vs. strong mutations

DETECTION OF SOMATIC MUTATIONS IN AA USING NEW GENERATION SEQUENCING

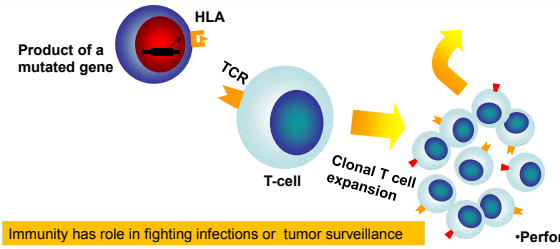


WHAT TRIGGERS IMMUNE AA?



Adopted from Maciejewski & Young , NEJM 1995

CAN ABNORMAL/MUTANT STEM CELL BE A TRIGGER?



Immunity has role in fighting infections or tumor surveillance

Thus is autoimmune response in AA reacting or overreacting to the presence of abnormal potentially malignant cells ?

Potential outcomes:

- Elimination
- Overreaction less specificity--- normal cells in cross
- Overwhelemed --- evolution of MDS

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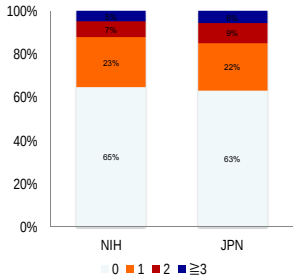
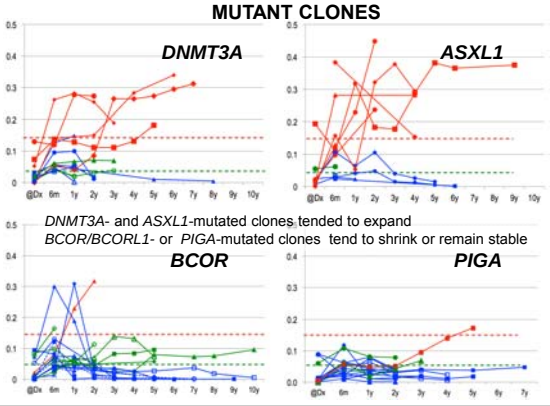
CAN THE PRESENCE OF MUTATIONS PREDICT LATER EVOLUTION OF MDS OR RESPONSE TO IMMUNOSPRESSION?

FREQUENCY OF MUTATIONS AA: ARE MUTATIONS USEFUL BIOMARKERS?

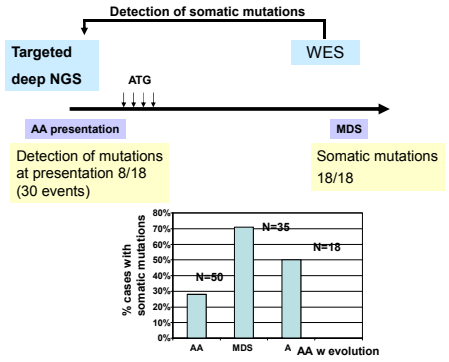


Mutations were found in ~1/3 of patients, of which 1/3 had multiple mutations.

CHRONOLOGICAL BEHAVIOUR OF COMMON MUTANT CLONES

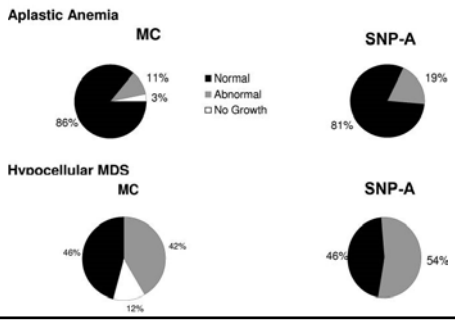


DETECTION OF SOMATIC MUTATIONS IN AA



CAN BETTER CYTOGENETIC ANALYSIS HELP TO DIAGNOSE MDS?

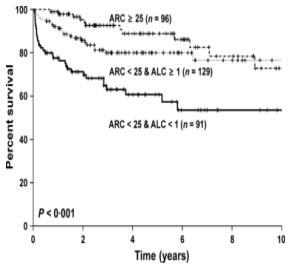
More chromosomal defects detected by SNP-Array Karyotyping compared to metaphase cytogenetics in AA and hypocellualr MDS



CAN A SIMPLE CLINICAL PARAMETER BE A USEFUL BIOMARKER?

Predictive/ Prognostic Biomarkers (ARC and ALC)

- NIH Study of 316 SAA patients (1989-2005)
- Defining important predictors of response to hATG +CsA therapy at 6 mos of therapy
- Factors looked at includes age, PNH clone, hematological factors like ANC, platelet count, Hgb, Absolute reticulocyte count (ARC), absolute lymphocyte count
- Presence of PNH clone is defined as presence of positive Ham test for samples until yr 2000 and subsequently GPI-(neg) Neutrophils or red cells >1%
- ARC and ALC are predictive



Scheinberg P et al. BJH . 2008

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IMPORTANT CLINICAL QUESTIONS TO BE ANSWERED

- Does the presence of PNH clone indicate that AA will never be completely cured?
- Is not achieving totally normal counts compatible with future cure?
- Will the usage of Promacta, Neupogen or similar agents stimulate outgrowth of later MDS
- Are minor changes worth: CsA/Prograft etc….
- Does lack of response to intense immunosuppression indicate that the disease is not immune-mediated?
- How to treat not severe AA?

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NEW THERAPEUTIC ASPECTS: GROWTH FACTORS

Concept: to stimulate and optimize stem cell growth/recovery

- G-CSG (Neupogen or Neulasta)
- Thrombopoietin (Nplate)
- Elthrombopag (Promacta)
- Erythrompoietin Procrit/Aransep
- Combinations

Supportive care: in combination with immunosuppression

Salvage therapy: prolonged therapy, multilineage responses

However, questions of progression to MDS or AML were raised although not proven

NEW THERAPEUTIC ASPECTS: IMMUNOSUPPRESSION

Concept: immunosuppression and immunomodulation

Older agents:
Prograft vs. Cyclosporine
Campath dose and route of administration

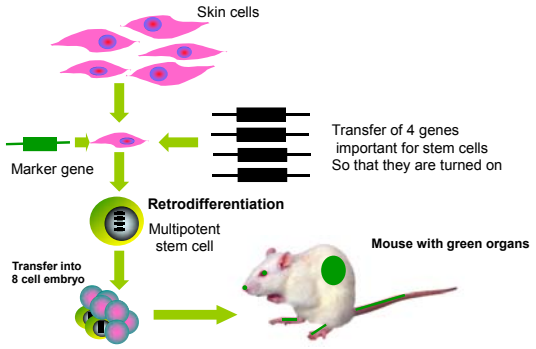
New agents with success in other diseases:
Arencia, Abatacept (soluble CTLA4)
Amevive, Alefacept (Soluble LFA-3)
Xelanjz (tofacinib)
Stelara (ustekinumab)
Actemra (Tocilizumab)

ADULT STEM CELL RETRO-DIFFERENTIATION

- All cells in the body have a silenced potential to produce all tissues, this potential is encoded in the DNA which is identical in all cells.
- Multipotent stem cells have a potential to produce all tissues, similar to the ultimate stem cell: the fertilized egg.
- Through a process of differentiation, tissues and organs are formed and assume specific function and shape

Why it would not be possible to isolate cells and revert them in to a multipotent stem cell and direct their program to regenerate diseased tissues?

POTENTIAL OF THE ADULT STEM CELLS



THERAPEUTIC POTENTIAL OF THE ADULT STEM CELLS

Allogeneic bone marrow transplant is limited by the availability of the donor, toxicity of GvHD and inability to replace diseased bone marrow stem cells