DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

Aldehydes: What Are They and Why Should They be Avoided

Alan D'Andrea, M.D.
Fuller-American Cancer Society Professor
Dana-Farber Cancer Institute
Harvard Medical School
Boston, MA, U.S.A.


Molly Nash
SPEAKER
SPEAKER

Fanconi Anemia (FA): An inherited Chromosome Instability Syndrome

Rare Autosomal Recessive Disease : 1/100,000 births

Characterized by

-Developmental defects

-Bone marrow failure (aplastic anemia by age 5)

-Cancer susceptibility (leukemia, squamous cell carcinoma, gynecologic cancers)

-Hypersensitivity to DNA crosslinking agents (Cisplatin, MMC)

-Sixteen different complementation groups of FA have been defined by somatic cell fusion studies (All sixteen FA genes have been identified)

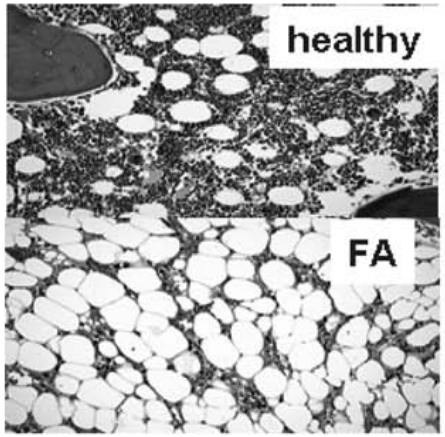
D'Andrea, A.D., Susceptibility Pathways in Fanconi Anemia and Breast Cancer, New Engl Jour Med 2010, 362: 1909-1919

Fanconi anemia

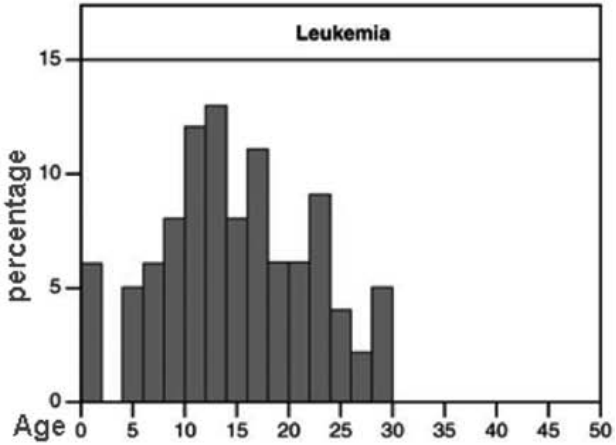
Mutation in any of 16 FA complementation groups

Developmental Abnormalities

Bone marrow failure

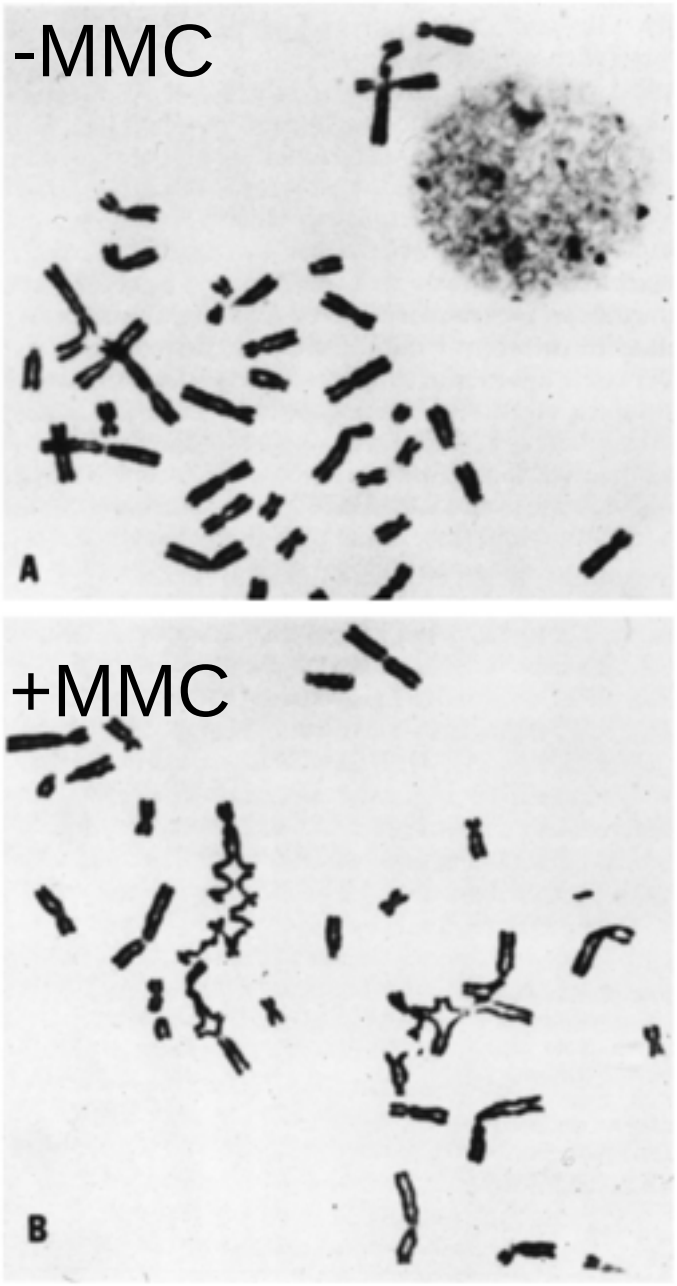


Cancer/Leukemia

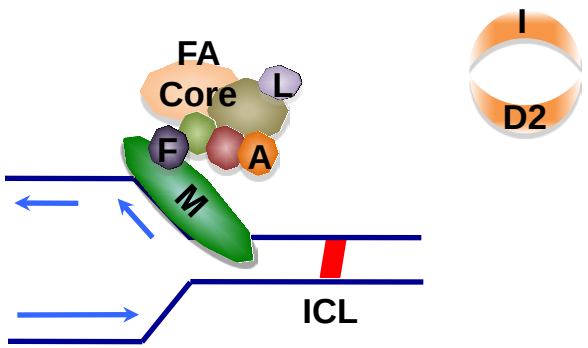


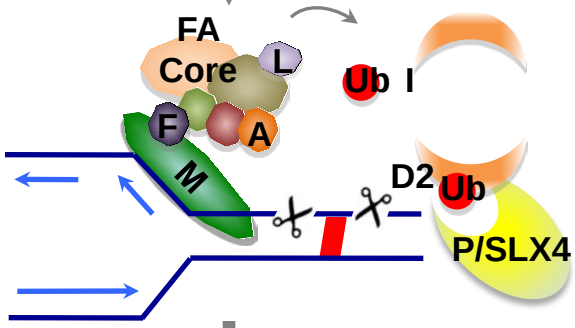
Fanconi Anemia
Cells have a characteristic
Cellular phenotype:

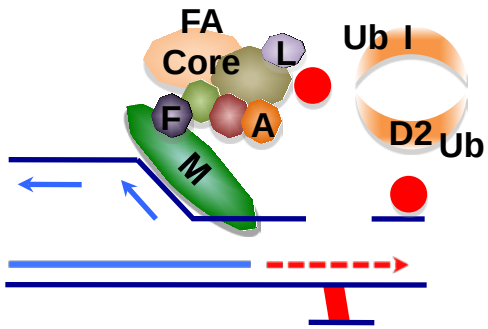
Hypersensitivity to DNA cross-linking agents, e.g. Mitomycin C, aldehydes



Sixteen FA proteins Cooperate in Aldehyde-ICL repair



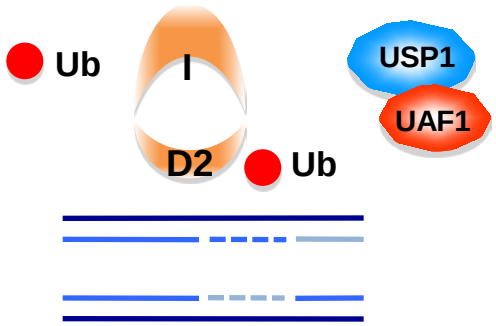




Translesion Synthesis (TLS)

FANCP/SLX4 is a multidomain protein complex that interacts with the XPF/ERCC1 nuclease

SLX4 has a UBZ4 (ubiquitin binding site).



Aldehydes:

- Reactive chemicals that can injure cells
- Can interact with (and crosslink) DNA molecules
- Some aldehydes (like formaldehyde) are endogenous and are formed within the body during normal metabolism
- Some are exogenous (say, from alcoholic beverages)
- Aldehydes are broken down by a family of enzymes (including ALDH2 and ALDH3)

Work from K.J.Patel Laboratory (LMB, Cambridge, UK)

- Showed the ALDH2 enzyme is of critical importance in individuals with FA

- A mouse model with defect in ALDH2 and FA gene has bone marrow failure (either spontaneous bmf or leukemia) and developmental abnormalities

- In Japan, 50% of the population has a deficiency in ALDH2

- Hira and Takata examined 55 FA patients in Japan. Two patients had severe ALDH2 deficiency and severe, early onset bone marrow failure (more severe than most FA patients in U.S.).

Implications/Recommendations:

-FA patients should limit alcohol consumption

-Alcohol and aldehydes can cross the placenta (i.e., a pregnant mother carrying an FA fetus should limit alcohol consumption)

Implications/Recommendations:

-We should:

-1) develop drugs to stimulate ALDH2 activity

-2) develop drugs to detoxify (sponge up) aldehydes from blood

-Early evidence suggests that low ALDH2/ALDH3 levels may correlate with increased incidence of Squamous Cell Carcinoma of the head and neck.

Future Studies:

-Why are only the stem cells specifically affected by loss of ALDH2 and FA gene?

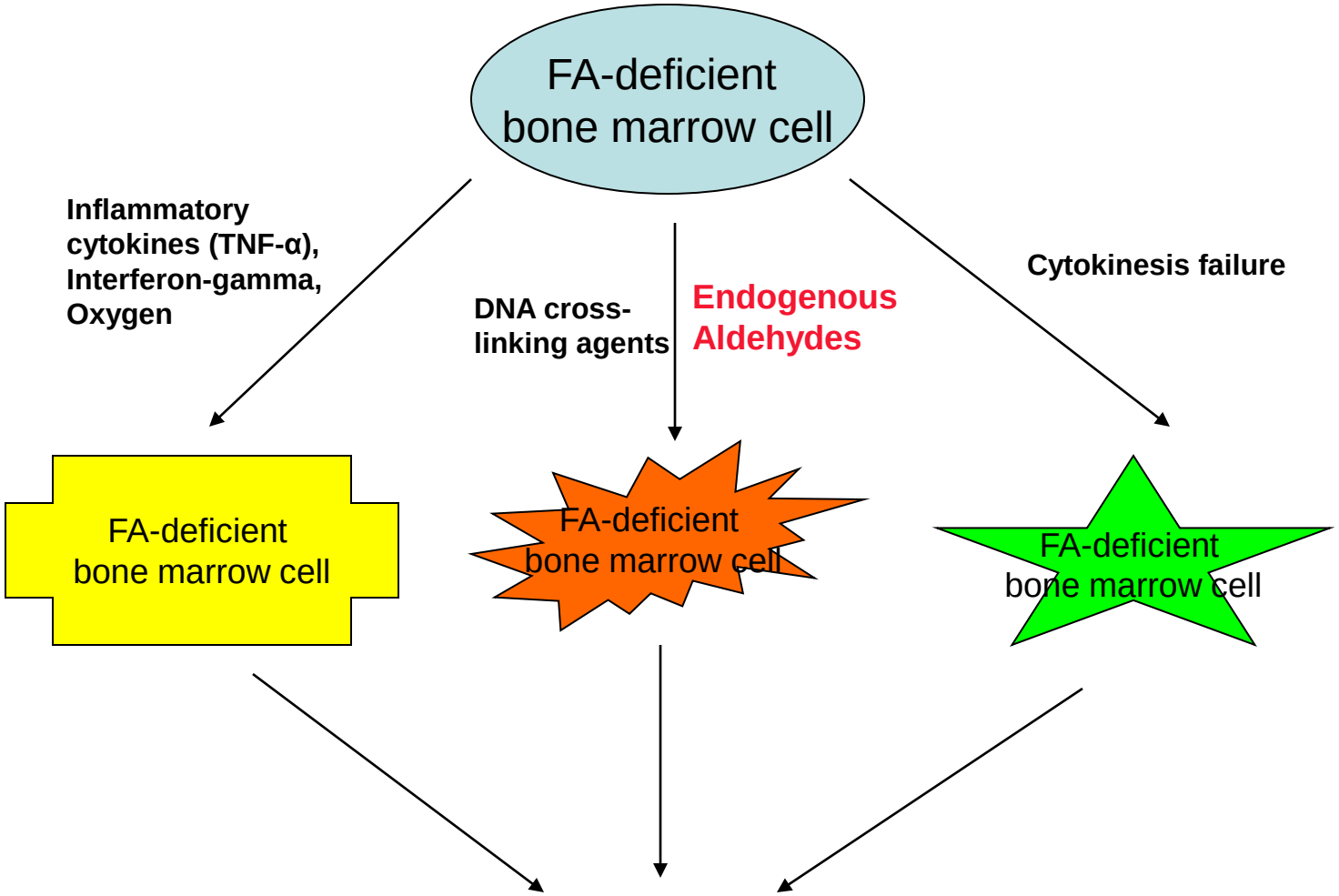
-Why do some FA patients have more ALDH2 than others?

-Do FA patients in Japan generally have a more severe disease due to low ALDH2 levels?

-Mice with ALDH2/FA deficiency have spontaneous bone marrow failure (helpful experimental model)

-Can we suppress aldehyde production? Or suppress its Accumulation? Dietary Effects?

CAUSES of bone marrow failure in FA patients



Mechanism of bone marrow failure in Fanconi anemia

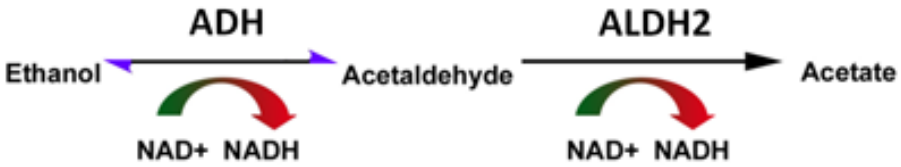
Attrition of hematopoietic stem and progenitor cells due to genotoxic stress

Which aldehydes are responsible for the pathophysiology of Fanconi anemia?

By-products of cellular metabolism: Potential physiological genotoxins for FA cells

- Formaldehyde: Reactive aldehyde, naturally occuring in plasma, highly reactive environmental human carcinogen, cells exposed to formaldehyde exhibit DNA-protein crosslinks.

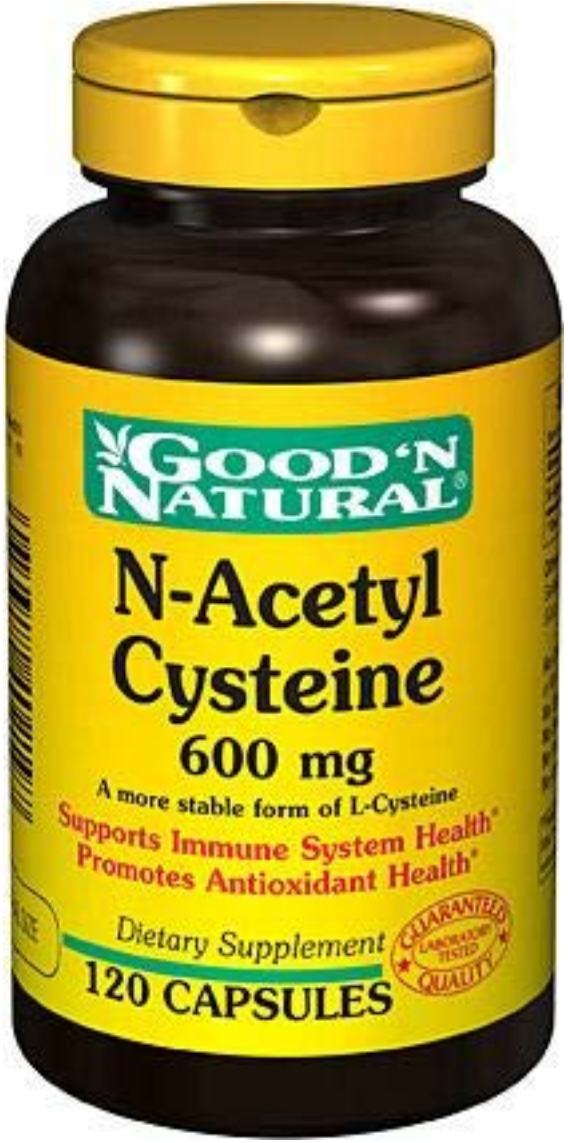
- Acetaldehyde: A degradation product of ethanol that, like several other alcohols, is itself produced during normal metabolism.

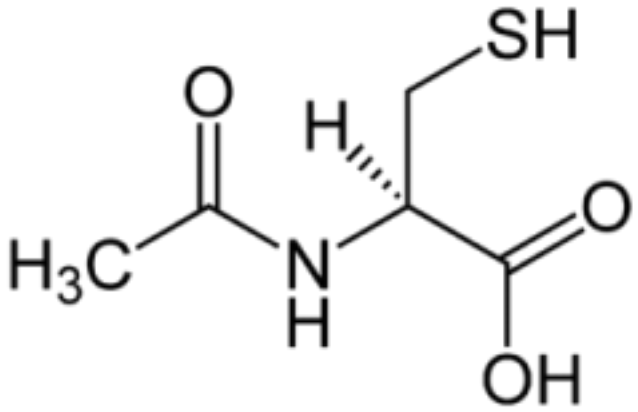


Aldehyde toxicity in FA

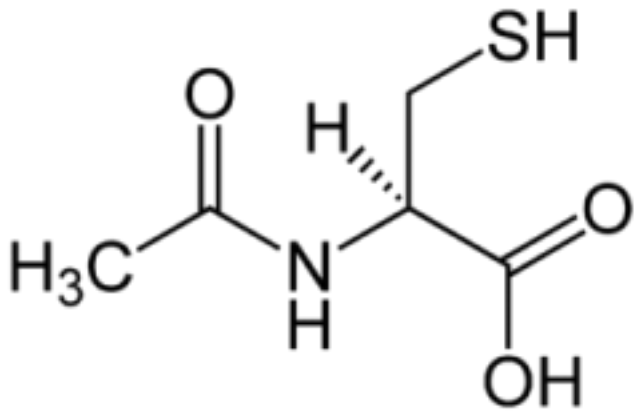
- FA pathway deficient cells are hypersensitive to plasma levels of Formaldehyde and Acetaldehyde (*Ridpath et al, 2007)*.
- Fancd2 counteracts the toxic effects of naturally produced Aldehdyes in mice *(Langevin et al, 2011*).
- Formaldehyde catabolism is essential in cells deficient for the Fanconi anemia DNA-repair pathway (*Rosado et al, 2011*).
- Mice deficient in both FA pathway and Acetaldehyde detoxification exhibit severe HSC defects and bone marrow failure (*Garaycoechea et al, 2012*).

Possible Treatments

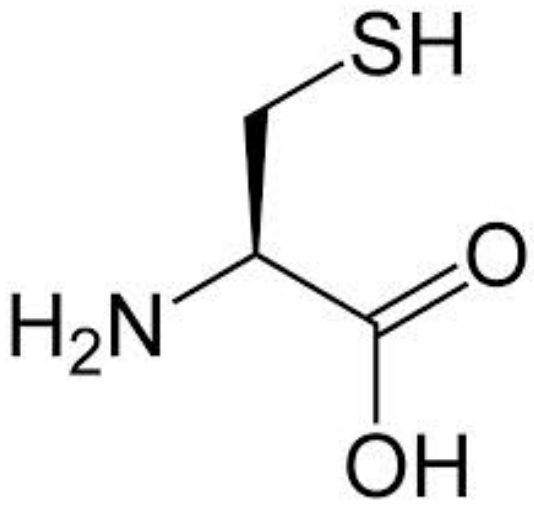




Thiol “Sponges” for removing reactive aldehydes from the blood



N-Acetyl Cysteine



Cysteamine

Therapeutic approaches to treat FA

~~Fanconi Anemia Program Project OHSU~~

Principal Investigator: Markus Grompe

- **Androgen, G-CSF**
- **Bone marrow transplant**

- **Tempol**
- **Resveratrol**
- **Anti-oxidants (N-acetyl-cysteine), anti-inflammatory agents**

- **Anti-apoptotic compounds?**
- **DNA-PK inhibitor?**
- **CHK1 inhibitor? P53 inhibitor?**
- **Gene therapy?**

FARF Research Meeting, October, 2012
Session Chair: Alan D'Andrea, MD
Dana-Farber Cancer Institute, Boston, MA

Gerry Crossan: Described a specific mechanism for the stem cell failure in FA- namely, a cell-type specific need for both a functional FA pathwa and strong aldehyde degradation

-what is special about bone marrow stem cells?

Juan Garaycoechea: Described how double knockout mice (ie, ALDH2 & FA-pathway deficient mice) develop either bone marrow failure or leukemia. Endogenous aldehydes are toxic to the bone marrow stem cells

-how can we study the anemia and leukemia in FA?

FARF Research Meeting, October, 2012
Session Chair: Alan D'Andrea, MD
Dana-Farber Cancer Institute, Boston, MA

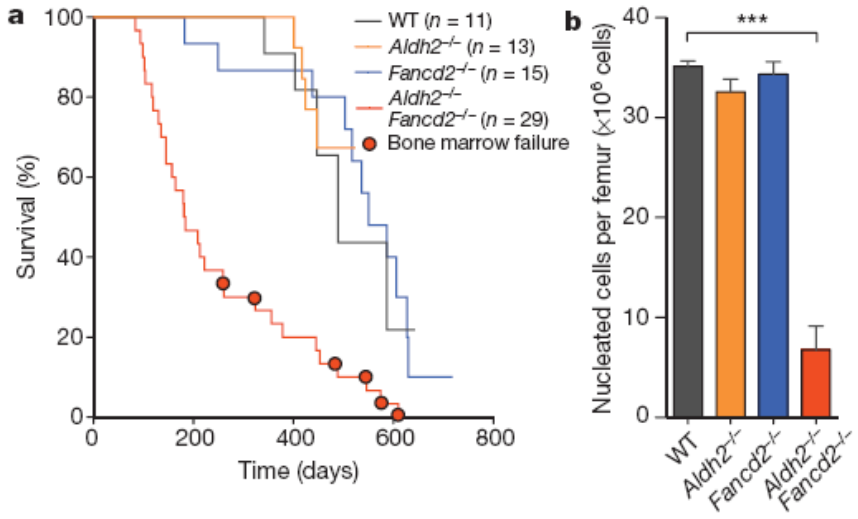
Nina Oberbeck: Described how the disease severity of the newborn mice depends on the degradation of aldehydes of the mother. A maternal source of aldehydes may be responsible, at least in part, for teratogenic consequences of the FA fetus.

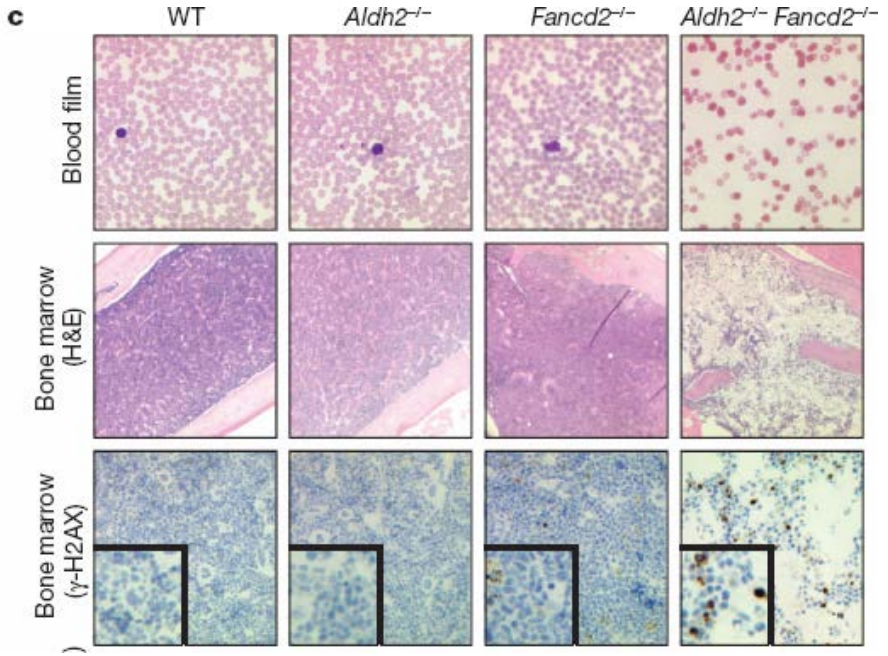
-(Issue of maternal diet and alcohol use?)
(Mild bone marrow phenotype of some FA-A patients?)

Asuka Hira: Described how a variant of ALDH2, prevalent in an Asian population, may accelerate anemia in patients with FA. Is there a need to genotype ALDH2 in order to find a subset of FA patients who are more likely to develop BMF early in their lives?

-Does level of ALDH2 expression impact the severity of FA

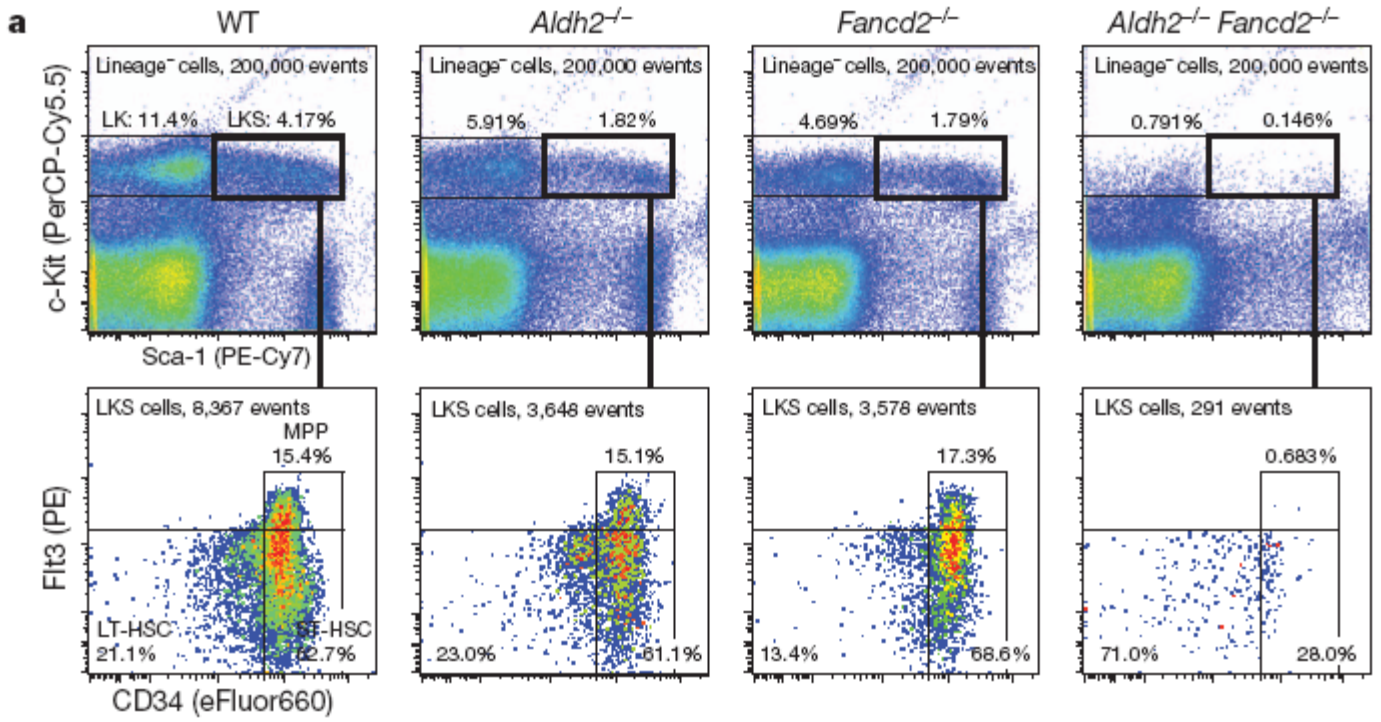
Aged Fancd2-/-Aldh2-/- double KO mice succumb to bone marrow failure





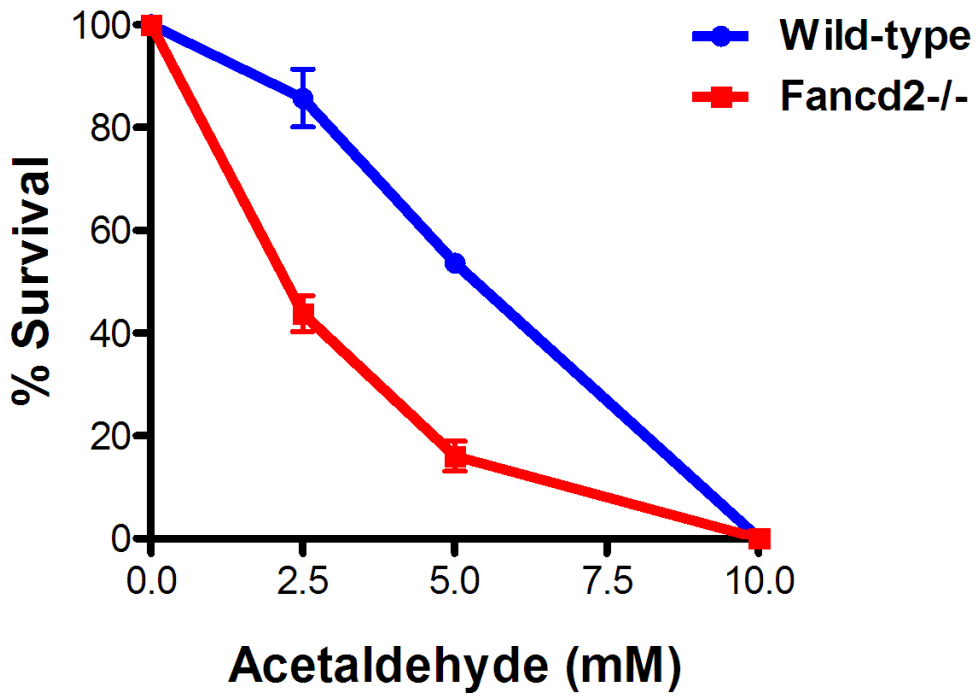
Garaycoechea JI et al, Nature, 2012

Young Fancd2-Aldh2-/- double KO mice have low amounts of the bone marrow stem cells



Garaycoechea JI et al, Nature, 2012

Fancd2-deficient murine bone marrow cells are hypersensitive to the Acetaldehyde treatments



BM cells were treated with Acetaldehyde (Sigma) for 4 hrs, washed, and then cultured in methylcellulose for 7-10 days. The survival of CFU-Cs was determined.

A new drug candidate: Alda-1

- Alda-1 (N-(1,3-benzodioxol-5-ylmethyl)-2,6-dichlorobenzamide) stimulates the ALDH2 enzyme and promotes the removal of aldehydes from the blood.

Summary

- FA bone marrow cells are hypersensitive to aldehydes (acetaldehyde, formaldehyde, others)

-importance of monitoring aldehyde levels in the blood

Treatment options;

-avoid dietary aldehydes

- drugs which “sponge” up aldehydes from the blood

-drugs which stimulate the enzymatic removal of aldehydes from the blood (ALDA1)

Acknowledgments

D'Andrea Lab
Min Huang
Helena Mistry
Kalindi Parmar
Kailin Yang
Eunmi Park
Hyungjin Kim
Donniphat Dejsuphong
Jenny Xie
Kwang-Hyun Baek
Sofia Vidal-Cardenas
Lucian Moldovan
Kevin O'Connor
Benjamin Primack
Lisa Moreau
Raphael Ceccaldi
Haojian Zhang

Nathanael Gray
Sara Burhlage

Guillaume Adelmant
Jarrod Marto

Geoffrey Shapiro
Neil Johnson
Andrea Richardson
Dan Silver
Erica Mayer
Julie Najita
Judy Garber

Elgene Lim
David Chi
Myles Brown

Shunichi Takeda
Junko Murai

Markus Grompe