Hematologic and immune defects associated with human GATA2 mutation

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Overview

• Dendritic cell, monocyte, B NK lymphocyte (DCML) deficiency
• Immune defects of GATA2 deficiency
• Genetic background
Why DCML deficiency?

• What controls the development of human dendritic cells?
• Are there differences between DC and monocyte development?
• What are the consequences of DC deficiency for human immunity?
Where is human DC deficiency?

Hypogamma SCID

T B NK DC

monocyte

granulocyte

Neutropenia CGD
What happens to DCs when there are no monocytes?
What happens to DCs when there are no monocytes?
Monocytopenia

- Screening using an automated blood counter:
DC Monocyte Lymphoid DCML deficiency

Control

Monocytes

DC

CD34+

B Cells

NK Cells

Patient

Prevalent clinical features

- Late onset 20s-30s
- Sporadic or autosomal dominant
- Grossly normal T cell count
- Preserved Ig, tetanus and pneumococcal titres
- Normal response to childhood infections and vaccines
- Progression to myelodysplasia and acute myeloid leukaemia
Human GATA2 mutations

Summary of 257 published heterozygous mutations

Collin and Dickinson BJHaem 2015
Preservation of Langerhans cells and macrophages


www.hudendritic.org
Peripheral macrophages do not require BM-derived precursors

GATA-2 | IRF-8
---|---

monocytopenia
>10 years

HSCT - recipient at one year
- non-proliferating

Male to female transplant

Tattoo pigment
- stable for decades
- even after HSCT
What happens to DCs when there are no monocytes?

Bone Marrow
- GMP
- CMoP
- CDP

Blood
- Dendritic cells
- Pre-DC

Monocytes

Tissue
- Langerhans cell
- Dendritic cells
- mo-DC
- mo-MAC
- Macrophage
- Lymphoid DCs
- Lymph node
Macrophage embryonic ontogeny

- Definitive
  - C-myb dependent
- C-myb independent
- Yolk sac
- Primitive

**Yolk sac macrophages**

**Fetal liver monocytes**

**Lung**

**Kidney**

**Liver**

**Langerhans cells**

**Microglia**

*Hoeffel, JEM 2012*

*Ginhoux, Science 2010*

*Hoeffel, JEM 2014*

*(Ginhaux, Science 2010)*
The evolution of mononuclear cytopenia

- Is DCML deficiency a genuine accessory phenotype?
- How does it evolve?
- When should we screen for GATA2 mutation?
DCML deficiency: the accessory phenotype of GATA2 mutation
GATA2 syndromes

- Monocytopenia
- M. Avium complex
- Dendritic cell, Monocyte, B and NK Lymphoid (DCML) deficiency

Venn Diagram:
- monoMAC
- DCML deficiency
- Hereditary MDS/AML
- Emberger’s
- Lymphoedema MDS
Unaffected ‘carriers’ exist

Pedigree 3 (R398W)

Pedigree 8 (R398Q)

Pedigree 9 (T354M)
Progressive loss of function

#5

- 2010
- 2012
- 2013

Graphs showing changes in cell counts and serum level over different years.
When should \textit{GATA2} mutation be suspected in MDS?
Symptomatic GATA2 vs ambulatory MDS patients

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>GATA2</td>
<td>20</td>
<td>4-60</td>
</tr>
<tr>
<td>MDS</td>
<td>65</td>
<td>42-83</td>
</tr>
</tbody>
</table>

**GATA2 Clinical score:** 1 point each: HPV; mycobacteria; URTI; lung; autoimmunity
Summary (1)

- DC/monocyte failure occurs in synchrony but peripheral Langerhans cells and macrophages are preserved
- DCML deficiency is an accessory phenotype of GATA2 mutation that may evolve over decades
- In MDS, suspect GATA2:
  - Young, family history
  - HPV/warts, mycobacteria, candida, sino/pulmonary infection
  - Lymphedema
  - Autoimmunity
  - Monocytopenia, lymphocytopenia
  - Elevated Flt3L
What goes wrong with immunity?
BM CD34+ progenitor compartment

CONTROL

CD38- CD38+

HSC MLP BNK 123hi

CMP MEP GMP

GATA2

CD38 CD38 CD45 RA

CD34 CD90 45.1% 14.0% 3.96%

MLP CD45RA

BNK 123hi
B/NK cell maturation

CD19+ lymphocytes

Total lymphocytes

CD56

CD38

CD27

CD56

CD3

CD62L

CD16

**Newcastle University**
Lymphocyte homeostasis

BM emigrant  Naïve  Mature  Terminally differentiated

Failure of supply  Immune stimulation
Lymphocyte homeostasis

Living on memories . . .
IFN\(\gamma\)/IL-12 axis disrupted by cellular deficiency

Mycobacteria

DC

NK

IL-12

Th1

IFN-\(\gamma\)

activated mo-mac

Resident mac

granulomata

immunosurveillance

HPV

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IFNγ/IL-12 axis disrupted by cellular deficiency

Mycobacteria

DC

NK

IL-12

Th1

HPV

activated mo-mac

Resident mac

GATA2 deficient Impaired function?

Disseminated infection

IFN-γ activated mo-mac

HPV in situ

ZN stain

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Summary (2)

- BM analysis shows early drop out of multi-lymphoid progenitor (LMPP), B/NK precursors and CD123\textsuperscript{hi} GMP (DC precursor)
- Immature cells lost from periphery
- Immunosenescence phenotype
- Th1 IFN\textgamma/IL-12 axis severely disrupted
Influence of genetic background
Familial Acute Myeloid Leukaemia with Acquired Pelger-Huët Anomaly and Aneuploidy of C Group

JUGINDER KAUR, D. CATOVSKY, H. VALDIMARSSON, O. JENSSON, A. S. D. SPIERS

British Medical Journal 1972

C group chr 6-12 (monosomy 7 and trisomy 8)
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AML/MDS

Low IgA

9: I

AML/MDS

9: II

9: III

Low IgA

1 2 3 4 5
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9: I

9: II

9: III

- ■ MDS with GATA2 mutation (p.T354M)
- ○ GATA2 wild type
- □ Asymptomatic GATA2 mutation (p.T354M)
- ? Unconfirmed genotype
ASXL1 p.I1436F (rs779722479)

- **Affected GATA2 mutation (p.T354M)**
- **GATA2 wild type**
- **Asymptomatic GATA2 mutation (p.T354M)**
- **ASXL1 mutation (p.I1436F)**
ASXL1 p.I1436F (rs779722479)

- Affected GATA2 mutation (p.T354M)
- GATA2 wild type
- Asymptomatic GATA2 mutation (p.T354M)
- ASXL1 mutation (p.I1436F)

PBMC

Buccal
ASXL1 p.I1436F: germline mutation

- Affected GATA2 mutation (p.T354M)
- GATA2 wild type
- Asymptomatic GATA2 mutation (p.T354M)
- ASXL1 mutation (p.I1436F)

PBMC
Buccal
G652S germline mutation

Pedigree 6

1. GATA2 mutation (p.G199fs)
2. GATA2 wild type
3. ASXL1 mutation (p.G652S)

pG625 a Finnish polymorphism with MAF 0.020
BUT children presented 20 years younger than father with disease
**ASXL1 mutation and progression of GATA2 disease**

Onset of symptoms (HPV)  
P=0.0025

Diagnosis of MDS  
P=0.0006

Transplant-free survival  
P=0.0178

- **ASXL1 wild-type**
- **ASXL1 mutated**

Comparisons by Log-rank (Mantel-Cox) test
**ASXL1 mutation and progression of GATA2 disease**

Onset of symptoms

- **WT vs polymorphism**: p=0.032 *
- **WT vs disease causing**: p=0.005 *
- **Poly vs disease**: p=0.473

- **WT vs germline**: p=0.002 *
- **WT vs somatic**: p=0.101
- **Germline vs somatic**: p=0.272
Summary (3)

• **ASXL1** variants can be present in germline and co-inherited with **GATA2** mutation

• Germline and somatic **ASXL1** variants both associated with MDS

• Co-inheritance may explain some ‘AML phenotype’ GATA2 pedigrees

• Co-segregation may not be stochastic: selection at meiosis/embryogenesis?
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