MPN Molecular Biology

Dr Jyoti Nangalia
Blood and bone marrow
The blood making factory

- Stem cell
- Progenitors
- Leucocytes
- Red cells
- Platelets
Myeloproliferative neoplasms

Blood stem cell

Progenitors

Leucocytes

Red cells

Platelets
SUR UNE FORME SPÉCIALE
DE CYANOSE S’ACCOMPAGNANT D’HYPERGLOBULIE EXCESSIVE ET
PERSISTANTE.

par M. H. VAQUEZ.

C R Soc Biol (Paris) 1892

Hämorrhagische Thrombocythamie bei vasculärer Schrumpfamilz.

Von

Privatdozent Dr. Emil Epstein und Privatdozent Dr. Alfred Goedel.

Mit 4 Abbildungen im Text.

(Eingegangen am 14. November 1933.)

Virchow’s Archiv Abteilung; 293; 233-247. 1934
Have been around for an even longer time . . .

Identification of JAK2 mutations in canine primary polycythemia

Stephanie Beurlet\textsuperscript{a,b,c}, Patricia Krief\textsuperscript{a,b}, Arnaud Sansonetti\textsuperscript{a,b}, Alexandra Briend-Marchal\textsuperscript{d}, Jean-Jacques Kiladjian\textsuperscript{e}, Rose Ann Padua\textsuperscript{a,b}, Christine Chomienne\textsuperscript{a,b,f}, and Bruno Cassinat\textsuperscript{a,b,f}
Myeloproliferative neoplasms

- What causes it?
- Why causes the differences between patients?
- Why do some people get it and others not in the first place?
Myeloproliferative neoplasms

• What causes it?
• Why causes the differences between patients?
• Why do some people get it and others not in the first place?
The code of life – counting chromosomes

Tjio and Levan 1955
A change in the gene **JAK2**

V617F mutation
“It all starts to make sense”

EPO

More red cells
Identification of JAK2 mutation

Recognition of new disease subtypes

Molecular testing in hospitals

Therapeutic JAK2 inhibitors

James et al, 2005; Baxter et al, 2005; Kralovics et al, 2005; Levine et al, 2005
The theme repeated… increased growth signal to cells

<table>
<thead>
<tr>
<th>JAK2 mutations</th>
<th>MPL mutations</th>
<th>Other mutations</th>
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<tbody>
<tr>
<td>EpoR</td>
<td>TpoR</td>
<td>EpoR</td>
</tr>
<tr>
<td>99% PV</td>
<td>3–4% ET</td>
<td>LNK 6% MPNs</td>
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<tr>
<td>50–60% ET/MF</td>
<td>4–8% MF</td>
<td>CBL 6% MF</td>
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? Pathogenic mechanism of 50% of ET and MF

*CALR* mutations in the majority of *JAK2*-unmutated MPNs

Nangalia, Massie et al 2013; Klampfl et al 2013
A new test for the clinic and patients....

DNA SIZE ➔

ABNORMAL CALR ➔ NORMAL CALR ➔

NORMAL CALR ➔ ABNORMAL CALR ➔

DNA SIZE ➔

AMOUNT ➔
Changes in the JAK2, CALR and MPL genes drive MPNs….

JAK2 mutations

Mutant JAK2

Signals inside the cell

Protein making factory

CALR and MPL mutations

Mutant CALR

Mutant MPL

Signals inside the cell
Myeloproliferative neoplasms

• What causes it?

• Why causes the differences between patients?

• Why do some people get it and others not in the first place?
Why do some patients get ET and others PV with **JAK2**?

1. Higher levels of JAK2 → PV

Why do some patients get ET and others PV with JAK2?

1. Higher levels of JAK2 → PV

2. Double copies of JAK2 → PV


Scott et al, Blood 2006
Why do some patients get ET and others PV with \( \text{JAK2} \)?

1. Higher levels of JAK2 \( \rightarrow \) PV

2. Double copies of JAK2 \( \rightarrow \) PV

3. JAK2 Exon 12 mutation \( \rightarrow \) PV
   - Scott et al, Blood 2006
Why do some patients get ET and others PV with **JAK2**?

1. Higher levels of JAK2 $\rightarrow$ PV

2. Double copies of JAK2 $\rightarrow$ PV

3. JAK2 Exon 12 mutation $\rightarrow$ PV
   - Scott et al, 2007

4. JAK2 acquired 1\textsuperscript{st} $\rightarrow$ PV
   - Ortmann, Kent et al 2015

Scott et al, Blood 2006
Half of MPNs have changes in other genes too

Nangalia, Massie et al, 2013
Each person is unique in terms of age, gender, their own DNA.
Same applies to MF, although additional mutations are more common

Grinfeld, Nangalia et al, 2018
What causes it?

Why causes the differences between patients?

Why do some people get it and others not in the first place?
The challenge of making blood

The bone marrow makes 200 billion red cells and 10 billion white cells every single cell.

Every time one cell is made, the parent cell has to divide into two cells.
The challenge of making blood

The bone marrow makes 200 billion red cells and 10 billion white cells every single cell.

Every time one cell is made, the parent cell has to divide into two cells.

Every cell division requires a copy of the entire DNA to be made by the cell.

3 BILLION nucleotides of DNA need to be copied each time.
Mistakes are to be expected

20-24 mutations acquired per year of life

unpublished
But are chance mistakes enough or is something else needed?

But are chance mistakes enough or is something else needed?

What could be going on?

CERTAIN NUMBER OF MUTATIONS NEEDED
What could be going on?

CERTAIN NUMBER OF MUTATIONS NEEDED

GRADUAL PROCESS
What could be going on?

CERTAIN NUMBER OF MUTATIONS NEEDED

ONE MUTATION IS ENOUGH

GRADUAL PROCESS
How do MPNs originate?
How do MPNs originate?

Accumulation of mutations
How do MPNs originate?

Accumulation of mutations

Will the clone expand?

MPN

JAK2, CALR, MPL

Other mutations
How do MPNs originate?

Accumulation of mutations

Will the clone expand?

Additional mutations

JAK2, CALR, MPL

Other mutations
How do MPNs originate?

Accumulation of mutations

Will the clone expand?

Additional mutations

MPN

Progression

JAK2, CALR, MPL

Other mutations

No MPN
How do MPNs originate?

Accumulation of mutations

Will the clone expand?

Additional mutations

MPN

Progression

JAK2, CALR, MPL

Other mutations

Clone detected

MPN

Progression
How do MPNs originate?

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Clone detected
Summary

• Mutations in the genes JAK2, CALR, MPL “drive” MPNs

• The exact features of MPN depends on each individual patient
  • the changes in the DNA that they have in their MPN blood cells
  • the unique characteristics of each person
  • the interactions between these factors

• We get MPNs because of chance mistakes that occur during the making of blood and copying of DNA.
  • Acquisition of mutations is probably sufficient in some patients
  • In others, additional factors are required (mutations, bone marrow conditions etc)
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PT1 trial team and patients
Any questions?