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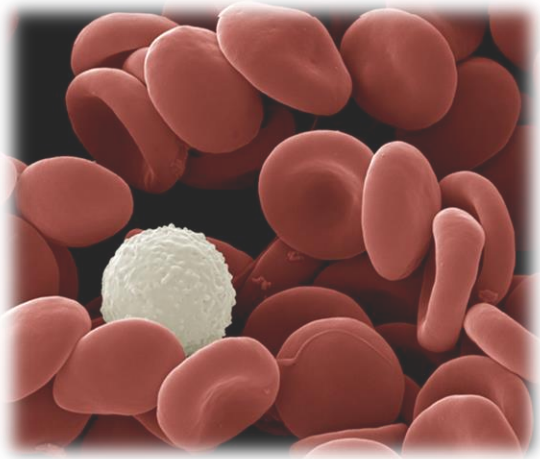
Clonal Hematopoiesis

Dr François Dachy

CHU UCL NAMUR

Plan



- Clinical case introduction
- The right term for the right biology.
- Lab tests ➔ *Seminar 1 : Laboratory Hematology*
- CHIP – CHOP – ARCH : main genes
- The clonal hematopoiesis family : characteristics
- CH and nonhematologic disorders
- Risk factors
- Roads to neoplasia
- Attitude & follow-up
- HCT & CAR-T context
- Challenges and perspectives
- Back to our initial case
- Conclusion – Take home message

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Nephro on call about anemia

- A 70 y old woman followed for moderate renal chronic disease.
- Hb 10 g/dL, macro, non regenerative. WBC and platelets are normal.
- Martial & vitamin evaluation correct. No inflammation. No toxics.

- Bone marrow aspirate with mild dysplasia.
- Normal karyotype
- NGS : TP53 VAF 10 %.

CHIP

CHOP

ICUS

CHUD

IDUS

ARCH

MDS

CCUS

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The right term for the right biology…

CHIP	Clonal Hematopoiesis of Indeterminate Potential
CHOP	Clonal Hematopoiesis of Oncogenic Potential
ICUS	Idiopathic Cytopenia of Unknown Significance
CCUS	Clonal Cytopenia of Unknown Significance
IDUS	Idiopathic Dysplasia of Unknown Significance
CHUD	Clonal Hematopoiesis of Unknown Drivers
ARCH	Age Related Clonal Hematopoiesis
MDS	Myelodysplastic syndrome

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CHIP - CHOP - ARCH A point of view

- 17.182 persons
- Median age 58 y (19 to 108 !).
- Sex ratio ~ 1

- 160 recurrent. mutated genes in myeloid & lymphoid cancers.

- < 40y : rare
- [60-69y] : 5,6%
- [70-79y] : 9,5%
- [80-89y] : 11,7%
- [90-108y] : 18,4%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D.,

N ENGL J MED 371;26 NEJM.ORG DECEMBER 25, 2014

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CHIP - CHOP - ARCH A point of view

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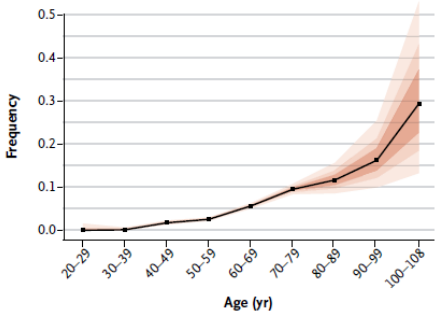

No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Figure 1. Prevalence of Somatic Mutations, According to Age.

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CHIP - CHOP - ARCH A point of view

Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes

David P. Steensma, Rafael Bejar, Siddhartha Jaiswal, R. Coleman Lindsley, Mikkael A. Sekeres, Robert P. Hasserjian, Benjamin L. Ebert

Blood (2015) 126 (1): 9–16.

CHIP define a phenotype in wich hematopoietic cells harboring **somatic mutations** clonally expand **without hematologic disease**.

But extremly high resolution sequencing reveals **CH with VAF* from 0,03%** in nearly all healthy 50-60 y.old population…

« Practical » VAF cutoff at least 2%.

**VAF = Variant Allele Frequency (%)*

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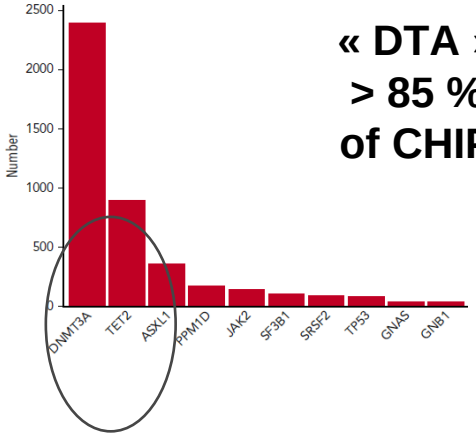
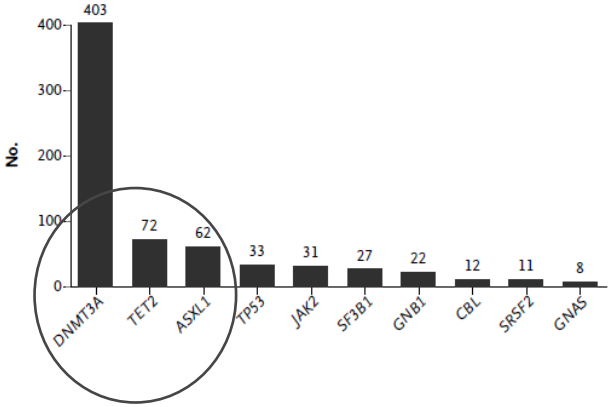
CHIP - CHOP - ARCH A point of view



« DTA »
> 85 %
of CHIP

Common CHIP driver mutations.

Candidate Driver	% of CHIP[a]	Mechanism
DNMT3A	~58.5%	Methyltransferase enzyme that catalyzes DNA methylation at CpG sites and alters epigenetic signature; tumor suppressor gene
TET2	~20%	DNA demethylase *TET2* (ten-eleven translocation-2) augments DNA methylation and affects transcription by recruiting histone deacetylases toward promoters; tumor suppressor gene
ASXL1	~8.0%	Epigenetic modulator and chromatin-binding protein, function relatively unknown
JAK2	~3.2%	Transmits intracellular signals downstream of cytokine receptors. *JAK2* tyrosine phosphorylates and activates *TET2* in response to cytokines, linking extracellular signals with epigenetic changes in hematopoiesis
PPM1D, TP53	~3.8%, 1.9%	DNA damage response pathway in regulatory feedback loop with the tumor suppressor p53.
SF3B1, SRSF2	2%, 2%	mRNA spliceosome complex components
No candidate driver mutation		Limits of detection methods, epigenetic changes not detectable, neutral drift, or mosaic chromosomal alterations



Jaiswal Blood 2020

Marnell et al. JMCC 2021

Jaiswal et al. NEJM 2014

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CHIP - CHOP - ARCH A point of view

- **CHIP mutations** create a **molecular background** of a potential neoplastic process.

- **CHOP mutations** include **disease-specific lesions** that trigger **differentiation and proliferation** of haematological neoplasms.

Table 3. Somatic mutations producing clonal hematopoiesis of oncogenic potential (CHOP).

	Effects of the Mutant on Clonal Cells			Affected
Mutation	**Differentiation**	**Proliferation**	**Oncogenesis**	**Myeloid Neoplasm**
BCR-ABL1$_{p210}$	+	+	+*	Ph+ CML
JAK2 V617F	+	+/-	-	MPN
CALR mutations	+	+/-	-	MPN
MPL mutations	++	+/-	-	
KIT D816V	++	+/-	-	ISM and AdvSM
FIP1L1-PDGFRA	+	+/-	-	CEL, MPN-eo
RUNX1- RUNX1T1	+/-	++	+	AML
CBFβ-MYH11	+/-	++	+	AML
FLT3 ITD mutations	+/-	+	+/-	AML
NPM1 mutations	-	++	+/-	AML
KRAS, HRAS mutations	-	++	+	AML
TP53 mutations	-	+	+	MPN, CMML, AML

Valent et al. Int J Mol Sci 2019

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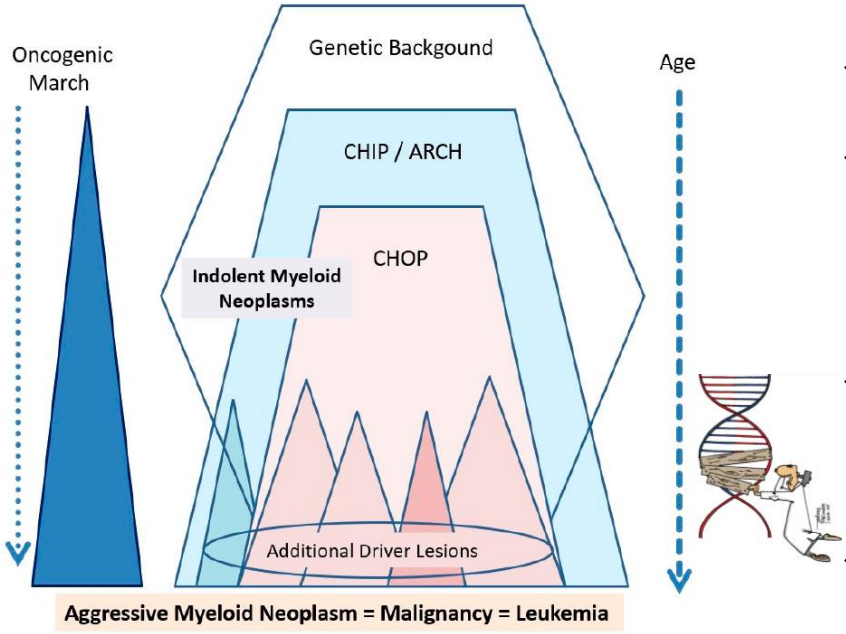
CHIP - CHOP - ARCH A point of view



- 50,000 to 200,000 HSCs/person.

- HSCs acquire ~ 20 somatic mut /year in the whole genome, including 0,1 in protein-coding exons.

- At 70 y. old… humans harbor 350,000 to 1,400,000 coding mutations within the HSC pool !
- If just one of these provide a selective advantage to the mutated-HSC…

Valent et al. Int J Mol Sci 2019

Jaiswal Blood 2020

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The clonal hematopoiesis family

	Cytopenia	Dysplasia	Clonality	VAF cutoff	Transfo to hemato malign.
CHIP	No	No (or <10%)	Yes	≥ 2%	(very) low
CHOP	No	No (or <10%)	Yes	≥ 2%	mod/high
ICUS	Yes (> 4 mo)	No (or <10%)	No	/	variable
CCUS	Yes (> 4 mo)	No (or <10%)	Yes	≥ 2(0)% *	Nearly 100% at 10 y
IDUS	No	Yes	No	/	/
MDS	Yes (> 4 mo)	> 10%	frequent		Risk of AML

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The clonal hematopoiesis family

There is no standardised variant allele frequency cut-off for CCUS, and some authors propose the same as for CHIP (>2%). In our opinion, CCUS should imply that cytopenias are solely driven by the clonal process resulting in ineffective haematopoiesis. Since this causation cannot be fully explained by the presence of a minute clone, we propose to apply the variant allele frequency cut-off of the dominant clone (>20%) for CCUS diagnosis.

In addition, using this higher variant allele frequency cut-off would possibly separate cytopenias that are due to the clonal process (such as CCUS) from other cytopenias that co-occur with incidental and inconsequential small CHIP clones

Gondek and DeZern Lancet 2020

CCUS	Yes (> 4 mo)	No (or <10%)	Yes	≥ 2(0)% *	Nearly 100% at 10 y

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The clonal hematopoiesis family

	Cytopenia	Dysplasia	Clonality	VAF cutoff	Transfo to hemato malign.
CHIP **CHOP** **ICUS** **CCUS** **IDUS**	Minimal diagnostic criteria for MDS never met and Exclusion of hematopoietic neoplasm and other diseases.				
MDS	Yes (> 4 mo)	> 10%	frequent		Risk of AML

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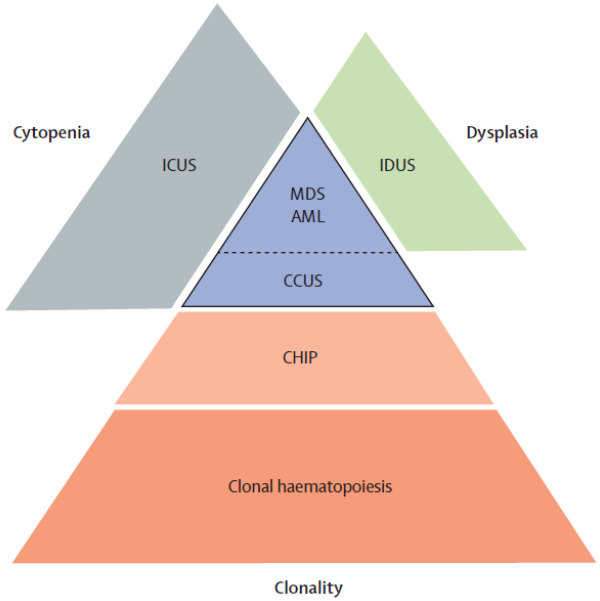
The clonal hematopoiesis family



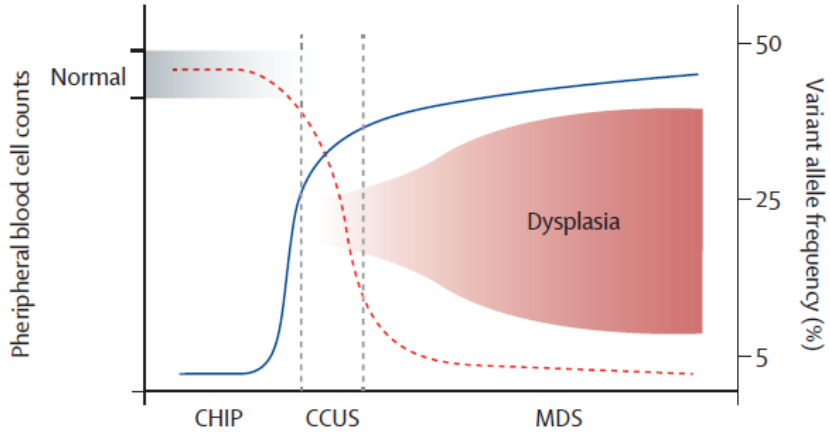


Figure 2: Peripheral blood cell count, variant allele frequency, and dysplasia as a continuum from asymptomatic CHIP to clinically obvious myelodysplastic syndrome

Gondek and DeZern Lancet 2020

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CHIP - CHOP - ARCH Consequences

- Follow-up and effect on overall survival :

➢ Increased all-cause mortality but **not only explained by hemato malignancies.**

➢ Cause-specific mortality analysis : **Mainly cardiovascular !**

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CHIP - CHOP - ARCH Consequences

- CHIP rises risk of death by 40%, so far greater than could explained by the risk of hemato malignancies, wich is around 10-fold.

- **CH is associated with an increased risk of cardiovascular disease.**
  - **Coronary heart dis.**
  - **Ischemic stroke**
  - **Atherosclerosis**
  - **Thrombosis**
  - **…**

MECHANISMS AND CLINICAL IMPLICATIONS OF CLONAL HEMATOPOIESIS

Clonal hematopoiesis and nonhematologic disorders

Siddhartha Jaiswal

Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease

Christopher S. Marnell [a,b,c], Alexander Bick [d], Pradeep Natarajan [a,b,c,*]

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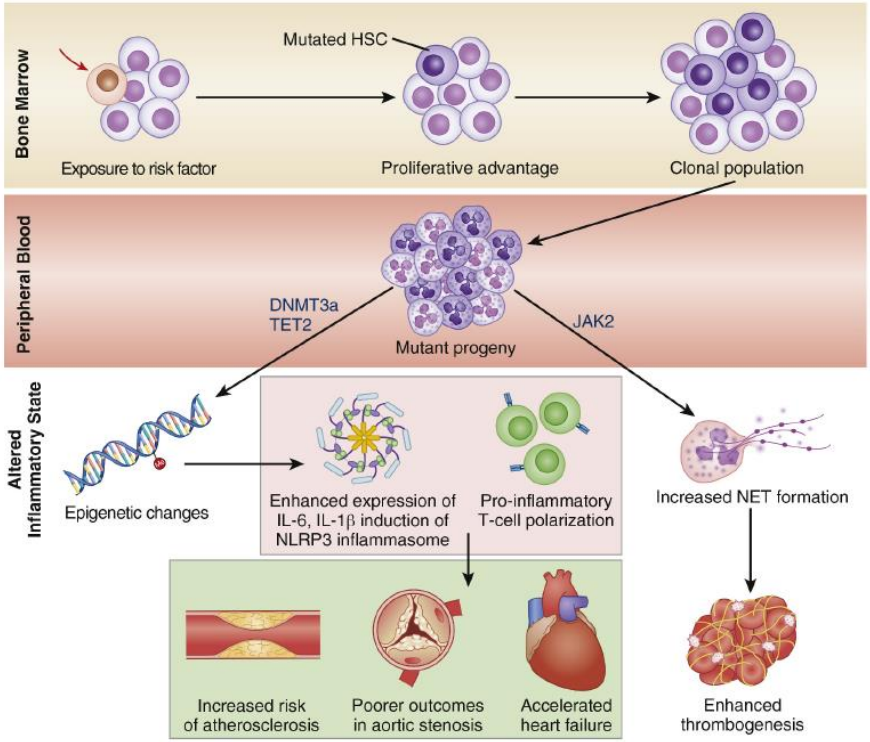
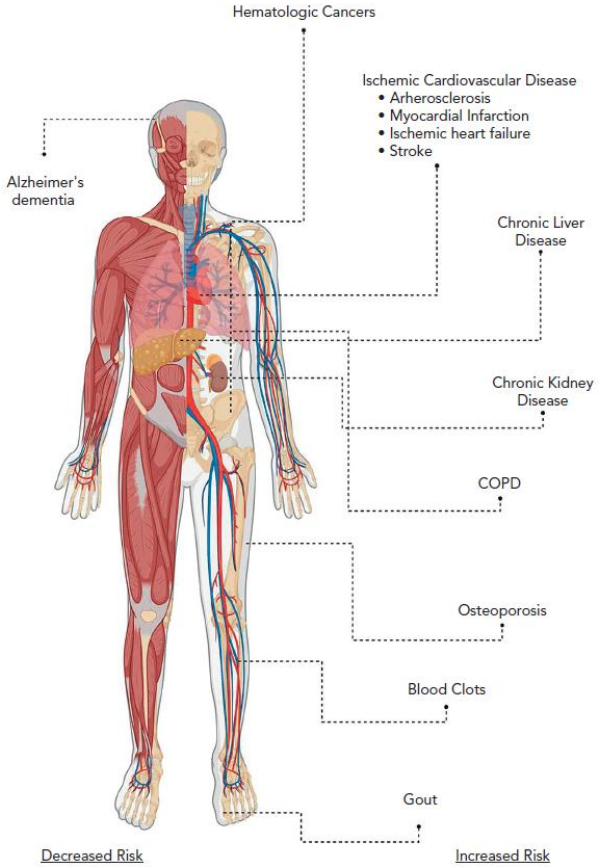
CHIP and “Inflammaging”





Marnell et al. JMCC 2021

Weeks and Ebert Blood 2023

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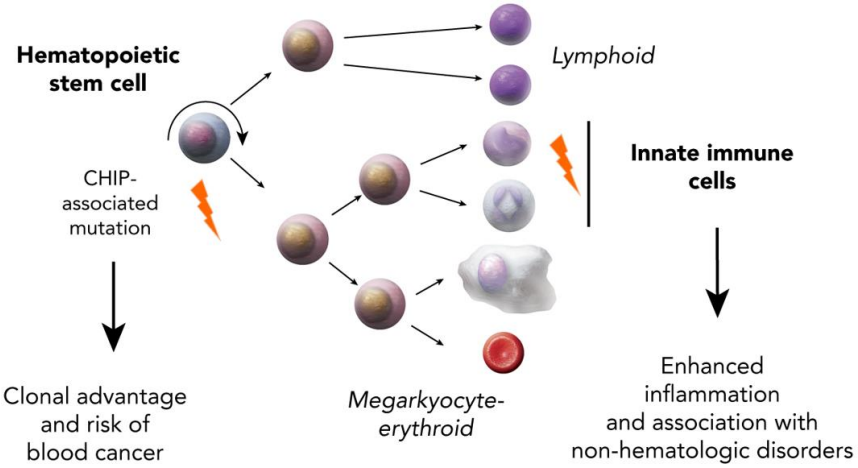
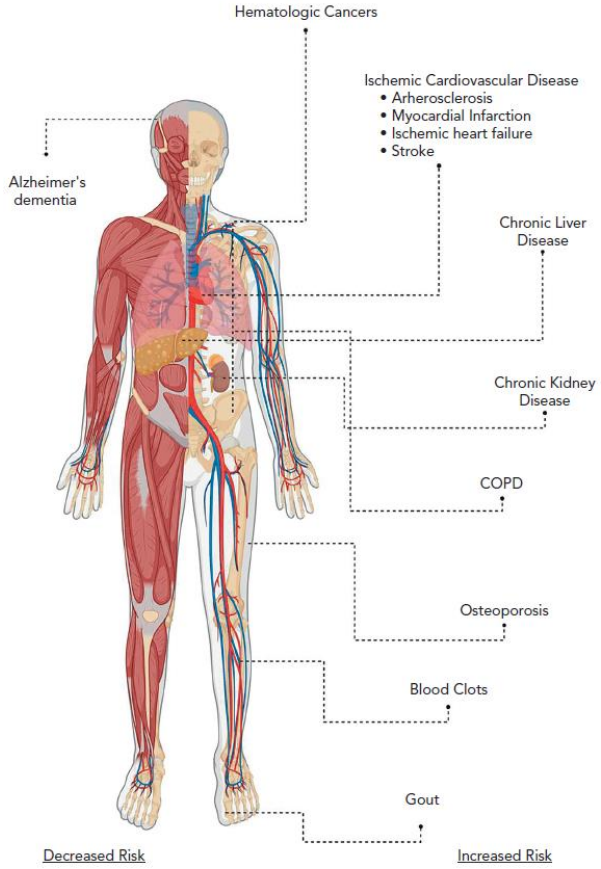
CHIP and “Inflammaging”





CHIP impact both risk and response to infections due to impaired function of downstream immune cells.

Florez et al. Cell Stem Cell 2022

Weeks and Ebert Blood 2023

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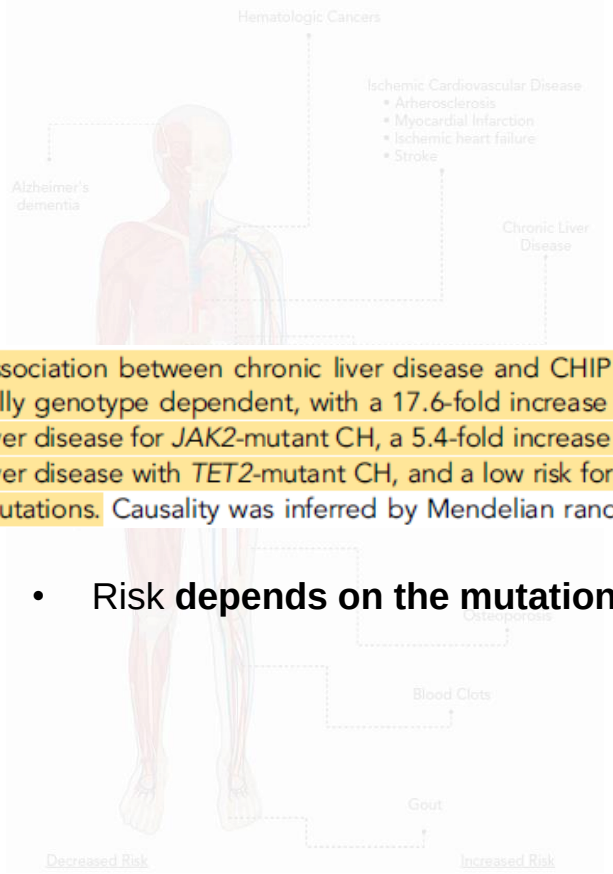
CHIP and “Inflammaging”

heart failure in patients with CHIP.[103] Clone size, a strong predictor of myeloid malignancy risk, is also prognostic of iCVD outcomes in CHIP/CCUS, such that individuals with VAF ≥ 10% had a greater likelihood of developing incident iCVD than those with smaller clones.[14]

- Risk **is proportional to the VAF**

Other age-related inflammatory diseases

Other age-related inflammatory diseases have been associated with CHIP, including chronic liver disease,[104] chronic kidney disease (CKD),[105-107] gout,[108] chronic obstructive pulmonary disease,[109] and osteoporosis (Figure 3).[110] Of these associations, the most robust observation is that CHIP with a VAF ≥ 10% doubles the risk of chronic liver disease, nonalcoholic hepatic steatosis, and cirrhosis.[104]



association between chronic liver disease and CHIP is powerfully genotype dependent, with a 17.6-fold increase in chronic liver disease for *JAK2*-mutant CH, a 5.4-fold increase in chronic liver disease with *TET2*-mutant CH, and a low risk for *DNMT3A* mutations. Causality was inferred by Mendelian randomization

- Risk **depends on the mutation**

Weeks and Ebert Blood 2023

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Risk factors & CHIP

Table 2
Emerging evidence of genotypic and phenotypic associations with CHIP.

Risk factor	Relevant studies
Germline Mutation	[24,37,43]
Aging and leukocyte telomere length	[24,37,48,50,51]
Smoking	[4,27,37,58,59]
Obesity, Insulin resistance & Type 2 Diabetes	[5,58,85]
Hyperlipidemia & Atherosclerosis	[53,54,58]
Sleep Deprivation	[38,62]
Premature Menopause	[64]
Chronic Inflammatory Conditions	[37]
	Systemic Sclerosis [65]
	Rheumatoid Arthritis [66]
	Ulcerative colitis [72]
Chronic Infection, including HIV	Chronic Infection [16]
	HIV [28,75]
Cancer therapy	[35,59,78]

Marnell et al. JMCC 2021

Complex interaction

- *« however, it is possible that CHIP driven inflammation contributes to the development of these diseases. »*
- *« […] inflammation itself is a driver of CHIP, setting up a feedforward loop of CHIP and disease. »*

Florez et al. Cell Stem Cell 2022

- History of cancer & treatment is linked to certain CHIP mutations.
- Mutations in DDR genes (TP53, PPM1D, and CHEK2) have the strongest association and these clones expand especially under specific cytotoxics.

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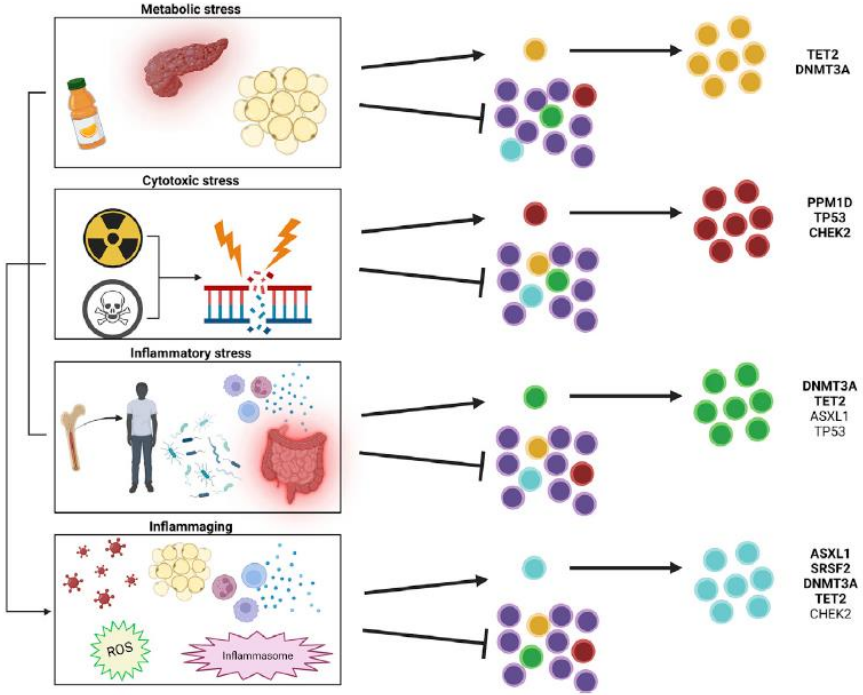
Risk factors & CHIP



Florez et al. Cell Stem Cell 2022

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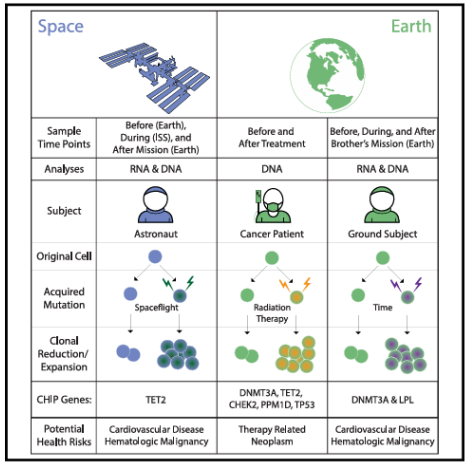
Risk factors & CHIP

Cell Reports

Report

Clonal Hematopoiesis Before, During, and After Human Spaceflight

Graphical Abstract



Authors

Nuria Mencia-Trinchant, Matthew J. MacKay, Christopher Chin, ..., Ross L. Levine, Duane C. Hassane, Christopher E. Mason

Correspondence

duane.hassane@gmail.com (D.C.H.), chm2042@med.cornell.edu (C.E.M.)

In Brief

Trinchant et al. examined twin astronauts for clonal hematopoiesis (CH). Some high-risk CH clones (TET2 and DNMT3A) were observed two decades before expected, with TET2 decreasing in spaceflight and elevating later post flight. Thus, CH is an important metric for overall cancer and cardiovascular risk in astronauts.

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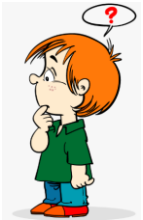
CHIP on the road to malignancy

- CHIP rises risk of hemato malignancies approx. by 10.
- Between 3 to 5-fold increased risk of developing AML.

DeZern et al. ASCO 2019

- Depends on
  - Clone size, as indicated by VAF.
  - The mutation itself (i.e. DNMT3A < TP53)
  - The number of molecular abnormalities

- Globally, **the absolute risk** remains small, with an estimated **rate of hemato malign. from 0,5 to 1% per year.**



Gondek and DeZern Lancet 2020

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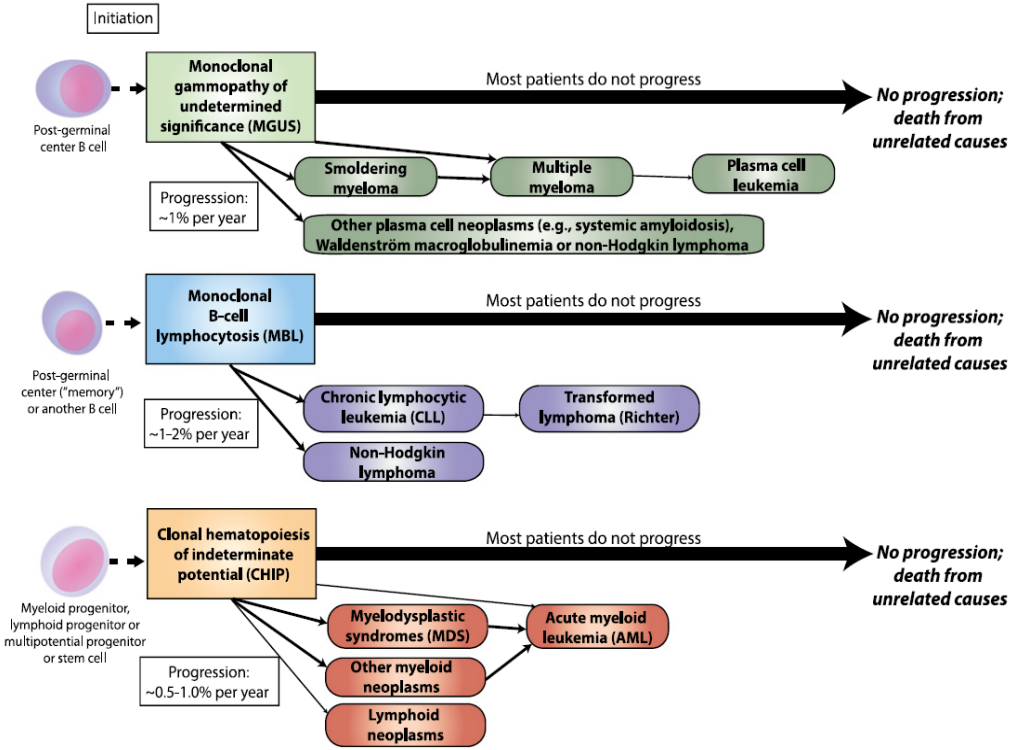
CHIP on the road to malignancy



Steensma Blood 2015

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CHIP on the road to malignancy

- **The clonal hematopoiesis risk score (CHRS)**
  - A clinical tool to estimate the risk of progression to myel. malign. In CHIP/CCUS

Table: CHRS values (Weeks et al. 2023).

SRSF2, *SF3B1*, *ZRSR2*, *IDH1*, *IDH2*, *FLT3*, *RUNX1*, *JAK2*, *TP53*

Table 2. CHRS Values.*

Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	Present	Absent			
High-risk mutation		Absent			Present
Mutation number		1		≥2	
Variant allele fraction		<0.2		≥0.2	
Red cell distribution width		<15			≥15
Mean corpuscular volume		<100			≥100
Cytopenia		CHIP	CCUS		
Age (yr)		<65	≥65		

* CCUS denotes clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; and CHRS, clonal hematopoiesis risk score.

3 categories

Low (score ≤9.5)

Intermediate (score 10-12)

High (score ≥12.5)

CHIP on the road to malignancy

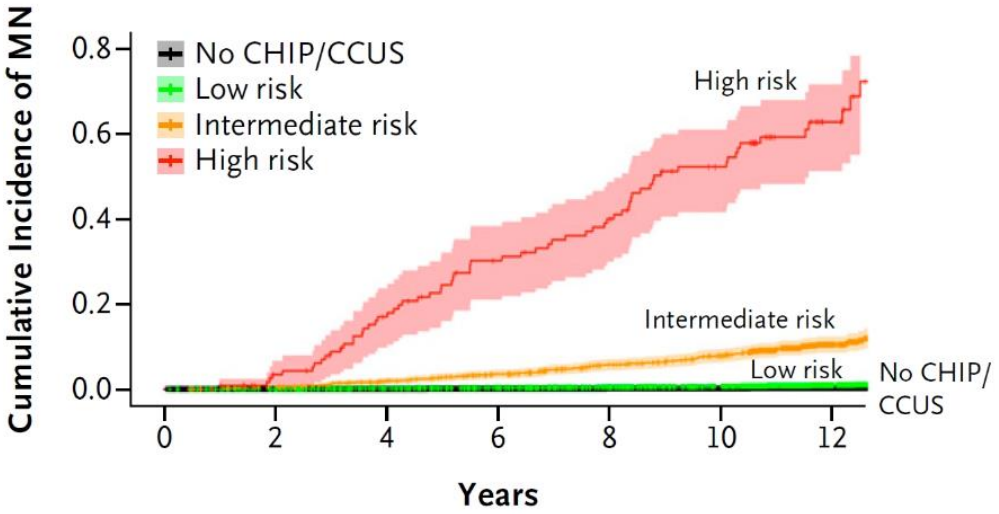

Figure: Cumulative curves for the incidence of MN according to CHRS risk category (Weeks et al. 2023).

Also correlate to comorbidity risk !

Weeks NEJM Evid. 2023

Weeks and Ebert Blood 2023

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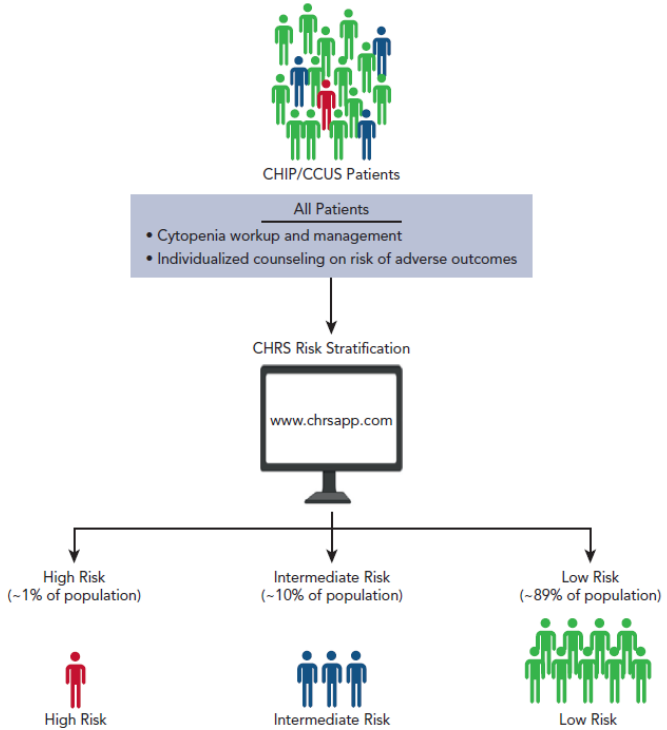
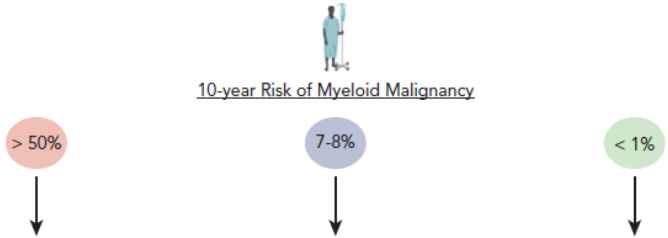
CHIP on the road to malignancy





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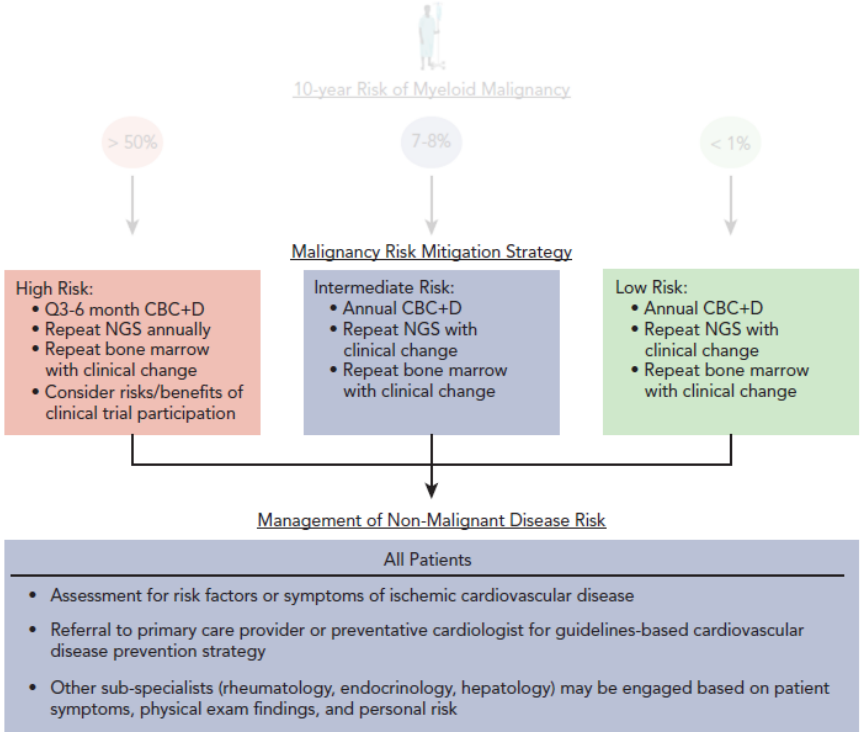
Attitude & follow up



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CHIP & Stem Cell Transplantation (SCT)

- About Autologous-SCT
  - Patients with CHIP mutations had inferior survival and higher incidence of therapy-related myeloid neoplasms (TMN's).
  - Inconstant unexplained cytopenias after ASCT in patients harboring CHIP, suggesting a mutation specific graft dysfunction.

Florez et al. Cell Stem Cell 2022

- About Allogeneic-SCT
  - Increased risk of TMN's after allo with TP53 donor CHIP.
  - Reduced relapse risk & higher rates of GVH disease for DNMT3A-mutant donor.

Weeks and Ebert Blood 2023

- In both ASCT & allo-SCT, the role of conditioning regimen (cytotoxics +/- irradiation) on the niche and de facto, the environment of CHIP carrier cells, could be relevant.

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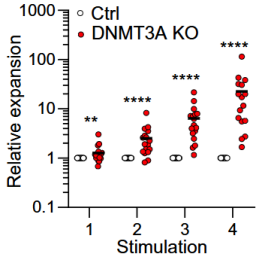
CHIP & Chim. Antigen. Rec. T (CAR T)

- To date, the impact of immunotherapies on CHIP remains controversial but CHIP mutations are known to affect CAR T cell function.

  - Clinical case of an exceptional responder with chronic lymphocytic leukemia (CLL) to CAR-T cells. **The patient harbored TET2-mutant T cells due to CHIP**, and **the CAR construct fortuitously disrupted the other copy of TET2**, leading to a TET2-null CAR-T clone.

    This clone had enhanced expansion, prolonged activation, increased cytokine production, and memory like properties, a consistent observation with the known role for DNA methylation in T cell function. Fraietta et al. Nat Med 2018

  - **Deletion of DNMT3A** in CAR T cells also promotes cell survival, limits exhaustion, and enhances therapeutic efficacy. *(In a mouse model).* Prinzing et al. Sci Transl Med 2021



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CHIP & Chim. Antigen. Rec. T (CAR T)

- To date, the impact of immunotherapies on CHIP remains controversial but CHIP mutations are known to affect CAR T cell function.
    - Patients with CHIP had a higher rate of complete response to CAR T therapy, but with increased rates of cytokine release syndrome.

Miller et al. Blood adv 2021

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CH Perspectives & Challenges

- Global medicine with a metabolic and cardiovascular view from molecular informations.
  - Follow up and wait & see period require already a multidisciplinary approach.

- Patient's somatic mutational background influences on cytotoxics choice, also beyond hematology in solid tumors.
  - Mitigate the risk of subsequent therapy-related MDS/AML.

Florez et al. Cell Stem Cell 2022

- Guide risk-specific management with CHRS. "Neither too much nor too little"

- "**CHIP clinics**" and personalized medicine !

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CH Perspectives & Challenges

- New or residual CHOP-like lesions as targets of hypomethylating agents ? Cappelli et al. Leukemia 2022

- Targeting candidate driver mutation as a preventive strategy ?
  - Vitamine C metabolites activate and can mimic restoration of TET2 in a mice model.
  - JAK2 inhibitors reduced abnormal NET's formation, deep vein thrombosis, and atherosclerosis in JAK2 mutant CHIP mice models.

  Marnell et al. JMCC 2021

- Risk-benefit balance of anti-inflammatory therapies (IL-6, IL-1β, …)

- "[…] *despite our tendency toward binary thinking, mutant clones may live in the liminal space between pathogenic and beneficial*."

Marnell et al. JMCC 2021

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Nephro on call about anemia

- A 70 y old woman followed for moderate renal chronic disease.
- Hb 10 g/dL, macro, non regenerative. WBC and platelets are normal.
- Martial & vitamin evaluation correct. No inflammation. No toxics.

- Bone marrow aspirate with mild dysplasia.
- Normal karyotype
- NGS : TP53 VAF 10 %.

CHIP

CHOP

ICUS

IDUS

CHUD

ARCH

MDS

CCUS

	Cytopenia	Dysplasia	Clonality	VAF cutoff	
CHIP	No	No (or <10%)	Yes	≥ 2%	
CHOP	No	No (or <10%)	Yes	≥ 2%	
ICUS	Yes …	No (or <10%)	No	/	
CCUS	Yes …	No (or <10%)	Yes	≥ 2(0)%	
IDUS	No	Yes	No	/	
MDS	Yes …	> 10%	frequent		

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Conclusion & Take-home message

- **CHIP** is defined by a **cancer-associated somatic mutation** in the blood or bone marrow, **without cytopenia and hematologic malignancy**, at variant allele frequency **≥ 2%.**
- DNMT3A, TET2 and ASXL1 are the most commonly mutated genes.
- **CHOP** mutations are associated with a **substantial risk to transform to hemato malignancy**.

- Most individuals never develop CHIP, suggesting that **environmental pressures** are critical determinants of clonal expansion. Some risk factors are linked to specific mutations.

- CH is linked to **altered immune function**, **inflammation** & **nonmalignant diseases of aging**.
- Cardiovascular disease is a challenge for **preventive medicine in CH**.

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Conclusion & Take-home message

- CHIP is a **pre-malignant condition**, comparable to MGUS and MBL.
- **C**lon. **H**ematop. **R**isk **S**core estimates the risk of progression to myeloid malignacy.
- Whereas some clones contribute to CV diseases, others may be neutral or may be beneficial by enabling long-term hematopoiesis in the elderly !

- Future will may be based on decision-making algorithms according to our somatic mutational background.
- Impact on other tissues and solid tumors is certainly underestimated… as the impact on patients' mental state !

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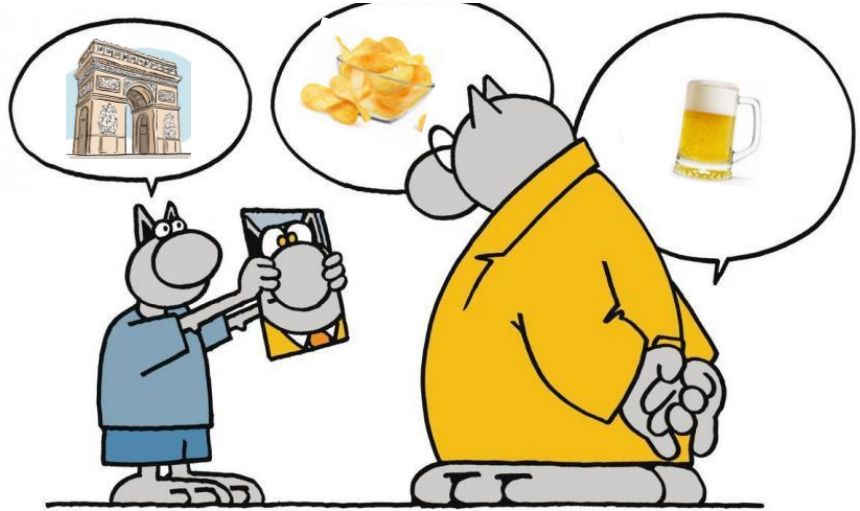
Thank you for your attention



Don’t hesitate if any questions

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