

CLONAL HEMATOPOIESIS OF UNKNOWN POTENTIAL AND CARDIOVASCULAR DISEASE – LITERATURE REVIEW

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КЛОНАЛНА ХЕМОПОЕЗА С НЕИЗВЕСТЕН ПОТЕНЦИАЛ И СЪРДЕЧНО-СЪДОВИ ЗАБОЛЯВАНИЯ – ЛИТЕРАТУРЕН ОБЗОР

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Abstract.

Somatic mutations in hematopoietic stem cells (HSCs) are an inevitable part of human aging. When these mutations reach a certain variant allele frequency (VAF), they may confer a proliferative advantage to mutated clones, leading to clonal hematopoiesis. Once the HSCs generate over 10^{10} - 10^{12} mutated cells, they can initiate various myeloid or lymphoid malignancies. In cases where the VAF exceeds 2% (roughly 10^4 mutated blood cells) but without clinical evidence of hematologic cancer, the condition is termed *clonal hematopoiesis of indeterminate potential* (CHIP). Numerous studies have identified that CHIP is frequently driven by mutations in genes implicated in hematologic malignancies, most notably *TET2*, *DNMT3A*, and *JAK2*. CHIP has also been strongly linked to cardiovascular diseases, particularly atherosclerosis. This dual role highlights a shared pathogenesis between cardiovascular and hematologic disorders through mutations in HSCs. CHIP-associated monocytes exhibit a pro-inflammatory phenotype, activating inflammasomes and overexpressing cytokines such as interleukin (IL)-1 β and IL-6, as well as chemokines like Cxcl1-3 and Pf4. This leads to a chronic inflammatory loop that contributes to endothelial dysfunction and atherosclerosis. Current data suggest that CHIP poses a cardiovascular risk comparable to traditional risk factors. Ongoing research continues to uncover the complex mechanisms underlying this association.

Key words:

somatic mutations, clonal hematopoiesis of undetermined potential, *TET2*, *DNMT3A*, *JAK2* V617F, cardiovascular diseases, heart failure

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Резюме:

Соматичните мутации в хемopoетичните стволови клетки (HSC) са неизбежна част от биологичното стареене на човека. При достигане на определена вариантна алелна честота (VAF) някои от тези мутации осигуряват селективно предимство и стимулират пролиферацията на клонове – феномен, известен като клонална хемopoеза (КХ). Натрупването на над 10^{10} - 10^{12} мутирани клетки може да доведе до развитие на миело- или лимфопрoлиферативни неоплазии. Когато VAF е $\geq 2\%$ (приблизително 10^4 клетки) и липсват данни за хематологично злокачествено заболяване, състоянието се определя като *клонална хемopoеза с неопределен потенциал* (CHIP). Най-често се засягат гени, свързани с предлевкемични промени – *TET2*, *DNMT3A* и *JAK2*. Интересно е, че CHIP се асоциира не само с хематологични, но и със сърдечно-съдови заболявания, особено атеросклероза. Модифицираните моноцити активират инфлазомози и засилват секрецията на провъзпалителни медиатори – interleukin (IL)-1 β , IL-6 и хемокини като Cxcl1-3 и Pf4, което води до хронично възпаление и съдова увреда. Така се оформя самоподдържащ

се възпалителен цикъл, в който се включват и традиционни рискови фактори. В този контекст CHIP се разглежда като нов, независим рисков фактор за исхемична болест на сърцето, съпоставим по значимост с артериалната хипертония, захарния диабет и тютюнопушенето. Макар наличните проучвания да са все още в ранен етап връзката между CHIP и атерогенезата поражда нарастващ научен и клиничен интерес.

Ключови думи: соматични мутации, клонална хематопоеза с неопределен потенциал, *TET2*, *DNMT3A*, *JAK2 V617F*, сърдечно-съдови заболявания, сърдечна недостатъчност

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INTRODUCTION

Two fundamentally diverse groups of diseases – cardiovascular and malignant blood neoplasia – can be pathogenetically linked through the same genetic mutations in pluripotent hematopoietic stem cells (HSC). Mutations in stem and progenitor cells most often affect genes responsible for specific signalling cascades regulating differentiation, proliferation, maturation, and apoptosis, i.e. biology, lineage development, and function of individual cell lines. Each mutation triggers unique pathogenetic mechanisms leading to a specific phenotypic manifestation. Depending on the abundance of the mutagenic burden, i.e. variant allele frequency (VAF), the mutated clone can gain a competitive advantage by proliferating uncontrollably with suppressed apoptosis. The cell pool with such biological superiority is the result of the so-called clonal haematopoiesis (CH) caused by multiple somatic mutations and epigenetic effects in the parent cell, which reproduces through identical daughter copies (clones). When CH “produces” more than 10^{10-12} mutated cells various myelo- and lymphoproliferative malignant blood neoplasia are triggered. At a VAF of at least 2%, which corresponds to about 10^4 mutated cells and in the absence of data on hematologic malignancy, CH is designated as **clonal haematopoiesis of indeterminate potential (CHIP)** [1]. This category also includes the so-called **clonal cytopenia of undetermined significance without myelodysplastic features (CCUS)** [2]. CHIP occurs in healthy individuals and increases tenfold with age, in which case the term *age-related clonal haematopoiesis* is also used [2, 3]. Modern genetic technology has allowed for the leading driver mutations of CHIP to be established. These include mutations commonly associated with certain acute and chronic malignant hemopathies [4, 5]. In most studies, CHIP represents an optional indefinite-duration pre-phase of hematologic malignancies, with important pathogenetic significance to a number of non-hematologic conditions and above all to atherogenesis [5]. Over the last decade, an increasing number of publications have indicated a surprisingly high correlation between CHIP and all-cause mortality. CHIP has also been associated

with a significantly elevated risk of adverse events in patients with cardiovascular diseases (CVD). Contemporary evidence suggests that CHIP is an important risk factor for coronary artery disease (CAD), comparable in significance to hypertension, diabetes, overweight, hypercholesterolemia, smoking, chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), chronic kidney disease (CKD). The correlation between CHIP, aging, atherosclerosis and above all CAD is yet to be determined as evidence is currently scarce. The mechanisms through which CHIP triggers or modulates atherogenesis are not clearly understood and so is its impact on real life clinical practice.

First reports on CHIP

In 1994, Fey MF first established CH in non-random inactivation of the X chromosome, which is reproducibly preserved during mitotic division [6]. In 2012, Busque et al. confirmed the presence of CH by establishing mutation of the *TET2* gene in about 5% of adult women [7]. The existence of an initial driver mutation – *AML1/ETO* translocation as a part of a HSC mutation was reported by T. Miyamoto et al. during remission in a case of acute myeloid leukemia (AML) [8]. Despite the 10-fold higher risk, malignant haematological transformation is an exceedingly rare phenomenon, requiring multiple additional gene mutations, i.e. most CHIP carriers will not develop malignant hemopathy throughout their lives.

Prevalence

It is assumed that HSCs are about 1/100,000 in the adult bone marrow, which corresponds to 50,000-200,000 cells. Of these, about 1% circulate in the peripheral blood, have the ability to self-renew to the highest degree and are identified by the surface marker CD34 [9]. With strictly determined apoptosis duration, individual cell lines produce about 200 billion erythrocytes, 100 billion platelets and 60 billion neutrophils daily. It has been estimated that each HSC acquires 1 exonic mutation/10 years of life, 0.13 ± 0.02 exonic mutations/year of life or about 5 coding gene mutations in each stem cell by the age of 50 years [10]. In an adult individual aged 70 years, this corresponds to

350,000-1,400,000 gene mutations or an average of 70 mutations per gene [11]. This leads to the conclusion that, with advancing age, mosaicism with different genotypes could be found in every individual [12, 13].

Reported prevalence of CHIP varies significantly depending on the literature source. Jaiswal S et al. performed complete sequencing of DNA exon for somatic mutations in 160 genes (involved in malignant hemopathies) in 17,182 individuals and found the following: detectable clones are rare in individuals under 40 years of age - less than 1%, at the age of 70-79 years they are 9.5%, at 80-89 years - 11.7%, and from 90-108 years - 18.5% [12]. Using deep-corrected targeted sequencing with a VAF $\geq 0.5\%$, K. C. Kiefer et al. found CHIP with at least one mutation in 87% of the studied cohort of 399 patients. The incidence of CHIP increased with age: in the range of 50-59 years - 81.6%, at 60-69 years - 90.7%, at 70-79 years - 88.8%, and 100% in patients above 80 years ($p < 0.026$) [5]. Similarly, A. L. Young et al. found stable clonal mutations in 93% of studied 50-60-year-old individuals with a VAF $\geq 0.01\%$ by targeted sequencing with error correction [13].

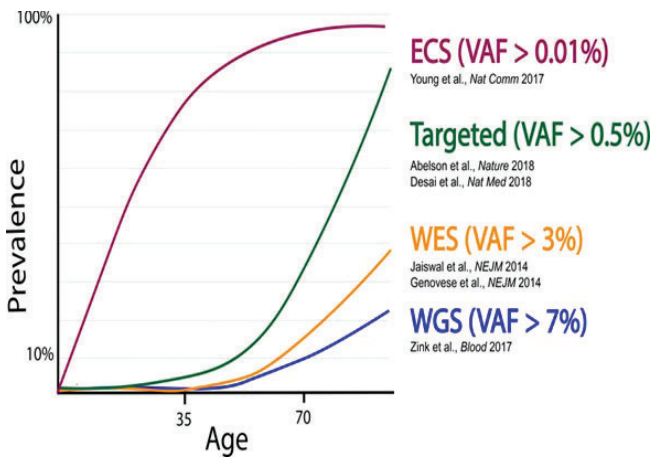


Fig. 1. Prevalence of CHIP depending on age and genetic method used [Jaiswal S, N Engl J Med, 2014]

On the one hand, these examples show, that CHIP with VAF $\geq 0.5\%$ is about twice as common a phenomenon as previously reported in literature. On the other hand, the prevalence of CHIP is not a function of age alone, but rather of the sensitivity of the genetic methods used (Fig. 1).

Mutational spectrum in CHIP

The mechanisms leading to the occurrence of mutational genomic disorders in CHIP are mainly loss of function or truncation of alleles in various epigenetic regulatory genes. According to literature, the range of genomic defects resulting in stable clonal selection is extremely wide and increases depending on the genetic methods and the availability of deep sequencing with low VAF. Kiefer K.C. and col. found that the most common mutations occur in driver genes: *DNA (cytosine-5)-methyltransferase 3A - DNMT3A* (226), followed by mutations in the genes *Tet Methylcytosine Dioxygenase 2 - TET2* (133), *BCL6 Corepressor Like 1 - BCORL1* (78), *ATRX* (54), *STAG2* (50) and in 43 other genes. Of the 399 patients, 21% had 1 mutation, 47% had from 2 to 4 mutations, and 19% from 5 to 12 mutations [5]. In reality, however, CHIP of sufficient clone size results from mutations in an extremely limited number of genes that form the so-called "risk panel." About 2/3 of clinically significant mutations occur in 3-4 genes: *DNMT3A*, *TET2*, *additional sex combs like 1 - ASXL1*, and *janus kinase 2 - JAK2*, the pathophysiological significance of which is discussed below.

CHIP - a new genetic biomarker and risk factor for cardiovascular disease

In 4 studies, including a total of 4794 cases and 3537 controls, Jaiswal et al. were the first to find that CHIP carriers had a 3.3-fold higher risk of coronary artery calcification above 615 Agatston units (computed coronary tomography) without incidental coronary artery disease and 1.8-fold higher risk of subsequent

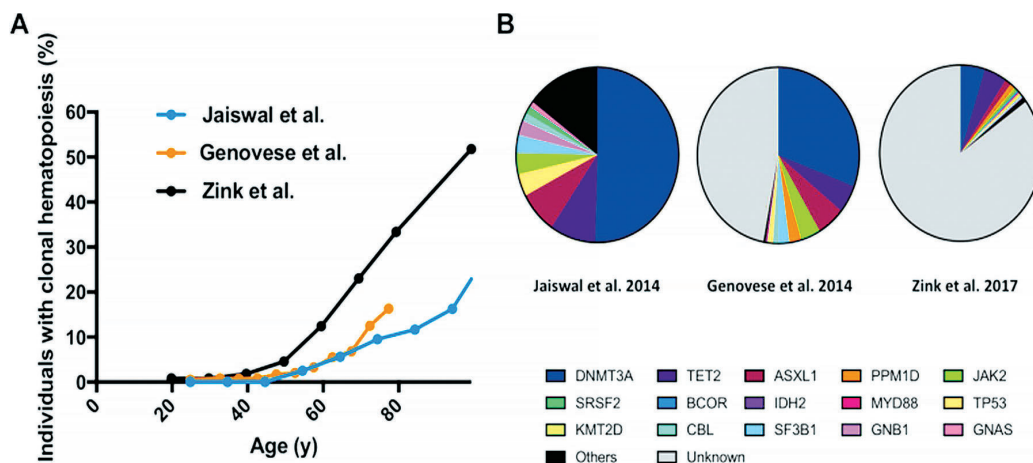


Fig. 2. CHIP and most common mutations found in 3 studies [by_Yura Y et al, 2020]

CAD ($p = 0.03$), a 1.9-fold higher risk of coronary artery disease and a 4-fold higher risk of early myocardial infarction.

The individual risk is proportional to the mutagenic burden (VAF variations) and is individually associated with single mutations in driver genes, but also with a wide variety of other mutations, as proven by advanced technology [12, 14, 15]. In the last 10 years, a constantly increasing number of studies have confirmed the significant relationship between CHIP and cardiovascular outcomes: higher all-cause mortality, higher risk of ischemic stroke, doubled risk of venous thrombosis, higher hospital mortality, higher mortality from CAD, higher mid-term overall mortality after successful transcatheter aortic valve implantation (TAVI), more frequent systolic and diastolic dysfunction, progression of HF and cardiogenic shock, more frequent unprovoked pulmonary thromboembolism, absolute arrhythmia, aortic aneurysm. Similar associations, proven through various multivariate statistical analyses, present CHIP as a new independent, prognostic risk factors for CVD, equal in significance to conventional risk factors (Fig. 3).

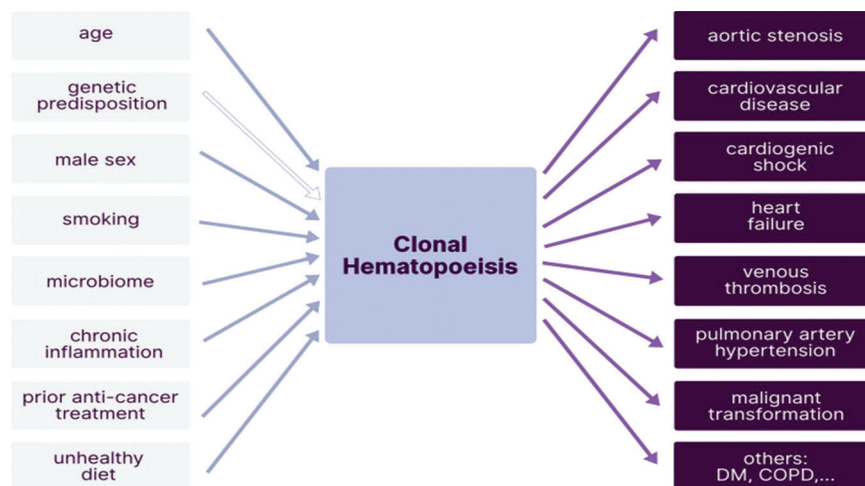


Fig. 3 CHIP, predisposing factors and cardiovascular disease [A. Stein, Basic Research in Cardiology, 2022]

Factors facilitating CHIP

The most common mechanism enabling CHIP mutations is spontaneous deamination with the replacement of cytosine by thymidine, a major phenomenon of aging due to reduced efficiency of DNA error correction. CHIP is an almost inevitable consequence of aging, and age is the strongest risk factor for its manifestation [16]. Anna Stein et al. analysed a number of studies and identified the following factors facilitating CHIP: male gender, smoking, chronic inflammatory and autoimmune diseases, Human Immunodeficiency Virus infection, previous chemotherapy and radiotherapy, unhealthy diet, changes in the microbiome, family predisposition (Fig. 3) [17].

Presumed pathogenetic relationship between CHIP and atherogenesis and cardiovascular disease

Theoretical knowledge of the mutation spectrum in CHIP and its significance is still in an early stage of research. Only the most common driver genes (*TET2*, *DNMT3A*, *JAK2* and *ASXL1*) have proved to play a pathogenetic role in CHIP mutations. Many other genes, identified through modern genetic methods, demonstrate mere statistical association and have no proven significance.

CHIP with *TET2* mutations

The first experimental mouse models with *Tet2* knockout by K. Moran-Crusio (2011) found increased self-renewal of HSCs with predominantly myeloid differentiation, splenomegaly, and extramedullary haematopoiesis [18]. Considering the high frequency of *TET2*-mediated CHIP in atherosclerotic CVD, experimental mouse models with a relatively uniform design were developed by two groups of authors in 2017: lethally irradiated mice with low-density lipoprotein receptor

deficiency *Ldlr*^{-/-} were transplanted with *TET2*^{-/-} and *TET2*^{+/-} cells and subjected to a high-fat diet. In a fundamental, well-designed, and scientifically substantiated study, J. J. Fuster et al. obtained results with theoretical significance and direction for future investigation [19]:

1. In *TET2*^{-/-} transplanted mice (resembling human CHIP with *TET2* mutations), haematopoiesis increases with a predominance of the myeloid population, and an increased number of monocytes is noted.

2. *TET2*^{-/-} and *TET2*^{+/-} deficient mice develop 60% larger atherosclerotic plaques in the aortic root than the control groups; there are no changes in the smooth muscle endothelium, necrotic nuclei, cell proliferation in the plaques, as well as abnormal apoptosis.

3. *TET2*^{-/-} haematopoiesis is characterised by proliferation of the proatherogenic macrophage population in the atherosclerotic intima, i.e. phenotypically altered macrophages are probably the key factor for accelerated atherogenesis.

4. *TET2*^{-/-} deficiency is a negative transcriptional regulator of the inflammatory response, i.e. it stimulates inflammatory processes. In *TET2*^{-/-} macrophages increased transcription of genes encoding cytokines, chemokines and signaling molecules results in expression of pro-inflammatory factors.

¹Ldlr – Low-Density Lipoprotein Receptor (gene, mouse model)

5. Minimizing the influence of *TET2* deficiency by humoral agents – oxLDL, TNF and interferon gamma (IFN- γ) resulted in a significant decrease in the expression of cytokines and chemokines, with the exception of interleukin (IL)-1 β , which was significantly elevated in *TET2*^{-/-} macrophages. A 2-fold increase in the expression of IL-1 β transcripts in the aortic arch of mice was also noted.

6. Cell cultures with macrophages overexpressing mutant *TET2* have reduced HDAC²-mediated histone deacetylation, i.e. loss of *TET2* function modulates IL-1 β expression in macrophages, regardless of its catalytic activity.

7. *TET2* deficiency affects IL-1 β secretion by activating the *NLRP3*³ inflammasome and increasing its main component – caspase-1 (stimulating the cleavage of pro-IL-1 β to an active form). The authors supported their thesis by blocking the *NLRP3* inflammasome with the MCC950 inhibitor, which led to a decrease in plaque size by about 50%, i.e. MCC950 exhibits a distinct anti-atherogenic effect and eliminates the difference with controls.

8. In addition to being a key mediator of *TET2* deficiency in CVD the pro-atherogenic IL-1 β correlates with increased expression of P-selectin in the aortic endothelium causing increased adhesion of monocytes to the atherosclerotic plaque [19].

Jaiswal S's team supported the available experimental results and added new evidence for the pathogenetic significance of *TET2* deficiency using a similar mouse model [14]. In their experiment, mice with *TET2*^{-/-} haematopoiesis developed atherosclerotic lesions in the aortic root of 2 to 2.7-fold greater average size, for the duration of 17 weeks. *TET2*^{-/-} macrophages increased the transcription of a chemokine gene cluster (Cxcl1, Cxcl², Cxcl³, Pf4) and of the classical pro-inflammatory cytokine genes – IL-1 β and IL-6, resulting in 2-4-fold elevation of their serum secretion. Another interesting finding was the increase in atherosclerosis in other tissues – spleen and middle ear xanthomas, accumulation of foam cells and large inflammatory infiltrates in the kidneys, liver, and lungs.

In 2018, S. Sano and colleagues presented experimental evidence for the association between HF and CHIP with *TET2* mutations in two *TET2*-deficient mice models [20]. In the first model, chronic ischemia was induced by permanent ligation of the left anterior descending coronary artery, and in the second, by increased pressure from transverse aortic constriction or angiotensin infusion. In both models of HF, *TET2* deficiency worsened cardiac remodelling with increased

hypertrophy, cardiac dysfunction and IL-1 β expression. The administration of a selective NLRP3 inflammasome inhibitor, as in the experiments of Fuster JJ et al, prevented the development of HF and eliminated the differences with controls.

CHIP with *DNMT3A* mutation

DNMT3A is the most common mutated gene in CHIP. It catalyses DNA methylation and is an important regulator of haematopoiesis and inflammatory responses. Similar to *TET2* deficiency, *DNMT3A*^{-/-} or +/- leads to myeloid expansion of haematopoiesis and to the development of myeloid neoplasia in experimental mouse models [21]. Although *TET2* and *DNMT3A* mediate the opposite catalytic reactions, mutations in both genes lead to convergent CHIP phenotypes. To demonstrate a causal relationship between *DNMT3A*-mediated CHIP and atherosclerosis, Rauch et al. used a mouse model similar to the ones described above and established the following:

1. The gene expression profile was similar to the *TET2*^{-/-} experimental setups – genes encoding the chemokine cluster Cxcl1, Cxcl2 and Cxcl3 as well as mRNA encoding the main pro-inflammatory cytokines IL-1 β and IL-6 were upregulated.

2. After 9 weeks the average size of atherosclerotic lesions was 40% larger in *Dnmt3a*^{-/-} mice, compared to controls ($p = 0.04$).

3. A population of lesional macrophages expressing genetic markers (Mrc1, Lyve1, F13a1), inflammatory mediators (Cxcl1, Pf4, Ccl2, Ccl7, Ccl8) and transcription factors (Jun, Fos, Egr1) characteristic of macrophages in atherosclerotic plaques was found in *Tet2* or *Dnmt3a* deficiency [22].

Using a lentiviral vector and the *Clustered Regularly Interspaced Short Palindromic Repeats – CRISPR/Cas9*, S. Sano et al. inactivated *Tet2* and *Dnmt3a* in bone marrow cells and then competitively transplanted them. CRISPR-manipulated cells not only proliferated in the bone marrow similar to *Tet2*-deficient mouse models, but also mediated pathological cardiac remodelling after angiotensin II infusion, resulting in worsening of cardiac function, and higher levels of fibrosis and inflammation [23].

CHIP with *JAK* mutation

JAK2 is a potent signal transducer that activates transcription of the signal transducer and activator of transcription (STAT) pathway, regulating the production of proinflammatory cytokines. The *JAK2* V617F (janus kinase) mutation is prevalent and coincidence in CHIP and myeloproliferative neoplasms (MPN). The *JAK2* mutation encodes and triggers 3 MPNs – polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). In *JAK2* CHIP the hemogram remains unchanged. *JAK2* mutation occurs in about

²HDAC – Histone Deacetylase

³NOD-, LRR- and pyrin domain-containing protein 3 (inflammasome)

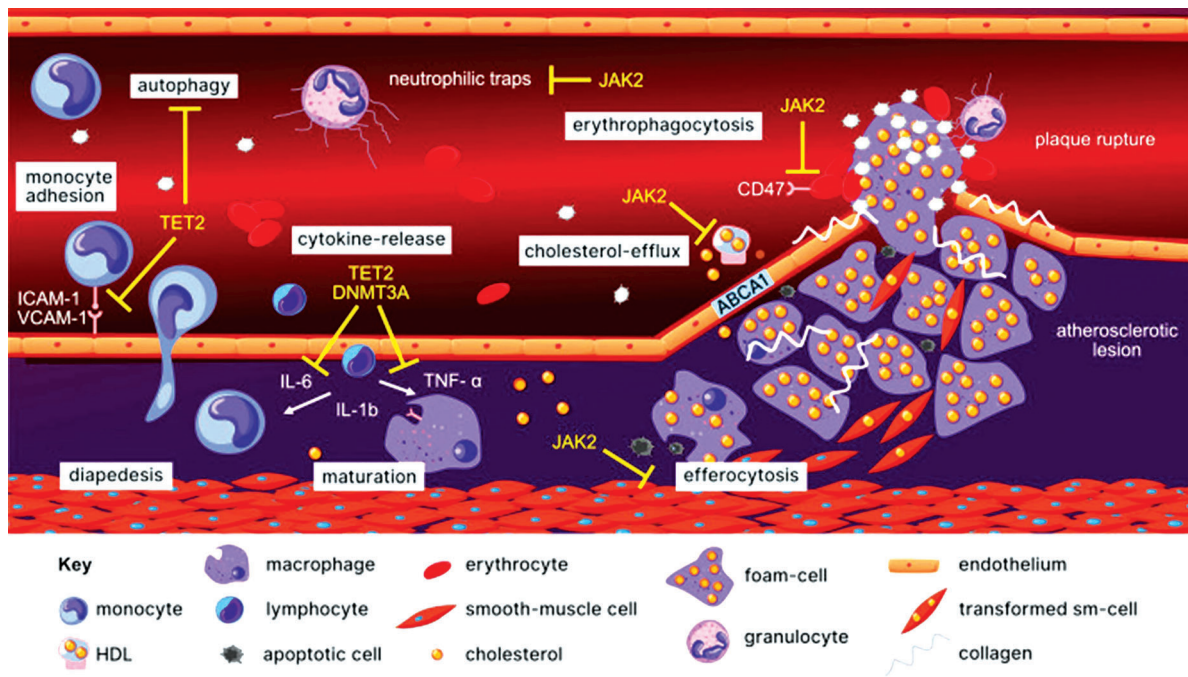


Fig. 4. CHIP, atherosclerosis, dyslipidaemia and inflammation [A. Stein, Basic Research in Cardiology, 2022]

3.1% of the general population and is most significantly associated with the risk of CVD and thrombosis [24]. Early studies of *JAK2* mutation in MPN focused on thromboembolic complications, a well-recognized clinical syndrome in PV and ET. *JAK2* mutation is a major thrombogenic risk factor with well-known phenotypic thrombogenic differences: a 2-fold increase in arterial thrombotic risk in ET and PV and a higher incidence of venous thrombosis in PMF. Interestingly, there was no significant correlation between thromboembolic events and *TET2*, *DNMT3A* or *ASXL1* mutations (rare in MPN but very common in CHIP). Moreover, in a study on 587 patients conducted by S. Cerquozzi et al., PV with *TET2* or *ASXL1* mutations was not associated with higher risk for arterial thrombosis [25]. According to Guglielmelli P et al, the *ASXL1* mutation in TE reduces the thrombotic risk [26]. The so-called neutrophil extracellular traps (NETs) are of pathogenetic importance for thrombotic complications in MPN [27]. They are the result of stimulated neutrophils, which push out extracellular strands of decondensed DNA in a complex with histones and other neutrophil proteins. In experimental models, O. Wallach et al. demonstrated that *JAK2*-positive HF is associated with an increased incidence of thrombosis, resulting from increased NET formation with a pro-thrombotic phenotype in mice. The authors found that overexpressed peptidyl-arginine deiminase 4 (PAD4) is essential for chromatin decondensation in NETs. PAD4 regulates both NET-osis and pathological thrombosis, and NET biomarkers reflect the activity of the underlying process [28]. In a recent study, Guy A investigated

NET-osis in two mouse populations in an experimental model – expressing *JAK2V617F* in all hematopoietic lineages (as in MNPs) and only in leukocytes. Ex vivo experiments show that *JAK2V617F*-mutated platelets trigger NET-osis by *JAK2V617F*-mutated neutrophils, i.e. *JAK2V617F* neutrophils alone are not a sufficient stimulus of thrombogenesis, and rather platelets cooperate with neutrophils to promote NET-osis in vivo [29].

Beyond the prothrombotic mechanism discussed above, *JAK2*-mediated CHIP has been implicated in atherogenesis, increased cardiac fibrosis, and pathological remodelling through activation of the *JAK*-*STAT* signalling cascade. Sano et al. performed competitive *JAK2* transgenic bone marrow transplantation in irradiated wild mice. They restricted *JAK2* expression to neutrophils, monocytes, and macrophages with *JAK2*-specific transduction by lentivirus. The model approximates CHIP with no changes in blood cell counts or other neoplastic features. After coronary artery ligation with induction of infarction or increased pre-load via aortic constriction, the authors demonstrated that *JAK2* expression in mice leads to enhanced inflammatory *STAT* signalling, increased levels of the inflammatory cytokines IL-1 β , IL-6, tumor necrosis factor-alpha (TNF- α), and CC chemokine ligand 2, larger infarct size, greater cardiac dysfunction, and de novo cardiac hypertrophy [30]. In the experimental model of Wang W *Ldlr*^{-/-} mice transplanted with *Jak2*-deficient bone marrow cells showed accelerated atherosclerosis and larger plaques with enlarged necrotic nuclei [30]. *Jak2*-mutated macrophages on the one hand have

an impaired ability to engulf dead cells (defective efferocytosis). On the other hand, they show increased erythrophagocytosis (stimulates local oxidative stress) and lipid efflux (prevents cholesterol leakage, so-called foam cells) [16, 31]. In contrast to TET2 and DNMT3A, where activation of the NLRP3 inflammasome is the predominant proatherogenic mechanism, recent data show that *ASXL1* and *JAK2* CHIP facilitate activation of the absent in melanoma 2 (AIM2) inflammasome [31].

The experimental data on the pathogenetic significance of CHIP for atherogenesis and CVD discussed above are schematically shown in Fig. 4.

CHIP and cardiovascular disease – clinical evidence

A review of literature, as well as convincing experimental evidence of a causal relationship, identifies CHIP as a potent pathogenetic and risk factor for atherogenesis and CVD.

Coronary artery disease. Myocardial infarction. Cardiogenic shock

In a recent German study of 1142 patients, J. Brett Heimlich and colleagues presented the first in literature trial assessing the correlation between CHIP and coronary artery disease (CAD) utilizing interventional coronary angiography. Correlation between CAD and CHIP was found in 18.4% of patients. A higher risk and more advanced left main disease hazard ratio (HR) 2.44 (95% Confidence Interval – CI, 1.40–4.27; $p = 0.0018$) and left anterior descending artery atherosclerosis HR 1.59 (1.12–2.24; $p = 0.0092$) was demonstrated in patients with CHIP, most commonly in TET2 mutation [32]. A significant association between CHIP and CAD HR 1.36 (95% CI 1.07–1.73) (from 23–49) was established in a study by M. C. Honigberg et al. conducted through whole genome sequencing in a cohort of 19,606 women with premature menopause [33]. The correlation between ST-segment elevation myocardial infarction (STEMI) and CHIP was analyzed in 2 Chinese studies by S. Wang et al., and Xiaoxiao Zhao et al. Targeted deep sequencing for DNMT3A and TET2 mutations (VAF $\geq 2\%$) was used. According to S. Wang, the incidence of CHIP was 12.4%. During the 3-year follow-up period CHIP patients had elevated IL-1 β ($p = 0.010$) and IL-6 ($p = 0.011$) plasma levels, higher mortality (30.9% vs. 15.5%, $p = 0.001$) and more major adverse cardiovascular events (MACE) (44.5% vs. 21.8%, $P < 0.001$) [34]. Xiaoxiao Zhao et al. reported equivalent results in patients with type II diabetes and myocardial infarction (MI) with ST-segment elevation. Overall, 10.6% of patients had CHIP. In this population mortality rate was higher – HR 2.03 (95%, CI 1.07–3.84, $p < 0.05$) and increased further in patients with CHIP with TET2 mutation HR 5.24 (95% CI 2.02–13.61, $p = 0.001$). The study also speculated that the devel-

opment of type 2 diabetes facilitates clonal haematopoiesis [35]. The risk of early MI in men < 40 years and women < 50 years is 4 times higher among individuals with CHIP, and so is the risk of abnormal aortic calcification. The risk depends on the mutagenic load and the type of somatic mutation. CHIP with JAK2 mutation increases the likelihood of MI 12 times compared to CHIP with TET2 and DNMT3A gene mutations [12, 14].

In the CULPRIT-SHOCK study by M. Böhme et al. CHIP with TET2 and DNMT3A mutations was found in 29% of the 446 patients with MI and cardiogenic shock. CHIP patients were older, had elevated N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) and inflammatory biomarkers, and had worse short-term outcomes and 30-day mortality (OR: 1.83; 95% CI: 1.05–3.21; $p = 0.03$) after adjustment for conventional risk factors [36]. In a Canadian study, Scolari FL et al analysed the association of CHIP, which was demonstrated in 22% of patients hospitalized with cardiogenic shock and with CHF, observed in outpatients in a 1:1 ratio. Patients with cardiogenic shock had a higher incidence of mutations (mainly TET2), higher levels of SC-D40L, INF- γ , IL-4 and TNF- α and significantly shorter survival at 30, 90 days and 3 years [37].

Heart failure and the left ventricle

K. C. Kiefer et al. presented the first study with deep-corrected targeted sequencing of 56 genes, with low VAF (0.5–2%) in 399 patients with chronic heart failure (CHF), followed for an average of 3.95 years. The authors found mutations in 87% of patients, most often in the genes *DNMT3A*, *TET2*, *CBL*, *CCAAT/enhancer-binding protein alpha – CEBPA*, *EZH2*, *GNB1*, *PHF6*, *structural maintenance of chromosomes 1A – SMC1A*, and *SRSF2*. The expanded risk mutation panel was associated with increased mortality compared to the average for the entire group. The authors minimized the influence of *DNMT3A* (165 patients) and *TET2* (107 patients) by excluding them from the analysis. However, surprisingly, the remaining 7 mutations with low VAF were also associated with increased mortality (HR: 3.1; 95%, CI 1.8–5.4; $p < 0.001$) [5]. D. A. Pascual-Figal presented the first evidence of accelerated clinical progression of HF in the absence of CAD in patients with CHIP [38]. Using deep sequencing with VAF $\geq 2\%$ for 54 genes in 62 patients with HF and left ventricular ejection fraction (LVEF) $< 45\%$ (age 74 ± 7 years, 74% men, 52% non-ischemic and LVEF $30 \pm 8\%$, follow-up 3.5 years) the authors found the following: CHIP was established in 38.7% of patients; *DNMT3A* and *TET2* mutations were associated with HF progression and higher mortality (HR: 2.79; 95% CI: 1.31 to 5.92; $p = 0.008$), more hospitalizations due to HF (HR: 3.84; 95% CI: 1.84 to 8.04; $p < 0.001$) and the composite of HF-related death or hospitalisation due to HF (HR: 4.41; 95% CI: 2.15 to 9.03; $p < 0.001$).

Arrhythmias

A series of studies in recent years have established CHIP's significant proarrhythmic effect. In a population-based study, A. Schuermans et al. analysed the correlation between the prevalence of CHIP with different mutagenic loads, subtypes of driver mutations and various incidental rhythm disorders such as supraventricular arrhythmias, bradyarrhythmias and ventricular arrhythmias (primary endpoint), cardiac arrest, atrial fibrillation and any arrhythmia (secondary endpoint) and myocardial interstitial fibrosis in 410,702 individuals [39]. In CHIP with VAF $\geq 2\%$ and with VAF $\geq 10\%$, the adjusted hazard ratio for supraventricular arrhythmias was 1.11 (CI 1.04-1.18; $p = 0.001$) and 1.13 (CI 1.05-1.22; $p = 0.001$), respectively, for bradyarrhythmias – 1.09 (CI 1.01-1.19; $p = 0.031$) and 1.13 (CI 1.03-1.25; $p = 0.011$), for ventricular arrhythmias – 1.16 (CI, 1.00-1.34; $p = 0.049$) and 1.22 (CI 1.03-1.45; $p = 0.021$). CHIP with VAF $\geq 10\%$ was associated with a risk of myocardial fibrosis with an odds ratio of 1.31 (CI 1.07–1.59; $P = 0.009$). The correlations were

independent of CAD and HF, they were strongest in sinus arrest and were also proven in other non-driver gene mutations. According to the authors, CHIP is an independent risk factor for the occurrence of rhythm disorders. Ahn HJ et al studied the influence of CHIP on the progression of atrial fibrillation (AF) in an East Asian cohort [40]. They included 1004 patients and 3341 healthy controls with a CHIP prevalence of 23.6% in patients with AF versus 10.7% in the control group. Overall, in CHIP, the adjusted odds ratio for AF was 1.4, more common in long-standing AF odds ratio (OR) 1.50 (CI 95% 1.14-1.99, $p = 0.004$), followed by persistent – OR 1.44, and paroxysmal atrial fibrillation – OR 1.33. Additional analysis showed that patients with AF and CHIP were older, more often diabetic, with longer duration of arrhythmia, higher E/E' and more dilated left atrium compared with those without CHIP ($p < 0.05$). Postoperative AF is a common complication in cardiac surgery. Ninni S and col. evaluated the prevalence and role of CHIP (576 genes with the HemePACT panel) in 104 patients with aortic stenosis undergoing aortic

Table 1. Clinical Studies on CHIP and Cardiovascular Disease

Study	Population	Key Findings	Main CHIP Mutations
Heimlich JB et al. 2024	1142 CAD patients (coronary angiography)	CHIP in 18.4%; higher risk of left main CAD (HR 2.44) and LAD disease (HR 1.59)	<i>TET2</i>
Honigberg MC et al. 2021	19,606 women with premature menopause	CHIP associated with CAD (HR 1.36, CI 1.07–1.73)	Multiple mutations
Wang S et al. 2022	STEMI patients (n not specified)	CHIP prevalence 12.4%; higher IL-1 β , IL-6, mortality (30.9% vs 15.5%) and MACE (44.5% vs 21.8%)	<i>DNMT3A</i> , <i>TET2</i>
Zhao X et al. 2025	STEMI with type 2 diabetes (n not specified)	CHIP 10.6%; higher mortality HR 2.03, <i>TET2</i> mutation HR 5.24	<i>DNMT3A</i> , <i>TET2</i>
Böhme M et al. 2022 (CULPRIT-SHOCK)	446 MI + cardiogenic shock	CHIP prevalence 29%; higher NT-proBNP, biomarkers, 30-day mortality OR 1.83	<i>TET2</i> , <i>DNMT3A</i>
Scolari FL et al. 2022	Cardiogenic shock and CHF	CHIP 22%; higher inflammatory markers, shorter survival at 30 d, 90d, 3y	Mostly <i>TET2</i>
Kiefer KC et al. 2021	399 CHF patients	CHIP in 87% (low VAF $\geq 0.5\%$); increased mortality HR 3.1	<i>DNMT3A</i> , <i>TET2</i> , others
Pascual-Figal DA et al. 2021	62 HF patients (LVEF <45%)	CHIP in 38.7%; associated with progression and mortality HR 2.79, hospitalization HR 3.84	<i>DNMT3A</i> , <i>TET2</i>
Dorsheimer L et al. 2019	Chronic ischemic HF	CHIP worsens prognosis; mortality 37% vs 24%, HR 2.1	<i>TET2</i> , <i>DNMT3A</i>
Schuermans A et al. 2023	410,702 population-based	CHIP associated with arrhythmias: supraventricular HR 1.11–1.13, ventricular HR 1.16–1.22	Multiple mutations
Ahn HJ et al. 2024	1004 AF patients vs 3341 controls	CHIP prevalence 23.6% vs 10.7%; OR 1.4 for AF, strongest in long-standing AF	Multiple mutations
Ninni S et al. 2023	104 AS patients (AVR surgery)	CHIP 29% (VAF $\geq 2\%$), 60% (VAF $\geq 1\%$); risk of postoperative AF OR 3.5	Multiple mutations
Saadatagah S et al. 2024	UK Biobank + ARIC ($\approx 200,000$ participants)	CHIP associated with AF; HR up to 1.45 depending on mutation subtype	<i>TET2</i> , <i>ASXL1</i>
Lin AE et al. 2024	Mouse model	<i>TET2</i> knockout linked with AF via Ca ⁺⁺ handling defects, NLRP3 inflammasome activation	<i>TET2</i>
Raddatz MA et al. 2021	6866 patients	CHIP 3.5% overall; associated with increased risk of severe aortic stenosis	<i>DNMT3A</i>
Mas-Peiro S et al. 2020	279 TAVI patients	CHIP (<i>DNMT3A</i> , <i>TET2</i>) in >30%; higher mid-term mortality HR 4.81	<i>DNMT3A</i> , <i>TET2</i>
Mas-Peiro S et al. 2023	453 TAVR patients	CHIP in >30%; higher long-term mortality HR 1.429	<i>DNMT3A</i> , <i>TET2</i>
Tan Y et al. 2025	425,211 UK Biobank participants	CHIP increases AAA risk HR 1.21; higher in VAF $\geq 10\%$ HR 1.35, <i>ASXL1</i> HR 2.10	<i>ASXL1</i>
Soudet S et al. 2021	61 unprovoked PE patients	CHIP in 20%, mainly <i>DNMT3A</i> ; no effect on mortality at 2y with anticoagulation	<i>DNMT3A</i>

valve replacement surgery, and postoperative AF. In this relatively small group of patients, there was surprisingly an almost twofold difference in the prevalence of CHIP depending on VAF: in VAF \geq 2% CHIP was 29%, while in VAF \geq 1% CHIP was 60%. In patients with CHIP, the risk of postoperative AF was 3.5 times higher (OR: 3.5; 95%CI: 1.52-8.03; $p = 0.003$), along with higher levels of activated CD64⁺, CD14⁺, CD16⁻ circulating monocytes and macrophages in the myocardium [41]. There was also one interesting population-based, prospective study of 199,982 adults (4131 participants in the Atherosclerosis Risk in Communities (ARIC) study and 195,851 from the UK Biobank cohort) by Saadatagah et al. Its objective was to assess the relationships between CHIP, mutation subtypes, inflammatory markers (high-sensitivity C-reactive protein – CRP; IL-6; IL-18), cardiac biomarkers (hs-TnT and hs-TnI, NT-proBNP, echocardiographic indices), structural changes, and incidental AF [42]. In the ARIC group (mean age 76 years, follow-up 7.0 years) CHIP had a frequency of 24.7%, of which 11.6% had a VAF \geq 10%. In the UKB cohort (mean age 56 years, follow-up 12.2 years) CHIP was 8.4%, of which 2.6% had a large VAF \geq 10% [42]. The hazard ratios for AF were 1.12 (95% CI, 1.01-1.25; $p = 0.04$) with variations up to 1.45 depending on the mutagenic load and the individual somatic mutation subtypes [42]. The large TET2 CHIP had higher levels of IL-6, the large ASXL1 had higher levels of hs-TnT, increased left ventricular mass index, and both subtypes had an increased risk of AF [42]. In an attempt to find a causal relationship between CHIP and rhythm disorders, Lin AE et al. studied calcium homeostasis with electrophysiological abnormalities as a potential proarrhythmic mechanism in cardiomyocytes in an experimental mouse model with *TET2* knockout. Cardiomyocytes isolated from *Ldlr*^{-/-} *Tet2* knockout mice were found to have impaired calcium release from the sarcoplasmic reticulum into the cytosol, increased expression of the *NLRP3* inflammasome, and activation of Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII). According to the authors, these are likely contributing mechanisms for the occurrence of arrhythmia in CHIP [43].

Aortic stenosis, TAVI, transcatheter aortic valve replacement, aortic aneurysm

It is known that both CHIP and atherosclerotic aortic stenosis (AS) progress with age. In a general population study of 6866 patients above 40, M. A. Raddatz et al. found CHIP in 3.5% of participants, and incidental severe aortic stenosis – AS (Vmax and aortic valve area – AVA), was observed in 2.7% and 8.8% of them, respectively. CHIP (particularly with DNMT3A mutation) significantly increases the risk of incidental AS [44]. Mas-Peiro et al. were the first in literature to find a significant correlation between CHIP and medium-term (up to 8 months) and long-term outcomes

(up to 4 years) in patients with degenerative atherosclerotic AS undergoing interventional implantations. The initial report analyzed 279 AS patients undergoing TAVI and later 453 patients undergoing transcatheter aortic valve replacement (TAVR), excluding all patients with intraoperative or early postoperative death. The results were similar – *DNMT3A*- or *TET2*-CHIP-driver mutations with VAF \geq 2% were found in over 30% of patients, with an age-dependent increase from 25% (55-69 years) to 52.9% (90-100 years) and more common in women. CHIP patients showed increased medium-term (HR 4.81, 95% CI 1.49–15.57; $p = 0.009$) and long-term mortality (HR 1.429, 95%CI 1.014-2.013, $p = 0.041$) after successful intervention, more pronounced in non-smokers and older patients. *DNMT3A* mutation was associated with an increased ratio of pro-inflammatory T-helper 17 (Th17) cells to anti-inflammatory regulatory T-cells, and *TET2* seemed to associate with increased levels of pro-inflammatory monocytes characteristic of chronic inflammatory diseases, as well as more frequent concomitant coronary and peripheral vascular disease [45, 46].

It is commonly believed that inflammation is a major feature of aortic aneurysms (AA). A number of studies have demonstrated the presence of numerous inflammatory cells, T-lymphocytes, macrophages, dendritic cells, neutrophils, B-cells, and mast cells, etc. in the walls of AA. AA are characterised by activation of inflammasomes and increased secretion of cytokines – the same cellular components induced by mutations in the driver genes in CHIP [47]. In this sense, the results of a population study on the correlation between CHIP (VAF \geq 2%) and genetic predisposition to abdominal aortic aneurysm (AAA) by Tan Y. et al. conducted on 425,211 individuals from the British Biobank [48] are not surprising. CHIP was associated with an increased risk of incidental AAA (HR 1.21, CI 95%, 1.01-1.44; $p = 0.034$), which was significantly higher in CHIP VAF \geq 10% (HR 1.35; CI 95%, 1.10-1.66; $p = 0.0045$) and more pronounced in ASXL1 mutation (HR, 2.10 CI 95%, 1.54-2.88; $P < 0.001$). On the other hand, the presence of 2 alleles IL6R p.Asp358Ala (genetic replacement of IL-6) reduced the risk of AAA in large CHIP clones (HR 0.48 CI, 95% 0.23-0.99; $P = 0.046$) [48]. Individuals without CHIP and those with a weak genetic predisposition had an insignificant risk of AAA (HR 2.15 95% CI, 1.63-2.85; $p < 0.001$) [48]. These results support the idea that a deficiency in IL-6 signaling may serve as a therapeutic target for the prevention and treatment of AAA.

Pulmonary embolism

Unprovoked pulmonary embolism (UPE) is not associated with conventional risk factors, including thrombophilia, and accounts for about 50% of reported PE cases. In a small study of 61 patients with UPE,

Soudet et al. reported CHIP in 20% of cases (VAF of 1%), mostly with *DNMT3A* mutations [49]. No difference was found in terms of age, location of the PE, presence of deep vein thrombosis (DVT), and risk stratification between CHIP carriers and non-carriers. Over a 2-year period, all patients were alive, on continuous anticoagulant treatment, and free of lesions or pulmonary hypertension. Despite the small cohort and the limited number of sequenced gene mutations, the study shows CHIP as a new risk factor for UPE.

Prognostic significance of CHIP in patients with heart failure

In the first study on the long-term prognostic significance of CHIP in CVD Dorsheimer et al. presented new data: 24% of patients without CHIP and 37% with CHIP died at a mean follow-up of 4.4. years, and 23 patients required hospitalization due to acute HF [50]. TET2 or DNMT3A somatic mutations significantly increased the risk for death + hospitalizations (HR, 2.1; 95% CI, 1.1-4.0; $p = 0.02$), death + HF + age (HR, 1.04; 95% CI, 1.01-1.07 per year; $p = 0.005$) [50]. The increased mortality was mainly due to progression of HF, rhythm, and conduction disorders, but not to the occurrence of acute coronary syndrome. These consequences of CHIP are independent of classical prognostic factors including the highly informative serum NT-proBNP levels [50].

CONCLUSIONS

The present literature review shows that CHIP is detected in almost all age groups, its incidence increases with age and is associated with higher mortality, mainly due to cardiovascular diseases. Experimental and clinical studies present CHIP as a new causal risk factor for atherogenesis, its clinical manifestation, evolution and prognosis. Clonal hematopoiesis with the most frequent mutations in preleukemic genes TET2, DNMT3A and JAK2 proliferates in a phenotypically altered monocyte/macrophage pool with increased atherogenic activity. Mutated monocytes activate inflammasomes, increase transcription and secretion of chemokine gene cluster (Cxcl1, Cxcl2, Cxcl3, Pf4) and of the main proinflammatory cytokines - IL1b and IL6. This results in a self-sustained vicious cycle of pro-inflammatory conventional risk factors and clonal expansion of dysfunctional monocytes in the vascular endothelium. CHIP studies are still in their initial stages and although the detailed pathogenetic mechanisms are yet unclear, they are becoming an interesting therapeutic target and a novel approach for the treatment of atherosclerosis.

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