A Vicious Circle of Clonal Haematopoiesis of Indeterminate Potential and Cardiovascular Disease

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Abstract

Clonal haematopoiesis of indeterminate potential (CHIP) represents a recently identified overlap between cancer and cardiovascular disease (CVD). CHIP develops as a result of certain acquired somatic mutations that predispose to leukaemia, but clinically even more prevalent, associate with increased risk for CVD and CVD-related death. Experimental studies suggest a causal role for CHIP aggravating inflammatory processes in CVD, and recent epidemiologic and genetic studies indicate that classical CVD risk factors may increase the risk of acquiring CHIP driver mutations, thus fuelling a vicious circle. The potential mechanism underlying the associative link between CHIP and CVD and mortality has been the focus of a few recent excellent experimental and observational studies which are summarized and discussed in this concise non-systematic review article. These data support a pathomechanistic view of a spiralling vicious circle in which CHIP aggravates the inflammatory immune response in CVD, and CVD-driven elevated haematopoietic activity promotes CHIP development.

Keywords
- clonal haematopoiesis
- cardiovascular disease
- somatic mutation

Zusammenfassung

Klonale Hämatopoese von unbestimmtem Potential (CHIP) stellt eine Überschneidung von Krebs- und kardiovaskulären Erkrankungen dar, die erst seit Kurzem Beachtung findet. CHIP entsteht infolge bestimmter erworbener somatischer Mutationen und prädisponiert für die Entwicklung von Leukämien. Aber klinisch häufiger ist die Assoziation mit einem erhöhten Risiko für kardiovaskuläre Erkrankungen und Tod. Experimentelle Studien weisen auf eine kausale Beziehung zwischen CHIP und einem verstärkten Entzündungsprozess bei kardiovaskulären Erkrankungen hin. Epidemiologische und genetische Studien suggerieren umgekehrt, dass die klassischen kardiovaskulären Risikofaktoren das Risiko für die Entwicklung somatischer CHIP-assoziierter Mutationen erhöhen und somit einen Teufelskreis antreiben könnten.

Schlüsselwörter
- klonale Hämatopoese
- kardiovaskuläre Erkrankung
- somatische Mutation

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Introduction

Clonal haematopoiesis of indeterminate potential (CHIP) is defined by the presence of an expanded blood cell clone carrying a somatic mutation [variant allele frequency (VAF) $\geq 2\%$] that is associated with a higher risk of developing haematological malignancies in the absence of any other haematological abnormalities at the time of diagnosis.[1,2] These mutations are acquired and provide a proliferation advantage to haematopoietic stem cells (HSCs), leading to the appearance of cell clones, predominantly affecting monocytes, neutrophils and natural killer cells.[3] CHIP driver mutations become more prevalent with age affecting more than 10% of individuals older than 70 years in the general population.[4] The most commonly mutated genes are those coding for the epigenetic regulators DNA-methyltransferase 3A (DNMT3A), Tet methylcytosine dioxygenase 2 (TET2) and additional sex combs-like 1, although most individuals differ in the nucleotides that are mutated within the respective genes. Even though such gene mutations function as leukaemia-driver genes, CHIP represents a neoplasia precursor state, that, despite a 10-fold increase of risk of developing cancer, only develops at a rate of 0.5 to 1.0% per year into overt haematologic neoplasia, hence the term 'indeterminate potential'.[5] Still, morbidity and mortality already increase in its precursor state by 40%, mostly driven by cardiovascular disease (CVD). Carriers of CHIP driver mutations have a 1.9-fold greater risk of incident coronary heart disease and a four-fold elevated risk for early-onset myocardial infarction, which increases with higher clonal burden (particularly VAF $\geq 10\%$).[6] One-third of an elderly patient cohort undergoing transcatheter aortic valve implantation carried DNMT3A and TET2 CHIP driver mutations, and mortality was increased almost five-fold in carriers compared with non-carriers within the first year post-procedure after adjusting for confounders.[7]

A study focusing on patients with heart failure reported a rise in mortality from 24% in non-carriers to 37% in carriers of CHIP driver mutations within less than 5 years, most of which affected DNMT3A and TET2.[8] When comparing event-free Kaplan–Meier survival curves for different VAFs, clone size correlates with adverse clinical outcome even with VAFs below the 2% threshold.[8,9]

While these clinical data describe an associative link between carrying a CHIP driver mutation and encountering CVD complications, current research efforts are aiming at deciphering whether this relationship is causal. Two possibilities, or combinations thereof, are being discussed: first, CHIP causing CVD, and second, CVD and associated risk factors stimulating CHIP development.

Evidence for CHIP Increasing Risk for CVD Development

Mechanisms underlying the link between CHIP driver mutations and CVD are incompletely understood. The clonal pattern of mutation carrying myeloid cells was modelled in mice. Jaiswal et al showed that TET2-deficient mice developed larger atherosclerotic lesions than heterozygotes and $TET2^{+/+}$ control mice expressing more interleukin (IL)-1β, IL-6, platelet factor 4 and chemokine ligands such as CXCL1 and 3. Increased atherosclerosis susceptibility in $TET2^{-/-}$ mice is considered a consequence of elevated chemokine and cytokine levels, monocyte recruitment, vascular smooth muscle proliferation, plaque destabilization and HSC proliferation.[6,10]

When reconstituting irradiated low-density lipoprotein receptor (LDLR)-deficient mice with a mixture of 10% $TET2^{-/-}$ and 90% $TET2^{+/+}$ bone marrow cells, $TET2^{-/-}$ clones expanded leading to increasing atherosclerotic plaque size and inflammasome-mediated IL-1β release by $TET2^{-/-}$ macrophages. The proatherogenic effect was abrogated by treating chimeric mice with the inflammasome inhibitor MCC950.[5,11]

Unlike $TET2^{-/-}$, bone marrow reconstitution with DNMT3A-deficient cells or those carrying inactivating mutations did not result in pronounced clonal expansion in mice. Still cardiac hypertrophy and renal fibrosis were pronounced in angiotensin-challenged chimeric mice carrying DNMT3A mutations, and atherosclerosis accelerated in mixed bone marrow chimeras. Mechanistically, loss of DNMT3A upregulated expression levels of chemokines and IL-1β and IL-6 in macrophages.[12,13] Single-cell RNA sequencing of aortic leukocytes isolated from atherosclerotic $LDLR^{-/-}$ mice reconstituted with either 10% $TET2^{-/-}$ or 10% $DNMT3A^{-/-}$ bone marrow cells documented in situ myeloid cell expansion and emergence of a distinct proinflammatory lesional macrophage population among mutant cells.[13]

Janus kinase 2 (JAK2), a protein tyrosine kinase involved in signalling cascades controlling cell growth and differentiation, is another prominent representative of CHIP driver mutations. The JAK2V617F point mutation increases the risk for myeloproliferative neoplasms. Mice carrying the JAK2V617F mutation showed increased proliferation of macrophages in atherosclerotic lesions, reversible through inflammasome inhibition.[14] In addition, JAK2V617F is associated with an increased risk for thromboembolic events even in individuals without prior haematological malignancy. Thrombus formation is likely enhanced via β1/β2 integrin activation and neutrophil extracellular trap (NET) formation, as shown in mice, and NET formation was inhibited by JAK2 inhibition with Ruxolitinib.[15–19]

A recent single-cell RNA sequencing analysis of peripheral blood monocytes from patients with heart failure or aortic valve stenosis compared those carrying CHIP driver mutations in DNMT3A or TET2 with age-matched controls ($n = 3$–4 per group). Inflammatory genes such as IL-1 β, CCL3, IL-6 receptor and scavenger receptor CD163 were relatively overexpressed in monocytes of patients carrying CHIP mutations.[20] In addition, monocytes of DNMT3A-mutation carriers with heart failure expressed elevated levels of T-cell-stimulating immunoglobulins, and indicators for T-cell-receptor repertoire skewing and T-cell-subset activation were identified.[21] These human data align with the experimental findings in mice, and argue in favour of CHIP-aggravating CVD.

Evidence for CVD Increasing Risk for CHIP Development

Atherosclerosis, in general, represents a state of elevated inflammatory and haematopoietic activity, as demonstrated both in animal models and humans.[22] Somatic CHIP driver mutations occur spontaneously and by chance, and with higher probability in rapidly proliferating cells. As atherosclerosis accelerates HSC division, somatic mutations occur more frequently. If these mutations confer a proliferative advantage, as in the case of CHIP driver mutations, mutant clones can expand even faster within the context of a generally heightened proliferation level. Thereby, by the age of 70, atherosclerosis has produced a 3.5-fold increased risk of developing clonal haematopoiesis.[22] Even though CHIP is defined by a VAF $\geq$2% in blood cells, the clone size is linked to clinical outcome even below this arbitrary threshold.[8] The speed of growth of clones is a function of both its competitive advantage and the general proliferation rate.[22] In atherosclerotic patients, a 2.4-fold increase in stem progenitor cell proliferation was described. Other conditions associated with leukocytosis, and as such conferring an increased theoretical risk of developing CHIP, are classical cardiovascular risk factors such as smoking and type 2 diabetes, but also addiction and psychiatric disease, human immunodeficiency virus infection and chronic heart failure.[22] The underlying mechanisms driving haematopoiesis in humans are still incompletely understood. Systemically increased cytokine levels and altered lipid levels have been proposed to stimulate haematopoietic activity and mutagenesis. Notably, retrospective studies of the United Kingdom Biobank and the Women's Health Initiative identified an unhealthy diet and obesity to be associated with CHIP prevalence.[23,24] In mice, adenosine triphosphate-binding cassette deficiency in HSCs impairs cholesterol efflux and increases their sensitivity to IL-3 and granulocyte-macrophage colony-stimulating factor, resulting in leucocytosis, myeloproliferative disorder and accelerated atherosclerosis.[22,25,26]

According to this new model, atherosclerosis and common cardiovascular risk factors are reversely linked to CHIP prevalence by facilitating mutagenesis and exponential expansion of mutant clones on the background of an overall accelerated stem cell proliferation rate.

Conclusion and Future Directions

CHIP represents a recently identified overlap between cancer and CVD. Myeloid cells carrying a CHIP driver mutation boost an increased inflammatory reaction, accelerating CVD. Atherosclerosis and its risk factors, such as smoking, diabetes, obesity, and dyslipidaemia, stimulate cell proliferation and in turn increase the likelihood of developing a CHIP driver mutation, in consequence entering a vicious circle (►Fig. 1).

This novel pathomechanistic concept can help identify patients at increased cardiovascular risk, which may benefit from aggressive treatment of cardiovascular risk factors and anti-inflammatory therapy, although specific targets remain to be validated in humans.

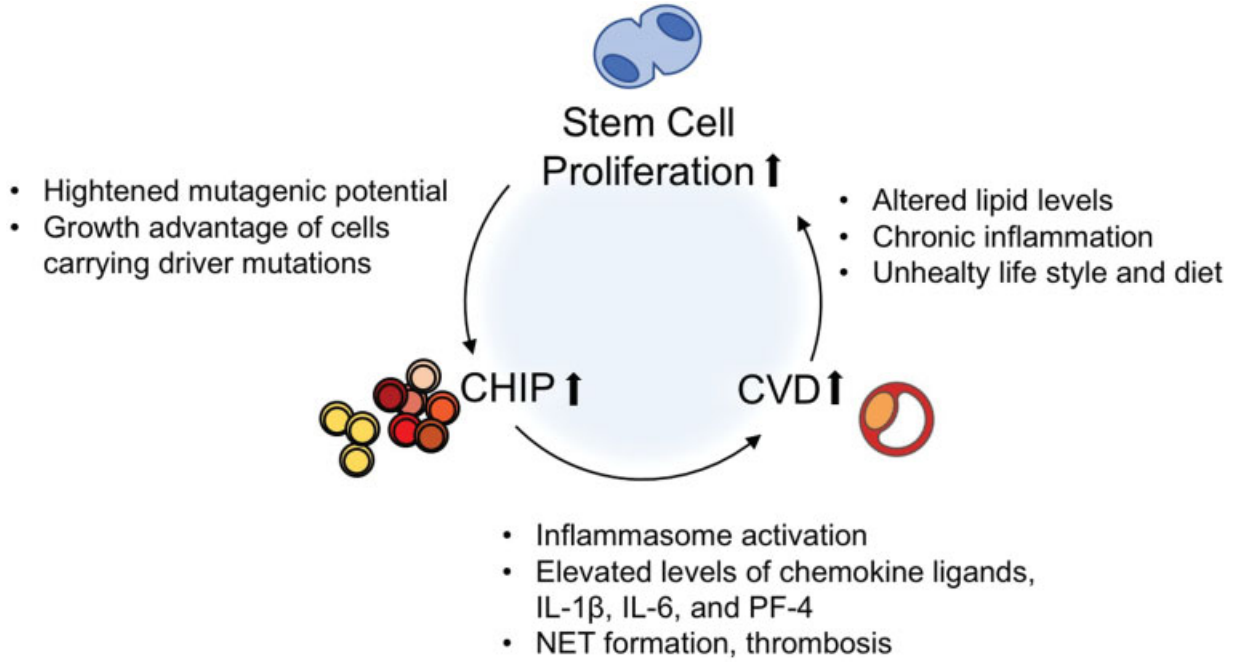

Fig. 1 Vicious circle of cardiovascular disease (CVD) and clonal haematopoiesis of indeterminate potential (CHIP). Somatic mutations in haematopoietic stem cells lead to a proliferative advantage, giving rise to clonal haematopoiesis (CH). CH is associated with inflammasome activation, NET formation and unfavourable plaque remodelling, all of which increase cardiovascular risk. Atherosclerosis and classical CV risk factors, such as smoking, obesity, hyperlipidaemia, and type 2 diabetes, in turn stimulate inflammation and haematopoietic turnover. Accelerated haematopoiesis increases the chance of developing somatic mutations and introduces a selection bias for those mutations that favour clonal expansion. CHIP thereby enters a vicious circle of self-reinforcement with CVD. CV, cardiovascular; NET, neutrophil extracellular trap.

Conflict of Interest

The authors declare that they have no conflict of interest.

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