Review Article

Pathogenic and Clinical Implications of the 2-Way Interplay Between Clonal Hematopoiesis of Indeterminate Potential and Multiple Myeloma

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Abstract

Clonal hematopoiesis of indeterminate potential (CHIP) is a common age-related phenomenon. CHIP is prevalent in multiple myeloma (MM) patients, and several lines of investigations suggest it might be relevant for MM pathogenesis and clinical course. Phylogenetic studies indicate that CHIP and MM do not share a clonal origin. CHIP does not consistently affect survival in MM. However, CHIP has been associated with increased treatment-related toxicities. Recent single-cell RNA sequencing data suggest that CHIP is associated with a more inflammatory and immunosuppressive tumor microenvironment (TME), characterized by dysfunctional myeloid and T cells. Furthermore, growing evidence highlights how anti-MM therapies such as alkylators and immunomodulatory drugs can favor the expansion of pre-existing mutant clones. Collectively, these data suggest a bidirectional interplay in which CHIP, acting as a modifier of the TME, may amplify inflammation driven by MM plasma cells and therapy, ultimately affecting MM progression and therapeutic response, while treatment pressure may reshape CHIP clonal architecture. Understanding CHIP dynamics in the context of MM treatment is therefore crucial to optimize therapeutic strategies, anticipate toxicities, and guide tailored approaches. This review summarizes current evidence supporting a translational and clinical impact of CHIP in MM.

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Introduction

Cancer evolution is driven by the stochastic acquisition of genetic alterations, followed by the selective expansion of clones with increased fitness. Much like Darwinian evolution in species, tumor development reflects an ongoing process of variation and selection, shaped not only by cell-intrinsic lesions but also by pressures imposed by the tumor microenvironment (TME).[1-3] These principles are particularly relevant to the emerging relationship between clonal hematopoiesis of indeterminate potential (CHIP) and multiple myeloma (MM), 2 age-associated clonal phenomena that may intersect biologically and clinically. CHIP refers to the age-associated clonal expansion of hematopoietic stem cells (HSC) supported by somatic mutations in genes recurrently mutated in myeloid malignancies, in the absence of overt hematologic disease.[4-7] CHIP is only part of a larger phenomenon of clonal selection of HSCs which is almost universal with age, often driven by unknown drivers, and collectively called age-related clonal hematopoiesis.[8-10] CHIP can be fostered by aging and inflammation[11,12] and a pro-inflammatory bone marrow (BM) microenvironment can lead to expansion of mutant clones.[13] In turn, CHIP itself can cause inflammation in a feed-forward loop that enhances the selection process and may result in clinically relevant conditions.[14] Although most individuals with CHIP do not develop overt hematologic malignancies, these small clones can have deleterious consequences for human health, as for example life expectancy of individuals with CHIP is reduced owing to increased inflammation and frequency of cardiovascular events.[15,16]

Multiple myeloma is a plasma cell (PC) neoplasm arising through a multi-step process that has caused or is at risk of causing end-organ damage, and requires treatment to prolong the patient's life.[17] Even if not always clinically recognized, MM develops through a premalignant phase called monoclonal gammopathy of undetermined significance (MGUS),[18] and often through an asymptomatic overtly neoplastic phase called smoldering MM (SMM).[19] MM evolution is dependent on intrinsic genetic features, but also strongly influenced by interactions with a disruptive and pro-inflammatory BM

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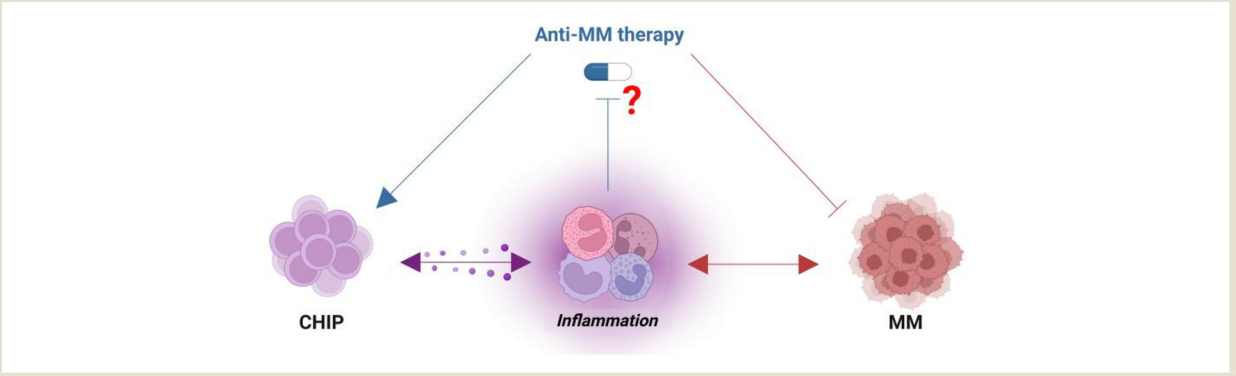
Figure 1 Two-way interplay between CHIP and MM: CHIP may amplify inflammation driven by MM PCs and anti-MM therapy, which in turn can affect CHIP clonal dynamics.



tumor microenvironment and immune system.[20] Recent studies revealed that CHIP is relatively common in individuals with PC dyscrasias. The co-occurrence of MM and CHIP within the BM of the same individual might affect both these clonal conditions, generating a "co-inflammatory state" and reciprocally influencing each other's dynamics (Figure 1). In particular, it could be postulated that clonal PCs may arise from a pre-existing clonal HSC or B-cell. The presence of CHIP could be a pro-inflammatory modifier of the TME that could foster the progression from MGUS or SMM to MM. Conversely, CHIP dynamics could be influenced by inflammation promoted by a PC clone or by anti-MM treatment. Furthermore, CHIP may contribute to treatment-related complications, including therapy-related myeloid neoplasms (t-MNs), and could influence outcomes of treatment with T-cell redirecting agents such as bi-specific antibodies or chimeric antigen receptor (CAR)-T cells.

In this review, we will summarize current evidence on the field of CHIP in the context of MM, addressing its translational impact and open questions that have the potential to improve prediction and precision medicine in asymptomatic and symptomatic MM.

CHIP in the General Population

Prevalence, Genes, and Clinical Consequences of CHIP

CHIP is formally defined by the World Health Organization and International Consensus Classification as the presence of at least one acquired mutation in genes associated with myeloid blood cancers at a variant allele frequency (VAF) of ≥ 2% and in the absence of a known hematologic disorder or unexplained cytopenia.[21,22] Seminal papers have described CHIP at heterogeneous but universally increasing prevalence with increasing age, ranging from < 1% in people younger than 50 to 60 years old to 18% to 19% in people aged more than 90 years.[4-7] Furthermore, as sequencing technologies improve, CHIP is being identified at increasingly higher prevalences across all age groups. Indeed, the estimated prevalence of CHIP is variable based on its detection method, making it impossible to compare results from different reports: even if the same gene panel is used, gene coverage, mutation detection algorithms and variant calling criteria crucially affect sensitivity and specificity of each sequencing effort. Smaller hematopoietic clones at VAF < 2% can be identified using more sensitive, error-corrected sequencing in nearly all individuals by the age of 50; however, the clinical implications of these low-level clones remain uncertain.[23,24]

The causal origins of CHIP are elusive in most individuals. CHIP is thought to arise from the interplay of drivers such as aging-related hematopoietic drift, chronic or recurrent inflammatory stress, inherited genetic susceptibility (eg including variants at the TERT locus), and environmental or iatrogenic exposures, including smoking, obesity, chemotherapy, and radiation therapy.[25] In unselected individuals, CHIP mutations involve most frequently the *DNMT3A, TET2,* and *ASXL1* genes (often referred to as "DTA mutations"). However, targeted re-sequencing of leukemia-associated mutation hot-spots in DNA from more than 4000 individuals showed that different mutations drive clonal hemopoiesis with a distinct age distribution, biological behavior and in response to different selective pressures.[7] In particular, variants in *TET2* and *DNMT3A* genes become more common with age, although being found also in young individuals, consistently with the increasing cumulative likelihood of their stochastic acquisition during time. Specifically, *DNMT3A*-mutant clones preferentially expand early in life and show slower growth in older age, while *TET2*-mutant clones display a more uniform growing behavior throughout life.[26] Interestingly, *ASXL1* mutations are associated with smoking.[27,28] Conversely, spliceosome gene (ie, *U2AF1, SRSF2, SF3B1, ZRSF2*) mutations are found almost exclusively in individuals aged 70 years or older, since they drive clonal outgrowth mostly in the context of an aging hematopoietic milieu. Indeed, clonal expansion is the result of selection that can be intrinsic and/or extrinsic to the mutant HSC, and often be mutation-specific. In this regard, splicing gene mutations may confer growth advantage by protecting ageing HSCs from telomere attrition[29] while *TET2* mutations may provide HSCs with a competitive advantage in an inflammatory microenvironment.[30] Above all, a clear role for cytotoxic agents has been demonstrated in the selection of clones harboring mutations in the DNA-damage response (DDR) genes *TP53* and *PPM1D*.[31-33]

Several lines of evidence link CHIP with a reduced life expectancy. Interestingly, this is not only related to the expected excess incidence of myeloid neoplasms but spans a wide range of causes of mortality. Based on a recent meta-analysis of 88 studies published from 2014 onwards, CHIP conferred a 4-fold increased risk of developing a hematological malignancy. Furthermore, CHIP was associated with a 1.34-fold increased risk of all-cause mortality as compared to the general population, including cancer mortality, composite cardiovascular events, coronary heart disease, stroke, heart failure, hematologic malignancy, lung cancer, renal impairment and severe COVID-19.[34] Subgroup analyses performed in an attempt to reduce heterogeneity indicated that larger clone sizes and non-*DNMT3A* mutations proved to be among the most important predictors of the risk of developing a myeloid cancer in people with CHIP. Indeed, compared with more frequent canonical drivers, clonal hematopoiesis (CH) driven by mutations in spliceosome genes carries a much higher risk of progression to myeloproliferative neoplasms.[35] As for *TP53*-CHIP, it was found to contribute to a wide range of outcomes, including myeloid neoplasm mortality and disease-specific mortality when combined with environmental factors.[36] Accordingly, these variables have been included in statistical models that generate time-dependent predictions of the risk of developing MNs along with clinical and laboratory data.[37,38] For example, Weeks et al. report on a clonal hematopoiesis risk score where a minority of high-risk individuals have about a 50% cumulative incidence of progression to MN at 10 years as compared to a majority of low-risk individuals where the risk is $< 1\%$.[38] These figures are also linked to the subsequent life history of the patient: while it has been known for decades that chemotherapy increases the risk of developing therapy-related MNs, pre-existing CH/CHIP identifies a population at higher risk, where cytotoxic therapy exerts selective pressure that promotes expansion of specific high-risk clones.[39] Pretreatment CHIP is associated with about a 5.8- to 13.7-fold increase in the odds/hazard of t-MNs in key early studies, with risk further enriched in patients harboring high-risk DDR mutations such as *TP53* and *PPM1D*.[27,32,33,40,41]

Onset and Dynamics of CHIP

To gain a better understanding of how massively widespread CH actually is, and of its times and modes of acquisition, researchers sequenced the whole genome of over 3500 single cell-derived hematopoietic colonies from 10 healthy individuals aged between 0 and 81 years.[5] This effort revealed that, while hematopoiesis is mostly polyclonal at a young age, rapidly decreasing clonal diversity is a universal feature of hematopoiesis in ageing individuals, supported by positive selection acting on many more drivers than the currently known genes. About 100% of older subjects showed clonality, and strikingly 30% to 60% of hematopoiesis was accounted for by 12 to 18 independent clones, each contributing 1% to 34% of blood production. Only 22% of clones carried known driver mutations. Modelling these clonal dynamics showed that the HSCs acquire driver mutations with moderate fitness benefits at a steady rate during early life, triggering expansion that takes decades to cause the abrupt loss of clonal diversity observed in the elderly. In search of additional drivers to fill this gap of knowledge, a recent analysis of whole blood exomes from 200,618 individuals in UK Biobank identified 17 additional genes under positive selection at a population-based level.[10]

However, many factors dictate that it will be hard to identify the causes of all cases of "driverless clonal hematopoiesis." This is not only -or not mainly- due to a lack of sensitivity of current sequencing techniques. Rather, the possibility of the presence of "private," nonrecurring drivers, noncoding driver mutations, or driver events such as copy-number alterations or chromosomal rearrangements, or epigenetic changes, will need to be investigated in this setting. However, given the translational angle of this review, we will focus on the best known and more consequential drivers of CHIP.

CHIP and Multiple Myeloma

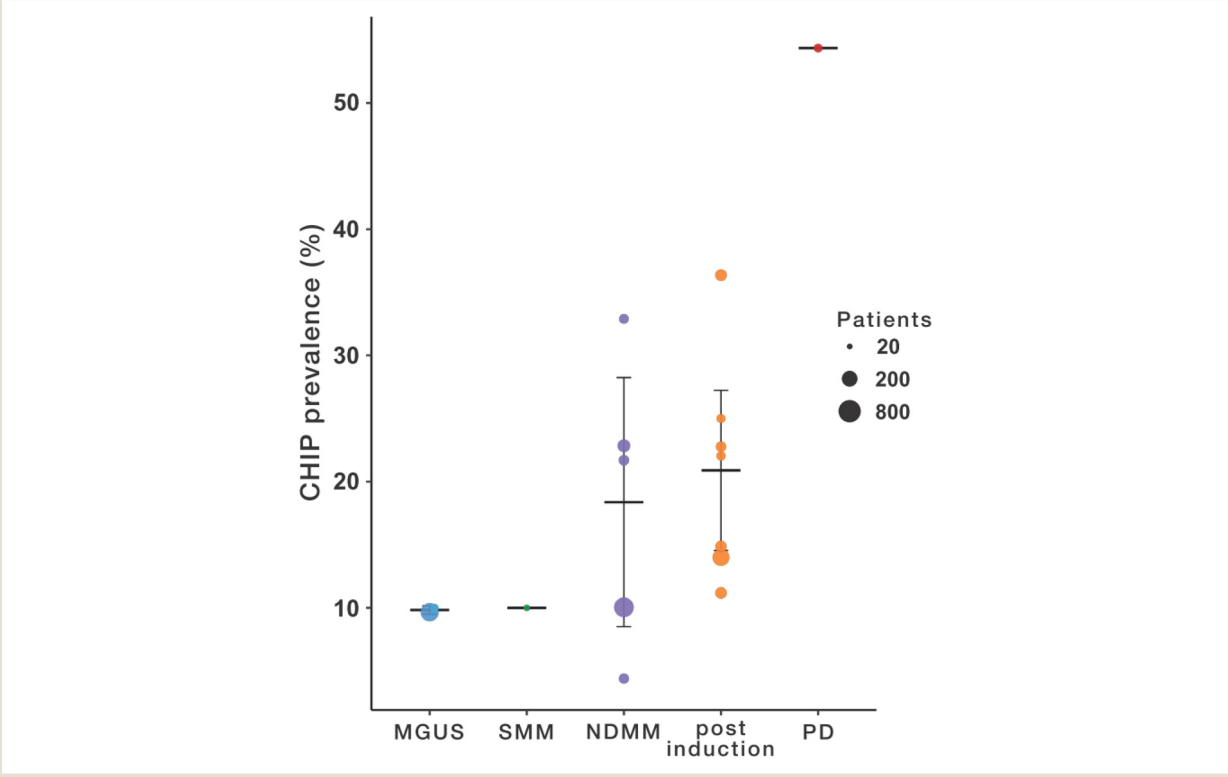
Prevalence of CHIP in Plasma Cell Disorders

CHIP is relatively common in individuals with PC dyscrasias. Several studies have investigated whether CHIP is more prevalent in plasma cell dyscrasias than in the general population and contributes to the development or progression of MM, or whether the 2 conditions merely coexist as age-related phenomena. Considering asymptomatic stages, Da Vià et al. showed in a highly selected older cohort (median age 91 years, 74.5% females) that CH was present in 9.7% of the patients with MGUS.[42] The 2 conditions did not show co-association and rather tended to mutual exclusivity, suggesting that myeloid and PC clonal expansions may occur as parallel age-related events. In a cohort with a high representation (37%) of Black/African-American individuals, CHIP was reported in 10% of MGUS and 10% of SMM patients, respectively.[43] A higher prevalence was reported in the study by Testa et al., who identified DTA-CH in 21% of both MGUS and SMM patients. Here, CHIP did not show association with a higher progression rate to symptomatic MM.[44] Conversely, CHIP has been linked to increased risk of progression in smoldering Waldenström macroglobulinemia[45] and with higher rate of Richter transformation in chronic lymphocytic leukemia (CLL),[46] raising the hypothesis that CHIP-driven inflammation or immune dysregulation could facilitate malignant evolution in specific contexts. In newly diagnosed MM (NDMM), CHIP prevalence ranges from 4% to 32.8% depending on sampling, analyzed cells, sequencing depth and variant allele frequency thresholds (Table 1).[43,47-52] Phylogenetic studies indicate that CHIP and MM arise from distinct clonal populations, with no shared founder mutations between HSC clones and malignant PCs, further supporting independent clonal origins.[48,50,53] Across multiple therapeutic contexts, CHIP in MM shows selection driven by treatment and/or disease progression (Figure 2). In particular, in 2 cohorts of MM patients undergoing autologous stem cell transplantation (ASCT), CHIP was identified in 11% and 14% of the stem cell products, respectively.[54,55] Similarly, Wudhikarn et al. reported CH in 23% of 101 MM patients analyzed prior to ASCT by targeted sequencing of CD138-BM mononuclear cells (MNCs).[56] Collectively, these data indicate that CHIP is frequently detectable already before transplantation. After ASCT, CHIP was detected in the PB of 13/59 patients (22%), with most mutations already present in the stem cell graft and expanding after transplantation, consistent with selective advantage for reconstitution of CHIP-mutated HSCs under hematopoietic stress.[57] In more advanced phases of therapy, CH prevalence raised

Table 1 Prevalence of CHIP in Newly Diagnosed MM Patients

References	N° of NDMM Patients	Sequencing Strategy	VAF Threshold	CHIP Prevalence
Lionetti et al.[48]	n = 106	Targeted NGS of PB cells (74-gene panel)	2%	21.7%
Mouhieddine et al.[49]	n = 986	WES of PB cells and CHIP calling in a subset of 110 genes	2%	10%
Guerrero et al.[50]	n = 232	Targeted NGS of BM sorted CD34+ HSCs (56 gene panel)	2%	23%
Gagnon et al.[43]	n = 91	Targeted NGS of BM and CHIP calling in DTA genes	2%	4%
Gelli et al.[52]	n = 76	Targeted NGS of PB mononuclear cells (36-gene panel)	2%	32.8%

Figure 2 Dot plot showing CHIP prevalence across disease stages (MGUS, SMM, NDMM, postinduction, and PD). Each point represents an individual study, with color indicating the disease stage and size proportional to the number of analyzed patients. CHIP was called using a VAF threshold ≥ 2%. The horizontal line indicates the mean prevalence for each stage, and vertical bars represent 95% binomial confidence intervals.[42,43,48-52]



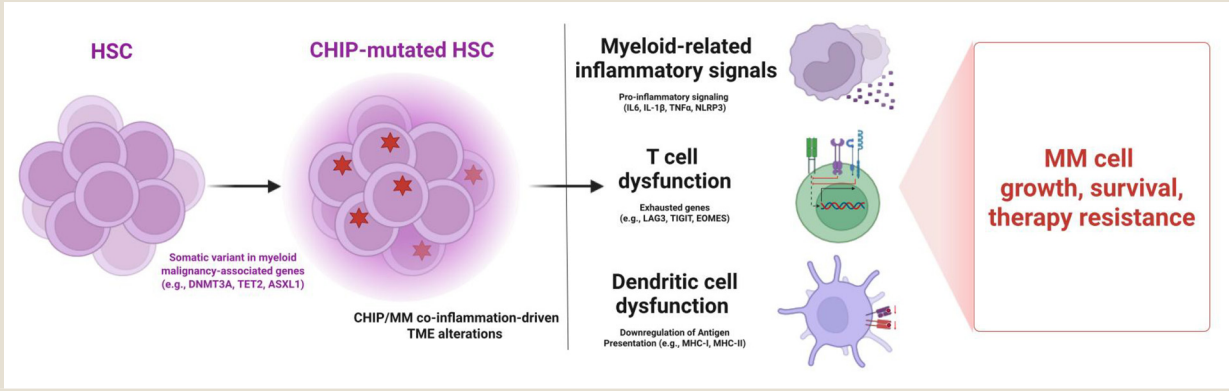
to 25% (13/52) and 40% (82/211).[49,50] In particular, patients in maintenance/at the end of treatment or at the time of progressive disease showed significantly increased prevalence, with 45% and 54% of positive samples, respectively.[50] Consistently, 30% of the 54 MRD-negative patients who discontinued therapy after at least 1 year of lenalidomide maintenance tested positive for CH in the study by Cooperrider et al.[58] In the near future, the use of high-dose chemotherapy and autologous transplant may decline due to the unprecedented efficacy of modern treatments, such as intensive quadruplet regimens and T-cell redirecting therapies.[59,60] In this scenario, the promoting effect of cytotoxic drugs on CHIP prevalence may become less prominent. However, the long-term impact of these newer treatments on CHIP clones remains to be defined.

CHIP-MM 2-way Interplay

Does CHIP Affect MM Pathogenesis or Microenvironmental Changes?

Within the interplay between CHIP and MM, the most compelling hypothesis is that CHIP modulates the MM microenvironment rather than acting as a direct precursor of the malignant PC clone. Recent data show that CHIP is relatively common at diagnosis and associates with low-grade inflammatory remodeling of the BM niche.[48] Single-cell RNA sequencing has revealed widespread activation of TNFα–NFκB, IFNγ, and IL6/JAK–STAT3 pathways in CHIP-positive T cells and monocytes, accompanied by a reduction in naïve T cells, increased expression of exhaustion markers (LAG3, TIGIT, EOMES), and an M1-skewed myeloid compartment with impaired dendritic antigen presenta-

Figure 3 Proposed model of CHIP as a modifier of the BM TME through inflammation and immune dysfunction, based on evidence from scRNA-seq data.



tion (Figure 3) compared to CHIP-negative MM patients. Collectively, these features recapitulate an inflamed yet immunologically dysfunctional TME, typically observed in advanced diseases. This heightened inflammatory state is associated with an enhanced cellular crosstalk between monocytes, T cells, and clonal PCs. Notably, ligand–receptor interactions enriched in CHIP-positive TME include immune-evasion axes (HLA–LAG3, CD48–CD244) and plasma cell survival/migration signals (CD40L–CD40, CCL5–SDC1, TNFSF13B–TACI/BCMA), suggesting a niche that is simultaneously pro-inflammatory and permissive to tumor growth. However, causality remains unresolved: CHIP-driven inflammation could favor MM expansion, but an alternative scenario is that the chronic inflammatory milieu of MM selects for CHIP-mutant HSCs. Both hypotheses are plausible. On one hand, recent evidence supports a role for CHIP in promoting pro-inflammatory signaling,[61] which can lead to a dysfunctional BMME[62] that favors MM growth. On the other hand, both inflammatory and dysfunctional microenvironment may promote the selective expansion of CHIP-mutant HSCs, through activation of the inflammasome and pro-inflammatory cytokine signaling pathways (NLRP3/IL–1β/IL–6),[25,63] as well as the emergence of inflammatory mesenchymal stromal cell programs,[62] previously described in MDS but also reported in MM. Additional datasets are needed to define directionality and clinical relevance, although current evidence supports CHIP as a potential TME modifier in MM.

Does MM or anti-MM Therapy Affect CHIP?

Emerging evidence suggests that the relationship between CHIP and multiple myeloma is not unidirectional. Beyond assessing whether CHIP influences MM, it is increasingly important to determine whether anti-MM therapy shapes the clonal hematopoietic compartment. Multiple myeloma represents a paradigm of multistep cancer evolution, typically arising from precursor conditions such as MGUS and SMM, and driven not only by additional genetic lesions of the plasma cell clone[64,65] but also by tumorigenic signals from a disrupted BM TME and loss of immune control.[20] We and others have indeed demonstrated that the PC clone creates, and feeds on, a pro-inflammatory BM TME.[66-68]

In this context, CHIP may contribute to a shared pro-inflammatory BM niche that supports PC survival and expansion. Conversely, inflammation driven by the plasma cell clone or by anti-MM therapies may further shape CHIP dynamics, reinforcing a bidirectional interplay between CHIP and MM.

Growing data indicate that therapy-related selection pressures can remodel hematopoietic clones independently of myeloma evolution.[69] Cytotoxic chemotherapy, particularly high-dose melphalan, exerts strong selective pressure on the HSC pool, resulting in loss of clonal diversity. Indeed, the prevalence of CHIP after ASCT and during maintenance is higher than at diagnosis. Multiple studies have shown preferential expansion of *TP53*- and *PPM1D*-mutated clones after autologous transplantation,[70] consistent with a survival advantage of DNA damage–resistant HSCs. Similarly, expansion of *TP53*-mutant clones has been observed during lenalidomide maintenance,[71] with a reduction after treatment discontinuation,[58] suggesting a reversible selective advantage. Similar findings have been reported during DRd (daratumumab-lenalidomide-dexamethasone)-based first-line therapy, although typically in a minority of patients and at low VAFs.[48] This may contribute to treatment-related hematologic toxicity, particularly to the development of t-MNs. In a large post-ASCT cohort, t-MDS/AML developed in 2.0% of patients.[72] In the CAR-T setting, the risk of t-MN seems to be even more prevalent: pooled CARTITUDE-1/CARTITUDE-4 data report myeloid neoplasms in 5% (13/285) of treated patients,[73,74] while this figure drops to 2.2% (5/222) in the KarMMa-3 study (https://www.fda.gov/media/176989/download). However, these events arise in heavily pretreated populations, and available case-level data suggest that pre-existing treatments with melphalan, lenalidomide and possibly other cytotoxic agents may contribute substantially to the risk. Indeed, it has been shown that *TP53*-mutated CHIP has been linked to higher incidence of therapy-related myeloid neoplasms.[75] Whether treatment with CAR-T cells or bispecific antibodies will confer a similarly high risk in a future setting where these agents are

used earlier, and in patients not treated with cytotoxic agents, is a question that remains to be answered.

However, CHIP at diagnosis does not correlate with the later development of t-MNs,[50] suggesting this is a dynamic phenomenon that requires longitudinal monitoring to be exploited as a predictive tool. Indeed, clonal dynamics do not necessarily correlate with myeloma outcomes. Recent data indicate that CHIP clone expansion or stability may occur irrespective of treatment response, disease progression, or overall clinical outcome,[50] supporting the notion that hematopoietic clonal evolution during therapy may follow trajectories independent of the malignant PC clone. Collectively, these observations highlight a bidirectional interplay between CHIP and myeloma therapy. Anti-MM treatments can reshape the hematopoietic compartment and influence CHIP dynamics, while CHIP may impair hematopoietic recovery and increase treatment-related toxicities particularly after autologous transplant or cellular immunotherapy. In this context, CHIP emerges not only as a biomarker of age-associated clonal expansion, but also as a potential modifier of therapeutic outcomes in MM. As survival in MM is significantly increased by novel treatments and risk of long-term complications such as development of t-MNs increases, monitoring of CHIP could become standard care for patients.

Does CHIP Affect MM Clinical Outcomes?

The relationship between CHIP and clinical outcomes in MM patients has been largely investigated in the last years. In some of the papers analyzing NDMM, patients harboring CHIP mutations exhibited features of increased disease aggressiveness, including higher β2-microglobulin levels and lower hemoglobin values, and were more frequently classified within high-risk ISS and R-ISS stages.[48,52,49] In terms of treatment outcomes, in the ASCT setting, Mouhieddine et al. and the PETHEMA Spanish group reported worse progression-free survival (PFS) and overall survival (OS) rates in CHIP-positive patients. Nonetheless, the negative impact was found to be abrogated by maintenance therapy with lenalidomide.[54,76] Similar findings supporting the compensatory role of immunomodulatory drug (IMID) maintenance were reported in a cohort of 101 patients at Mayo Clinic.[56] Interestingly, the coexistence of 2 or more mutations, or the presence of some specific ones (eg p.R882 *DNMT3A* or *PPM1D*), were associated with poorer outcomes.[54,77] As for non-transplant eligible (NTE) patients, a subgroup with a higher age-related pretreatment prevalence of CHIP, data from the CoMMpass cohort confirmed the absence of differences in survival outcomes in association with the presence of CH mutations.[49,51]

Conversely, when focusing on safety, CHIP-positive patients seem more prone to develop toxicities. A longer period of neutropenia after ASCT (8.1 vs. 6.7 days, $P = .008$) was reported by Ortmann et al., while Li et al. found a higher median time to platelet engraftment (42 vs. 29 days, $P < .0001$) and a nonsignificant trend toward delayed neutrophil engraftment (20 vs. 17 days, $P = .12$) in patients with CHIP.[57,78] Notably, in a German cohort, *DNMT3A* and *PPM1D* mutations were correlated with lower platelet counts before ASCT and at post-transplant nadir, ultimately leading to delayed engraftment. Moreover, these authors also found a lower number of harvested CD34+ stem cells, both in cases with a single mutation and with co-mutation.[79] Consistently, Mouhieddine et al. reported a poorer CD34+ yield in the presence of CH mutations.[54] However, the impact of increased toxicity on nonrelapse mortality (NRM) rate has not been demonstrated. In the Mayo cohort of MM patients undergoing ASCT, no treatment-related mortality excess was observed when CHIP coexisted.[56]

More recently, the influence of pre-existing CHIP on CAR-T efficacy and safety was addressed. Overall, response rates and survival outcomes were not affected by the presence of CHIP mutations.[80,81] However, preliminary data presented at the 2025 ASH Meeting highlighted reduced PFS (HR 2.00, $P = .008$) and OS (HR 2.00, $P = .008$) in the int-high CCRS (Clonal Cytopenia Risk Score) patient subgroup.[82] In terms of adverse effects, CHIP was found to be positively correlated with the risk of prolonged cytopenias and independently associated with delayed time to independence from red blood cell transfusion and G-CSF.[81] Additionally, Avigan et al. reported that the combination of CHIP and an elevated ferritin further predicted a delayed hematologic recovery (HR 0.38, $P = .006$).[75] Regarding CAR-T-specific toxicities, grade ≥ 2 cytokine release syndrome (CRS) developed more frequently in patients with CHIP mutations both in retrospective and prospective cohorts.[80,83]

For what concerns cardiovascular toxicities associated with CHIP in MM, data are more sparse. While Mouhieddine et al. did not find any association in MM patients undergoing ASCT,[54] Rhee et al. reported a higher 5y-incidence of heart failure, coronary artery disease, or stroke in the CHIP-positive subgroup (21.1% vs. 8.4% in CHIP-negative; $P < .001$).[84] In the Mayo cohort, venous thromboembolism rates were not different in patients with CH mutations compared to patients without.[56]

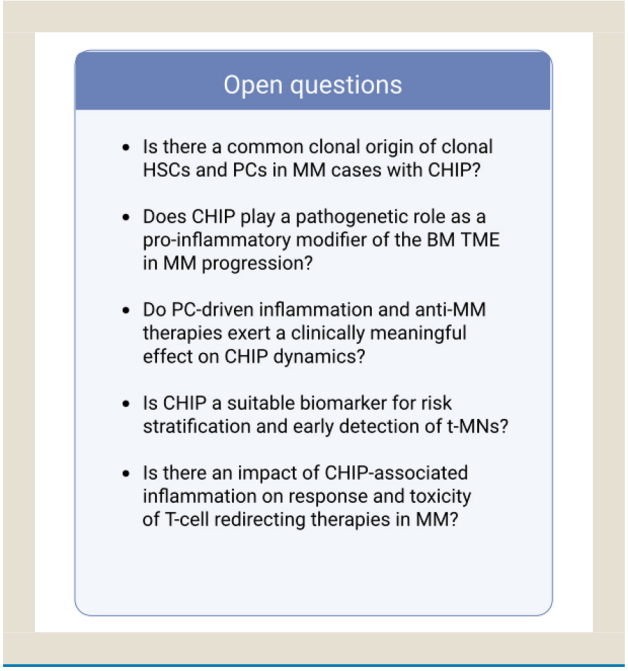
In summary, despite strong rationale and convincing evidence highlighting CHIP-related effects on ASCT and CAR-T treatments in patients with MM, these appear to be context-specific and don't significantly affect "hard" survival outcomes. The treatment landscape in both newly diagnosed and relapsed/refractory MM is rapidly evolving, and there will be an expected significant survival improvement. It remains thus to be defined if CHIP will have a meaningful impact on patients treated with first-line quadruplets and early T-cell redirecting therapies, and/or it will remain a precision medicine tool highlighting increased risk of toxicities in a minority of patients.

Conclusion

Literature to date seems to show that the prevalence of CHIP in MM is higher than in the general population. With an aging population and prolonged survival of MM patients, we can anticipate that this will even increase in the future. Mechanistic studies will be needed to understand if any CHIP subset increases MM risk by acting as a direct driver of disease progression, or whether, on the contrary, CHIP simply represents a therapy-modulated and/or therapy-modulating comorbidity (Figure 4).

At present, we have no unanimous evidence supporting CHIP as a determinant of worse clinical outcomes in MM, but scRNA-seq data suggested that it is associated with a more inflammatory and

Figure 4 Clinically relevant research questions.



immunosuppressive BM microenvironment, enriched in dysfunctional immune cells. These observations, if properly confirmed, should be analyzed in the future in the context of medium-long term outcomes in patients treated with T-cell redirecting therapies, which will gain wider usage in early lines of transplant-eligible and -ineligible patients. Indeed, in this setting, CHIP may create a dysfunctional immune bone marrow TME that reduces the effectiveness of novel immunotherapies. More broadly, current evidence suggests already that CHIP can affect patient outcomes after treatment by increasing the risk of hematologic[70,75,78] and nonhematologic complications.[84] To this we must add the evidence that therapy itself may determine de novo CHIP emergence (melphalan) or favor the expansion of pre-existing mutant clones (IMIDs, CAR-T), making CHIP-related risks, such as development of t-MNs, particularly relevant. In light of all this, future work is needed to understand whether the implementation of predictive and preventive strategies (ie, less genotoxic regimens, closer monitoring, preventive management) can be clinically relevant, at least in certain contexts/high-risk subgroups. For example, it might be conceivable to integrate CHIP risk scores in risk stratification before ASCT/CAR-T, and advise on CHIP monitoring in patients showing prolonged cytopenias after such treatments. To this aim, it would be essential to design prospective studies in MM cohorts that longitudinally track CHIP status in the framework of therapy exposure and clinical outcomes. Only with the information obtainable from this type of studies will it be possible to reach a consensus on whether to screen for CHIP in MM and on how to act in the event of CHIP occurrence. Indeed, if CHIP was confirmed to influence clinical outcomes in MM, interventional trials comparing standard versus modified anti-MM therapy or testing the benefit of intensive comorbidity prevention in CHIP-positive patients could be envisioned.

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CRediT authorship contribution statement

Margherita Scopetti: Writing – review & editing, Writing – original draft, Visualization. **Filippo Viviani:** Writing – review & editing, Writing – original draft. **Emanuele Calvi:** Writing – review & editing, Writing – original draft. **Juan C. Entizne:** Writing – review & editing. **Francesca Lazzaroni:** Writing – review & editing. **Matteo C. Da Vià:** Writing – review & editing. **Marta Lionetti:** Writing – review & editing, Writing – original draft. **Niccolò Bolli:** Writing – review & editing, Writing – original draft, Conceptualization.

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