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THE ROLE OF TET2 MUTATIONS IN THE DEVELOPMENT OF CHIP-ASSOCIATED ATHEROSCLEROSIS

Gaziyeva Anastasiya Ruslanovna
Student at Kimyo International University in Tashkent

Matkarimova Dilfuza Saburovna
Doctor of Medical Sciences, Professor

ABSTRACT

TET2 (Ten-Eleven Translocation 2) mutations are among the most common in CHIP (Clonal Hematopoiesis of Indeterminate Potential) and the most clinically significant in cardiology. Loss of TET2 function leads to hyperactivation of the NLRP3 (NOD-like receptor family pyrin domain containing protein 3) inflammasome in macrophages and overproduction of the interleukins IL-1β, IL-6, and TNF-α, which causes chronic vascular inflammation. This inflammation contributes to endothelial dysfunction, the formation of unstable atherosclerotic plaques, and increases the risk of myocardial infarction and stroke by 2–4 times. Given these findings, it is suggested that CHIP can be considered a new independent risk factor for atherosclerosis, and patients with TET2-mutant CHIP may be the best candidates for therapy with IL-1β inhibitors.

KEYWORDS

CHIP, TET2, NLRP3 inflammasome, myocardial infarction, atherosclerosis, cardiovascular disease.

Introduction

Cardiovascular disease (CVD) remains the leading cause of death and disability worldwide, claiming approximately 18 million lives each year [22]. Despite significant progress in managing traditional risk factors—dyslipidemia, hypertension, diabetes, and smoking—residual risk persists, particularly in the elderly population [19, 21]. This has spurred an active search for new biomarkers and pathogenic mechanisms linking aging to atherothrombosis. One of the most striking discoveries of the past decade has been the description of the phenomenon of clonal hematopoiesis of undetermined potential (CHIP) [2, 12, 13], which is diagnosed in the presence of somatic genetic mutations (most commonly TET2, DNMT3A, ASXL1, JAK2) in peripheral blood cells with a mutant allele frequency ≥ 2%, but in the complete absence of criteria for myelodysplastic syndrome, myeloproliferative neoplasm, or acute leukemia [13, 25]. The risk of CHIP progressing to malignant hematologic disease is approximately 0.5–1% per year; however, the primary contribution of CHIP to disease progression and mortality is associated specifically with CVD [10]. The prevalence of CHIP increases exponentially with age: in individuals younger than 50 years, it is less than 1%; in those aged 60–70

years, it is 5–10%; and in those over 80 years, it can reach 20–30% [33]. Among all mutations causing CHIP, mutations in the TET2 gene (along with DNMT3A) are the most common, accounting for up to 40–50% of all cases [4]. However, it is TET2 mutations that have attracted particular attention from cardiologists, as experimental models have shown their closest association with the inflammatory reprogramming of monocytes and macrophages [9, 14, 15].

Objective

To analyze the molecular mechanisms of TET2-mediated inflammation in CHIP-associated atherosclerosis.

Materials and Methods

To prepare this review, a literature search was conducted in the PubMed, Scopus, and Web of Science databases covering the period from 2014 to 2026. The analysis included original studies, systematic reviews, meta-analyses, and clinical trials in English and Russian.

Results

The TET2 (Ten-Eleven Translocation 2) gene is located on chromosome 4q24 and encodes the protein of the same name, which belongs to the family of α-ketoglutarate- and Fe^{2+}-dependent dioxygenases [20]. TET2 catalyzes the sequential oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine, and 5-carboxycytosine [20]. This is a key step in active DNA demethylation, particularly in regulatory regions—promoters, enhancers, and super-enhancers [20]. In somatic TET2 mutations (most commonly nonsense mutations and frameshift mutations, less frequently missense mutations in the catalytic domain), a loss of enzymatic activity occurs [14, 18, 20]. In a heterozygous state (which is typical for CHIP), haploinsufficiency is observed, leading to a decrease in the level of 5hmC (5-hydroxymethylcytosine) in the genome [20]. This causes hypermethylation of the promoters of a number of genes involved in myeloid cell differentiation and the regulation of the inflammatory response. In particular, the derepression of genes encoding components of the inflammasome pathway, such as NLRP3 (a protein of the NOD-like receptor family containing a pyrin domain), PYCARD (ASC) (Apoptosis-associated speck-like protein containing a CARD), and CASP1 (Caspase-1), becomes a key pathogenic event [7].

The TET2 mutation arises in a hematopoietic stem cell (HSC) during the early stages of hematopoiesis. The mutant HSC gains a competitive advantage due to increased proliferative activity, resistance to apoptosis, and, possibly, better survival in the bone marrow niche [18]. Over time, the proportion of mutant HSCs increases, and VAF can reach 10–30% or higher; it is important to note that VAF ≥ 2% is the diagnostic threshold for CHIP, but higher values are associated with a greater risk of both hematologic and cardiovascular events [28]. The differentiation of TET2-mutant HSCs shifts toward the myeloid lineage due to epigenetic regulation of transcription factors (PU.1 (Purine-rich Box-1), C/EBPα (CCAAT/enhancer-binding protein-α)). As a result, the number of monocytes increases in peripheral blood, and in tissues, the number of macrophages derived from the mutant clone increases [23]. These cells carry the same mutation and exhibit the functional abnormalities described below. It is important to emphasize that even a small clone (VAF (Variant allele frequency) 2–5%) is capable of exerting a significant pro-inflammatory effect due to the constant production of

cytokines [30]. Loss of TET2 function in monocytes/macrophages leads to an enhanced inflammatory response.

A key finding from experimental mouse models was the hyperactivation of the NLRP3 inflammasome in TET2-deficient macrophages [9]. Normally, the inflammasome is activated in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) [5, 21]. In TET2-deficient cells, even subthreshold concentrations of lipopolysaccharide (LPS) or cholesterol crystals trigger massive inflammasome assembly, caspase-1 activation, and the maturation of IL-1β and IL-18 [24]. The mechanism of this hypersensitivity is associated with hypermethylation and subsequent derepression of the NLRP3 (NOD-like receptor family pyrin domain-containing protein 3) gene, as well as with increased expression of IL-1β and IL-6 [15]. In addition, TET2 directly regulates the expression of genes involved in oxidative stress and mitochondrial function, which also modulates inflammasome activity [32]. IL-1β, secreted by activated macrophages, acts autocrinically and paracrinically, inducing the expression of hundreds of genes, including IL-6, TNF, CXCL8 (C-X-C motif chemokine ligand 8), and PTGS2 (Prostaglandin-Endoperoxide Synthase 2). This results in a systemic pro-inflammatory background with elevated levels of IL-6 and high-sensitivity C-reactive protein (hsCRP) [21]. In humans, carrying a TET2-mutant CHIP is associated with significantly higher levels of IL-6 and hsCRP compared to individuals without CHIP, and this effect persists after adjusting for age, sex, and body mass index [13]. Concurrently with cytokine overproduction, TET2-deficient macrophages acquire a sustained M1-like (classically activated) phenotype: they express high levels of CD86, iNOS, and TNF-α, and low levels of M2 markers (CD206, Arg1, IL-10) [15]. Furthermore, they lose the ability to perform efferocytosis—the phagocytosis of apoptotic cells—which is critically important for resolving inflammation and preventing necrosis in atherosclerotic plaques [31].

Pro-inflammatory cytokines produced by mutant macrophages exert multifaceted effects on the vascular wall. IL-1β and TNF-α act on endothelial cells, reducing nitric oxide synthesis (endothelial dysfunction) and increasing the expression of adhesion molecules—VCAM-1, ICAM-1, E-selectin, as well as the chemokine MCP-1 [19]. This enhances the adhesion of circulating monocytes (including non-mutant ones) to the endothelium and their migration into the intima. Within the intima, mutant macrophages demonstrate increased uptake of oxidized low-density lipoproteins (oxLDL) via the scavenger receptors CD36, SR-A (Scavenger Receptor Class A), and LOX-1 (Lectin-like Oxidized Low-Density Lipoprotein Receptor-1), transforming into foam cells—a key cellular component of atherosclerotic plaques [17]. This process is further enhanced by IL-1β-mediated activation of lipoprotein receptors. In experimental models of atherosclerosis, the most compelling data have been obtained by transplanting $Tet2^{-/-}$ bone marrow into mice deficient in the low-density lipoprotein receptor ($Ldlr^{-/-}$) or apolipoprotein E ($Apoe^{-/-}$), which were then fed an atherogenic diet. In such studies, the area of atherosclerotic lesions in the aortic arch and aortic root was 2–3 times greater compared to mice that received control $Tet2^{+/+}$ bone marrow [9, 29]. Histological analysis revealed an enlarged necrotic core, thinning of the fibrous cap, an increased number of macrophages, and a reduced number of smooth muscle cells and collagen in the plaques of $Tet2^{-/-}$ recipients, which is characteristic of unstable, “vulnerable” plaques [9, 27].

The transition from experimental models to human studies confirmed the clinical significance of TET2-mutant CHIP. The first large-scale study linking CHIP to CVD was published in The New

England Journal of Medicine in 2017. The authors analyzed data from four case-control studies involving 4,726 patients with CHD and 3,529 controls, and found that CHIP carriage was associated with a 1.9-fold increased risk of CHD (95% CI 1.4–2.7) [12]. In subgroup analysis, the strongest association was observed for TET2 and ASXL1 mutations. [13] In a subsequent study by Bick et al., published in 2020, the exome sequences of 35,416 individuals from the UK Biobank without cardiovascular disease at the time of enrollment were analyzed. CHIP (DNMT3A or TET2 mutations with VAF ≥ 2%) was identified in 1,079 (3.0%) participants, of whom 432 (1.2%) had large clones (VAF > 10%). [3] Dorsheimer et al. (2019) examined 200 patients with chronic ischemic heart failure (mean age 65 years). CHIP with VAF ≥ 2% was identified in 38 individuals (18.5%). The most common mutations were in DNMT3A (14 patients) and TET2 (9 patients). Over 4.4 years of follow-up, the presence of TET2 or DNMT3A mutations increased the risk of death or hospitalization for heart failure by 2.1-fold. [8] In a subsequent expanded study by Assmus et al. (2021) involving 419 patients with the same condition, VAF thresholds were identified at which clones begin to influence prognosis: 1.15% for DNMT3A and 0.73% for TET2. Five-year mortality was 18% in patients without mutations (VAF <0.5%), 29% in those with a single mutation above the threshold, and 42% in those with mutations in both genes above the threshold values. [2] An important question is whether the association between CHIP and CVD is causal or reflects common aging factors. Mendelian randomization using TET2 germline variants associated with a CHIP-like phenotype confirmed the causal role of TET2 loss of function in elevated IL-6 levels and CVD risk [6, 27]. This reinforces the position of TET2-mutant CHIP as an independent risk factor.

Discussion

Taken together, the presented data suggest that TET2-mutant clonal hematopoiesis of undetermined potential can be considered a novel and potentially modifiable risk factor for atherosclerotic cardiovascular disease [16, 21, 29]. It is crucial that this risk is primarily mediated through inflammatory mechanisms, which distinguishes CHIP from traditional metabolic factors [15, 16, 19]. Despite compelling molecular and epidemiological evidence, the implementation of the CHIP concept into clinical practice faces a number of unresolved issues. The first of these is the appropriateness of screening asymptomatic individuals. Currently, no clinical guidelines support routine detection of CHIP in the general population, due to the lack of randomized trials demonstrating the clinical benefit of such an approach. Furthermore, it remains unclear whether the detection of CHIP will lead to a change in patient management strategies. At the same time, the possibility of selective testing in patients with premature atherosclerosis or recurrent thrombotic events without obvious risk factors is under discussion [2, 8, 16, 21]. A second important aspect is the interpretation of variant allele frequency (VAF). Although an increase in VAF is associated with an increased cardiovascular risk, there are no clear cut-off values for clinical decision-making [2, 6, 16]. An additional challenge is posed by the phenomenon of low-frequency clones (VAF <2%), whose clinical significance remains a matter of debate [1]. A third consideration is the ethical issue of patient disclosure. The detection of CHIP, especially when sequencing is performed for other indications, creates a clinical dilemma: the patient is informed of the presence of a mutation with a potential risk of hematologic transformation and cardiovascular events, yet the absolute risk remains relatively low. This necessitates the development of standards for genetic counseling and accurate

risk communication. The fourth issue concerns therapeutic strategies. Currently, there is no evidence that the presence of CHIP should lead to a revision of standard lipid or blood pressure targets. However, given the leading role of inflammation, the possibility of more active use of anti-inflammatory strategies in this patient population is being discussed. In particular, IL-1β inhibition has demonstrated a reduction in cardiovascular events in clinical trials, making this approach promising for patients with CHIP, especially in the presence of a persistent inflammatory response [21]. Thus, despite significant progress in understanding the role of TET2-mutant CHIP, its clinical integration requires further prospective studies aimed at defining indications for screening, risk stratification, and the development of targeted therapeutic approaches [11, 16, 25, 27, 28].

Conclusion

TET2 mutations within clonal hematopoiesis of undetermined potential are an important molecular risk factor for atherosclerotic cardiovascular disease, acting through chronic inflammation. This mechanism complements traditional views on the pathogenesis of atherosclerosis and highlights the role of immuno-inflammatory processes. Despite compelling evidence, questions regarding screening, VAF interpretation, and patient management remain unresolved. Therefore, further research is needed to integrate CHIP into clinical practice and to develop personalized approaches to prevention and treatment.

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