

Extinguishing the Fire of Inflammation in Clonal Hematopoiesis

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Chronic inflammation is associated with an increased risk of developing cancer, involving multiple potential mechanisms such as compensatory hyperproliferation with reduced DNA-repair fidelity, immune evasion and clonal dominance of mutated cells.¹ The biological mechanism of clonal evolution is also very complex and depends on cell-intrinsic, as well as cell-extrinsic, factors. With the recent advent of single-cell sequencing, tracking genetic evolution over time has become possible at the single-cell level. Single-cell sequencing allows basic biological mechanisms to be studied, which holds promise for the discovery of new therapies that may influence clonal outgrowths of cancer cells in the early stages of disease. Investigating cell-extrinsic mechanisms remains challenging, however, and requires models that can reliably reproduce the cancer microenvironment. In this context, animal models are important but remain limited in providing the full spectrum of information on heterotypic cellular interactions.

Easy access to all cells at different stages of development makes hematological neoplasms the ideal model for investigating and understanding clonal evolution.² For example, clonal hematopoiesis (CH) has emerged as an age-associated phenomenon characterized by the occurrence of single mutations in driver genes like *TET2*, *DNMT3A* or *ASXL1* at low allele frequency.³⁻⁵ Therefore, CH has the potential to reconstitute the full spectrum of quasi-normal hematopoietic differentiation.⁶ Exogenous stressors (e.g., infections, tissue damage, inflammation) can lead to subtle functional changes that alter biological interactions during hematopoietic differentiation, resulting in a pro-inflammatory phenotype.

At an early stage, CH seems to be innocuous for affected, generally elderly, individuals. However, slight changes in mutated stem cells, as well as their progenies, can be observed. The inflammasome, a multiprotein complex integrating cell-intrinsic and cell-extrinsic stressors, is activated in CH. It plays a fundamental role in NF-kappa- and IL-1-beta (β) driven inflammation,⁷ clonal dominance of mutated stem cells and exhaustion of normal stem cells.⁸ This observation explains why clonal cells expand over time without any proliferative advantage, laying the foundation not only for the development of hematological

malignancies but also for several important degenerative-inflammatory disorders observed in the elderly population with CH.⁹ Inflamming is characterized by an age-associated proinflammatory condition that contributes to an array of inflammatory-degenerative diseases such as atherosclerosis, chronic obstructive pulmonary disease (COPD), diabetes, dementia and also cancer.¹⁰ We are just starting to gather a deeper understating of the interaction of CH with aging, degeneration, inflammation and cancer. CH with activation of the inflammasome is just one piece of the puzzle. By using drugs that interfere with NF-kappa, IL-1 β or inflammasome activation,

the risk of hematological malignancies and other age-related inflammatory-degenerative disorders may potentially be reduced. Let us hope these developments help extinguish the fire of inflammation in CH!

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1. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell.* 2011;144(5):646-674. doi:10.1016/j.cell.2011.02.013
2. Miles LA, Bowman RL, Merlinsky TR, et al. Single-cell mutation analysis of clonal evolution in myeloid malignancies. *Nature.* 2020;587(7834):477-482. doi:10.1038/s41586-020-2864-x
3. Genovese G, Köhler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med.* 2014;371(26):2477-2487. doi:10.1056/NEJMoa1409405
4. Chaniias I, Bonadies N. Diagnostic Approach, Clinical Implications and Management of Clonal Cytopenia of Undetermined

Significance. *healthbook TIMES Onco Hema.* 2022;14(4):24-33. doi:10.36000/hbT.OH.2022.14.091
5. Schmidt A. Clonal Hematopoiesis of Indeterminate Potential: New Insights from Recent Studies. *healthbook TIMES Onco Hema.* 2021;9(3):44-49. doi:10.36000/hbT.OH.2021.09.042
6. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood.* 2015;126(1):9-16. doi:10.1182/blood-2015-03-631747
7. Andina N, Bonadies N, Allam R. Inflammasome Activation in Myeloid Malignancies-Friend or Foe? *Front Cell Dev Biol.* 2022;9:825611. doi:10.3389/fcell.2021.825611

8. Caiado F, Kovtonyuk LV, Gonullu NG, Fullin J, Boettcher S, Manz MG. Aging drives Tet2+/- clonal hematopoiesis via IL-1 signaling. *Blood.* 2023;141(8):886-903. doi:10.1182/blood.2022016835
9. Winter S, Shoaie S, Kordasti S, Platzbecker U. Integrating the "Immunome" in the Stratification of Myelodysplastic Syndromes and Future Clinical Trial Design. *J Clin Oncol.* 2020;38(15):1723-1735. doi:10.1200/JCO.19.01823
10. Jaiswal S. Clonal hematopoiesis and nonhematologic disorders. *Blood.* 2020;136(14):1606-1614. doi:10.1182/blood.2019000989