The effects of inflammation on the mutational spectrum of clonal hematopoiesis of indeterminate potential (CHIP)

Inflammatory cytokines promote clonal hematopoiesis with specific mutations in ulcerative colitis patients.

Zhang CRC, Nix D, Gregory M, Ciorba MA, Ostrander EL, Newberry RD, Spencer DH, Challen GA (2019) *Exp Hematol* 80:36–41.

The aging-related premalignant condition known as clonal hematopoiesis of indeterminate potential (CHIP) is characterized by a distinct subset of hematopoietic stem cells (HSCs) carrying one or more somatic mutations, typically in myeloid malignancy–associated genes. This subset of HSCs produces a clonal population of blood cells that can be identified in blood samples from individuals before symptoms are ever present (in ~10% of people over 65 years old). Even with CHIP, most of these individuals are at low risk of acquiring a hematologic malignancy.

In their recent *Experimental Hematology* paper, Zhang and colleagues investigated the role of environmental factors, specifically inflammation, on the mutational spectrum of CHIP blood cell subpopulations. They postulated that in addition to compromising HSC function, an inflammatory environment may also exert selective pressure on HSC mutations associated with CHIP. In their study, they sequenced 40 CHIP-associated genes in the peripheral blood mononuclear cell DNA from 187 patients >50 years old with ulcerative colitis (UC). UC is an inflammatory bowel disease that leads to T cell infiltration of the colon, as well as the overproduction of two pro-inflammatory cytokines, tumor necrosis factor α (TNFα) and interferon γ (IFNγ). They found that the most frequently mutated gene in those UC patients with CHIP was *DNMT3A*, followed by *PPM1D*, suggesting that inflammation associated with UC may exert selective pressure on the CHIP mutational spectrum.

In addition to analyzing DNA sequences, Zhang and coauthors quantified patient TNFα and IFNγ levels using the corresponding Invitrogen™ ProQuantum™ Immunoassay Kit, which provides a sensitive qPCR-based immunoassay that can detect as little as 0.01 pg/mL cytokine in serum using small sample volumes. The pro-inflammatory cytokine data from the UC patients were matched for patient age and sex, and further grouped into three categories: CHIP$^-$ (n = 21), CHIP-hs$^+$ (CHIP-high sensitivity with variant allele fraction >0.5%) without *DNMT3A* mutations (CH$^+$*DNMT3A*$^-$, n = 17), and CHIP-hs$^+$ with *DNMT3A* mutations (CH$^+$*DNMT3A*$^+$, n = 19). Whereas serum TNFα levels were not significantly different among patient groups, the CHIP-hs$^+$ CH$^+$*DNMT3A*$^+$ patients exhibited significantly higher serum IFNγ levels (Figure 1).

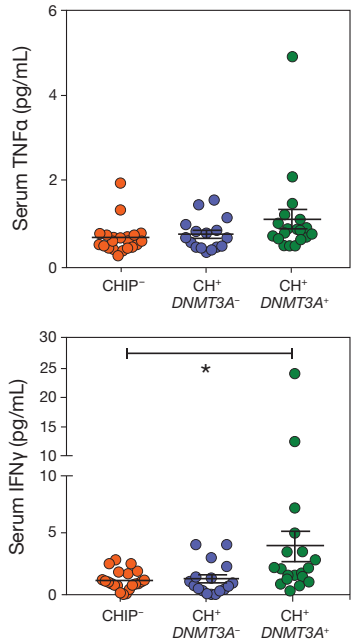

Figure 1. Clonal hematopoiesis of indeterminate potential (CHIP) dynamics in ulcerative colitis (UC) patients. TNFα and IFNγ levels in serum of UC samples in patients surveyed in this experiment, measured using Invitrogen™ ProQuantum™ Immunoassay Kits. Each dot indicates the level of a given cytokine in the serum of one patient. Graphs represent means ± SEM. * $p < 0.05$, one-way ANOVA with Bonferroni multiple test correction. Reprinted from Zhang CRC, Nix D, Gregory M et al. (2019) *J Exp Hematol* 80:36–41, with permission from Elsevier.

In summary, this study showed that UC patients were slightly more likely to have CHIP, and that inflammation associated with UC may be selecting for HSC clones with specific mutations. Further research is needed to explore the relationship between IFNγ levels and *DNMT3A* mutations. ■

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