What Is clonal Hematopoiesis of Indeterminate Potential (CHIP)?

Siddhartha Jaiswal / Stanford Univ., USA

Diseases of aging such as heart disease and stroke are usually thought to occur due to a combination of hereditary and environmental influences. Recently, we discovered that somatic mutations (DNA alterations acquired after birth) in blood cells may be another factor that contributes to these diseases. Approximately 15-20% of people age 70 or older carry a cancer-associated somatic mutation in a substantial proportion of their blood cells, even though the vast majority do not have cancer. This condition has been termed “clonal hematopoiesis of indeterminate potential”, or CHIP. It most commonly arises due to loss-of-function mutations in regulators of DNA methylation. CHIP carriers develop blood cancers at a higher rate than the general population, which is expected because it represents the “first-hit” on the path to cancer. Surprisingly, CHIP is also associated with increased all-cause mortality and higher risk of developing non-neoplastic diseases, like atherosclerotic cardiovascular disease. This association has been shown to be causal based on mouse models of *Tet2* deficiency in atherosclerotic mice. Mechanistically, these mutations appear to increase inflammation in innate immune cells, which predisposes to atherosclerotic progression. We hypothesize that carriers of CHIP will be responders to drugs targeting inflammation. In summary, CHIP is a common condition of aging associated with increased risk of hematological malignancies, cardiovascular diseases, and mortality.