BRIEF CLINICAL UPDATE

Stem Cell Diseases: Clonal Hematopoiesis of Indeterminate Potential (CHIP) as a Disease of Aging

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The importance of stem cells for the homeostasis of the organism is introducing a new perspective in medicine: dysfunction or aberrancy of stem cells as the pathological basis of disease. Processes that depend on mutations occurring in a cell and its subsequent progeny from cell division and growth are clonal in nature.

Cancer is an example: Stem cells have been identified in many cancers and there is abundant evidence favoring the hypothesis that cancer is a stem cell disease.[1] Cancer is a clonal process, which is often initiated by a mutation occurring in an epithelial stem cell. Mutations in a more differentiated cells have fewer consequences, because the mutation can be repaired and/or the cell is eventually eliminated from the organism.[2] The epithelial origin of many cancers[3] is not surprising because epithelia are constantly renewing and the cells of these tissues are dividing more often than those of other, more quiescent tissues.

Mutations in stem cells can also give rise to pathological conditions other than cancer. Many of these conditions can turn into cancers over time, and could be viewed as stepping stones in tumorigenesis. Stem cells accumulating additional mutations can give rise to clones of cancer cells. Clonal Hematopoiesis of Indeterminate Potential (CHIP) is one such condition.[4] Clonal hematopoiesis (CH) refers to a genetically distinct subpopulation of myeloid cells that share an acquired (not inherited) mutation, which distinguishes them from other tissues and unaffected hematopoietic cells.[5] CH may be detected in healthy individuals with few or no hematologic manifestations. Although clonality is also a feature of myelodysplastic syndromes, acute leukemias, and myeloproliferative neoplasms, these malignancies are generally associated with substantial hematologic findings.

CHIP is caused by a mutation in any of a number of genes, most frequently the TET-2 gene, but also in epigenetic regulators DNMT3A, ASXL1, DNA damage repair genes PPM1D, TP53, the regulatory tyrosine kinase JAK2, or mRNA spliceosome components SF3B1, and S RSF2 (4).[4] CHIP is essentially characterized by the presence of a clonally expanded hematopoietic stem cell caused by a leukemogenic mutation in individuals without evidence of hematologic malignancy, dysplasia, or cytopenia.[4] This illustrates the role of stem cells in the development of CHIP and reveals its nature as a disease of stem cells.[5]

CHIP is age related, and prevalence increases with age. By the age 70, 10–20% of the otherwise healthy population have a peripheral blood leucocyte clone with a VAF of at least 2% and meet the criteria for CHIP.[6-11] Conversely, CHIP is found in fewer than 1% of patients under age 50.[6,8,11]

CHIP causes a pro-inflammatory state[4] that contributes to worsening atherosclerosis and cardiovascular disease,[9,11,12] because the mutated cells tend to adhere to the wall of blood vessels adding to the atherosclerotic plaque.[13] CHIP carriers have a marked increase in the risk of heart failure,[12,14] myocardial infarction,[14] stroke,[14,15] and perhaps venous thrombosis and pulmonary embolism.[13] CHIP has also been linked to the development of atrial fibrillation, which can also be counted as a disease of aging.[16,17] Atrial fibrillation can lead to the development of stroke as well as other arrhythmias and is in itself potentially lethal. CHIP is also associated with a 0.5-1.0% risk per year of leukemia.[4,8]

Diagnostic criteria for clonal haematopoiesis of indeterminate potential (CHIP) include: (a) the absence of overt haematological malignancy; (b) a normal peripheral blood count and (c) mutant cells bearing relevant driver mutations in ≥2% of peripheral white blood cells (variant allele frequency [VAF] ≥ 2%).[4,18]

In summary, CHIP is a newly described disease of aging which is one of the underlying causes of other age-related pathologies, such as cardiovascular disease,[9,11] heart failure,[12,14,18] atrial fibrillation[16,17] and cancer.

Aging-related clonal hematopoiesis (ARCH) is another condition that has been described in the literature, but it is essentially the same as CHIP, since the gene mutations involved are the same as in CHIP.[11] Also, as in CHIP, ARCH mutations are rarely found in individuals younger than 40 years of age, with frequency increasing with age.[11]

CHIP/ARCH is an example of how the homeostasis of the entire organism can be disrupted by a stem cell aberration and allows us to deduce how stem cells can affect the development of cancer and the aging process.[19] Because the hematopoietic stem cell is also the immune stem cell, it is not surprising that CHIP also leads to inflammation and immune disorders.[19]

CHIP was discovered due to the development of next generation sequencing.[12] This allowed for the discovery of the involved gene mutations and demonstrates the utility of genomic technologies in medicine.

CHIP is currently vastly underdiagnosed because DNA sequencing is not a widespread diagnostic tool. Given that it is a risk factor for cardiovascular disease, heart failure and atrial fibrillation, more attention should be given and Tet-2 gene sequencing may become an important predictor test in medical check-ups.

Stem cells are not just relevant to "regenerative" medicine or bone marrow transplants, but affect the whole spectrum of medicine. If we were able to edit and correct mutations in stem cells, perhaps with gene editing technology, we could prevent the development of CHIP and lower the incidence of its many cardiovascular complications. Treating a fundamental aging process like CHIP could also impact development of other conditions. This would be preferable to treating each individual condition after it has developed. It is likely that other stem-cell mediated conditions (like CHIP and cancer) may exist. This will only be discovered by deploying technology like next generation sequencing and single cell sequencing, to track the fate of individual stem cells and their cellular offspring in the organism. Analyzing large amounts of sequencing data and keeping track of stem cells and the cell population that originate from them could be greatly aided by artificial intelligence progress.

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