EDITORIAL

CHIP: A NEWFANGLED PERIL FOR CORONARY HEART DISEASE IN PAKISTAN

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Certain somatic mutations are capable to confer a selective benefit to blood stem cells become much more common with aging1. This state was entitled “clonal hematopoiesis of indeterminate potential,” (CHIP), and found that it upsurges the risk of developing a blood cancer more than 10-fold and it seemed to escalate mortality from heart attacks or stroke. But looking at the current understanding of Coronary heart disease CHD is that CHD in the world is the solitary empire where death rules, dictated by tobacco smoking and metabolic syndrome. Worldwide the anticipated rise in CHD is twice in the next 20 years in South Asia compared to any where else.2,3

There is scarcity of undeviating evidence about the contributing factors of CHD in South Asia and especially in country like Pakistan. Cardio metabolic ailments are considered main culprit but unwavering causality is not established4,5. The possible distinct risk profile of South Asian populations, seemingly earlier inception of MI and greater familial clustering of CHD6, highlight the requirement of genetic studies in this region2,3. Pakistan is fortunate that a research titled Pakistan Risk of Myocardial Infarction Study (PROMIS:5,000 confirmed MI and 5,000 controls in urban Pakistan), a genome wide association study (GWAS) in 2009 was conducted. PROMIS was a large resource of epidemiological pool for Coronary heart disease in South Asia which laid the basis to ascertain and assess inherent and other risk factors of MI in South Asia along with discovery of new pathways6.

Scientists at the Broad Institute of MIT and Harvard University7 explored whole-exome sequencing data from two retrospective case-control studies8, the Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group (ATVB) and the Pakistan Risk of Myocardial Infarction Study (PROMIS). These studies (PROMIS) evaluated early-onset of MI in subjects age less than 50 years (40-50) comparing them with controls from the same medical centers who did not have cardiovascular disease. However ATVB participants were 45 years of age or younger, and with controls were age matched.

A set of genetic mutations was observed in blood cells that are usually seen during aging. These mutation may be a main new risk factor for coronary heart diseases. Contrary to genetic tendencies and outmoded lifestyle risk factors like tobacco smoking and unhealthy dietary habits, the fresh mutations are “somatic mutations” that instigate in stem cells in the bone marrow as age advances. Because the mutations are comparatively communal in elderly people (over 10% of people over the age of 70 encompass at least one of these mutations), the presence of these mutations2 in CHD opens the wider canvas illustrating the pathogenesis in coronary heart disease by supporting the hypothesis that inflammation, in addition to raised cholesterol levels, contributes an imperative part in CHD and possibly other diseases of aging as well.
A crucial outcome from NEJM study is that somatic mutations are truly modulating risk for CHD, some what, which haven’t been perceived other than cancer. " Previous research already ascertained that these somatic mutations are due to clonal hematopoiesis of indeterminate potential." (CHIP), and found its relation with cancer and cardiovascular diseases. In the new study, the researchers evaluated data from four case-control studies including PROMIS and ATVB on more than 8,000 people and found that having one of the CHIP-related mutations nearly doubled the threat for CHD, with the mutations conferring an even greater risk in people who have previously had a heart attack before age 50. In both ATVB and PROMIS, MI patients had enrichment of CHIP, compared to controls. A combined fixed-effects meta-analysis of these two cohorts showed that CHIP was associated with odd-ratio of 4.0 (95% CI, 2.4 to 6.7; P<0.001) for early-onset MI and this is the thump point for Pakistan that CHD have crabbed the adult population and alarmed to secure preventive as well as curative grounds.

As the human genetic data disclosed a resilient association between CHIP and coronary heart disease, further experiments were done on a mouse model prone to atherosclerosis to disclose the underlying mechanisms. It was observed that loss of one of the CHIP-mutated genes, Tet2, in bone marrow cells leads to development of atherosclerotic plaques in blood vessels, indicating the role of mutation in acceleration of atherosclerosis in mice. Atherosclerosis is supposed to be a disease of chronic inflammation that can develop due to excess cholesterol in the vessel wall. Further experiments revealed the presence of an immune cell in atherosclerotic plaques that can develop from CHIP stem cells and carry the same mutations. Mutations in Tet2, JAK2, and ASXL1 Tet2 are CHIP-related mutations also named as "epigenetic regulators" that can alter the activity of other genes. Gene expression levels in the Tet2-mutated macrophages from mice seem to be "hyper-inflammatory" with increased expression of inflammatory molecules that contribute to atherosclerosis. In support of this finding, humans with Tet2 mutations also had higher levels of one of these molecules, IL-8, in their blood. Significant enrichment mutation in Tet2, JAK2, and ASXL1 was also found among participants with early-onset MI, the studies identified Tet2 mutations in 12 of 13 participants, ASXL1 mutations in all 8 participants, and JAK2 mutations in all 16 participants. JAK2 accounted for 19% of the total mutations among patients with myocardial infarction in ATVB and PROMIS. By combining genetic analysis on large cohorts with disease model and gene expression studies, CHIP’s surprising role in cardiovascular disease is opening new avenues for a new genetic mechanism for atherosclerosis — mutations in blood stem cells that arise with aging.

Future research grounds can be found by finding role of other mutated genes in CHIP in increased inflammation. Interventional trials for possibility of cholesterol lowering therapy or anti-inflammatory drugs in people with CHIP can also be the focus of researchers. A noteworthy clinical impact can be achieved through prospective screening for the mutations in blood cells which would categorize persons at increased risk for coronary heart disease and diminish risk in those individuals through lifestyle modifications or therapeutic mediations.

REFERENCES