# CHIPping Away at CHIP

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**Julie McDowell:**

The incidence of genetic mutations increases with age, and age-related mutation. Hematopoietic stem cells in the absence of hematologic malignancy is termed Clonal Hematopoiesis or CH. "While CH took the hematology field by storm several years ago, there is increased awareness of the identification of CH, not just underlining hematologic neoplasms, but in the background of solid tumors as well", explains Dr. Annette Kim. In this cap cast, Dr. Kim, who is a member of the CAP's Personalized Healthcare Committee, wrote in an article on this topic that was recently posted to the precision medicine section of CAP.ORG.

Dr. Kim, your article opens with a reference to aging. Can you explain what happens with aged cause CH?

**Dr. Annette Kim:**

Sure. We all start off life with a single genome in a single fertilized egg. However, once that cell divides, the daughter cells can acquire mutations as a result of mistakes in DNA replication. As the daughter cells continue to divide, different subsets of cells may carry different mutations. So in effect, we are all like mosaics of many, many genomes. In addition, different types of cells are exposed to different environments, including sun-exposure of the skin or ingested toxins in the gastrointestinal tract pollution or smoking exposures in the lung. In a landmark study of mutations found in eyelids published in 2015, aged and sun exposed skin was found to be actually a patchwork of cells with thousands of different evolving clones. Now, our body has some mechanisms for repairing some of the damage, and in some cases, the consequences of a mutation is really minimal.

In other cases, the cells containing the mutation are lost during sort of natural attrition of cells. However, some of these events were in fact cancer driving mutations by themselves. These mutations may not have been sufficient for transformation to a bonafide cancer since these were all individuals without skin cancer. But they may have laid the groundwork for future skin cancers evolving from those clones when these mutations affect the hematopoietic stem cell and are therefore carried into the differentiating hematopoietic lineages that make up all of our blood cells clonal hematopoiesis results. The current estimate is that our hematopoietic stem cells are acquiring as many as 20 mutations per year of life.

Certain events may speed up this process as well, including chemotherapy, other toxic exposures and stem cell transplantation. As in the skin cancer example, some of these mutations actually lay the groundwork for future hematopoietic neoplasms. Those events that speed up this process result in an increased risk of these future neoplasms and unlike your eyelid cells, we are constantly being sloughed off regularly. The role of the hematopoietic stem cell is not just to reproduce itself and maintain the hematopoietic stem cell pool and as well as to differentiate into all of your blood cells, which of course reach every part of your body. So the potential impact of mutations in these pluripotent and multi-potent cells is much more far-reaching in the case of CH.

**Julie McDowell:**

Now, what led to your interest in this subject for research?

**Dr. Annette Kim:**

As a diagnostic Hematopathologist, I spent much of my career studying disease called Myelodysplastic Syndromes, or MDS. MDS is a disease predominantly of the elderly and presents as ineffective hematopoiesis that can be manifest clinically as cytopenias and pathologically with dysplasia or funny looking cells. Now, I'm going to date myself here a bit, but at the time when I trained, there was very little understanding about the origins of MDS, so I spent many years studying the causes of MDS. Therefore, I spent many years studying the causes of MDS. Therefore, when MGS became available and large scale studies came out on acute myeloid leukemia and MDS, finding somatic mutations in all of these diseases, I was sort of immediately enthralled. In 2014, the first clonal hematopoiesis papers emerged demonstrating a progression rate of approximately 0.5 to 1% per year of clonal hematopoiesis to bonafide hematopoietic neoplasms such as MDS.

And this led to my participating in a working group on mutational patterns in myeloid neoplasms, including clonal hematopoiesis with the Association for Molecular Pathology or amp. This work was contemporaneous with my transition as well to my current institution where we have a very large practice involving frequent NGS of myeloid neoplasms sort of cementing my interest and providing me with almost unparalleled exposure to NGS on all of these cases. It also doesn't hurt that much of the work on clonal hematopoiesis has come out of Ben Ebert's group here at the Dana-Farber and Brigham and Women's Hospital. So I have been essentially immersed in clonal hematopoiesis during my tenure here and have easy access to all the groundbreaking research in the field.

**Julie McDowell:**

Now you noted there were correlations between CH and several disease processes. Can you briefly discuss what these disease associations are?

**Dr. Annette Kim:**

Well, as I just mentioned, there is an association of clonal hematopoiesis with hematopoietic neoplasms. However, there's some really fascinating work on the association of clonal hematopoiesis with other diseases. The most sort of initially surprising was the association with cardiovascular disease. CH has been associated with both risk of coronary heart disease and risk of ischemic stroke. And while this may seem a little counterintuitive, in fact, what is plaque, but a gamish of macrophages, platelets, neutrophils, as well as other inflammatory cells derived from the hematopoietic stem cells. So in fact, it actually does make sense.

The presence of a clonal hematopoiesis mutation carries a higher hazard ratio for coronary heart disease than high BMI or high blood pressure. And CH mutations are also carrying a higher risk for ischemic stroke more so than high blood pressure and with comparable hazard ratios as type two diabetes or elevated BMI. So sort of shockingly high hazard risks associated with CH. Similarly, some recent work has shown that CH has been associated with the risk of severe Covid-19 in a pre-print out of Sloan Kettering. Again pointing to the effect of clonal hematopoiesis on the inflammatory state of the patient.

**Julie McDowell:**

So you describe a pattern of acquisition of mutations in the development of myeloid neoplasms. So two questions. What is the difference between the age-related myeloid neoplasms and the therapy related myeloid neoplasms? And can these patterns suggest which process is occurring in a patient with a history of another cancer who now gets myeloid neoplasm?

**Dr. Annette Kim:**

Sure. This association of clonal hematopoiesis is sort of highest with myeloid neoplasms such as MDS and AML. As you mentioned. In these cases, the development of MDS and AML can be age-related or slowly evolving from founding clonal hematopoiesis driver mutations. The mutations in this age-related process tend to be what I refer to as the usual suspect mutations such as mutations in DNMT3A AXL1, TET2, SRF2, and SF3B1 amongst others. I also like to refer to these as sort of the hallmarks of an old stem cell and you'll see these mutations acquire with age. In addition, the development of MDS or AML can be therapy-related or secondary. This arises in a patient who's receiving chemotherapy for another neoplasm. There is a selection under these adverse conditions for clones that have a survival advantage. In many cases, this is related to the type of chemotherapy the patient is receiving, such as DNA-damaging agents leading to an outgrowth of clones with mutations in DNA damage repair genes from which a therapy-related myeloid neoplasm can arise.

So these genes are things like PPM1D, TP53, CHEK2 and ATM. So again, there are sort of two avenues from which development of a myeloid neoplasm can arise from clonal hematopoiesis, one which is age-related, and one which is related to prior cytotoxic exposures, which can progress on an accelerated timeframe under repeated cytotoxic pressure. And so the mutational patterns can point to different pathways to neoplasia.

**Julie McDowell:**

Finally, Dr. Kim, looking ahead, what should pathologists expect in upcoming research related to CH?

**Dr. Annette Kim:**

Well, we're constantly learning more and more about CH and hematopoietic neoplasms, not just myeloid neoplasms can be associated with CH, but also lymphoid neoplasms. This association is most clear with the T-cell neoplasm Angioimmunoblastic T-cell lymphoma. It's well documented in these cases that these patients have highly recurrent type 2 DMNT3A and IDH2 mutations that are found in the T-cell neoplasm, and that can also be found in the hematopoietic stem cell from which may arise a clonally related but completely separate myeloid neoplasm. Since the time I first wrote my article for the precision medicine website, there's been even additional publications showing similar mutations in other types of T-cell lymphoma such as large granular lymphocytic leukemia and other neoplasms. However, we've shown some unpublished work where we found that it is less likely in the case of some B-cell neoplasms where the identification of what I like to refer to as the usual suspect clonal hematopoiesis genes appears to be in a separate population than the B-cell lymphoma.

So the relationship of T-cell lymphomas with the mutated hematopoietic stem cells is sort of an exciting and evolving area in HemePath. But stepping aside from the HemePath realm even more generalizable is the sort of increasing focus on using mutation information to inform treatment. Already, there's a number of studies, some published and many ongoing that are monitoring mutations in response to various chemotherapies and the consequences of those mutations. We know that patients with prior chemotherapy have an increased risk of developing a therapy-related myeloid neoplasm.

I hope that we can get to the point where we can be using peripheral blood monitoring of all cancer patients undergoing treatment and use that data to sort of modify the therapeutic regimens and minimize the risk of secondary myeloid neoplasms without affecting the efficacy of the treatment against their primary cancer. Similarly, there are trials ongoing that explore the role of early cardiovascular intervention for patients with CH, and the role of CH in infection remains to be elucidated. So these are all really exciting avenues that could mean that we use peripheral blood CH monitoring to manage a wide range of patient care in the future.

**Julie McDowell:**

Well, thank you, Dr. Kim. Please visit CAP.org. Enter Precision Medicine in the search function to find Dr. Kim's article, which is entitled Chipping Away a Chip, or What It Means If your team or Solid Tumor NGS Panel identifies CH.

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