Onco-histone H3.3K36M reprograms the epigenome of chondroblastomas

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With the expansion of cancer genome sequencing, many chromatin-regulating genes are found mutated. The surprising finding is that of histone proteins, the basic structural components of the human chromatin and is mutated in a variety of cancers. Specifically, a somatic histone H3.3 lysine 36 to methionine (K36M) mutation is identified in over 90% of chondroblastomas. In human genome, there are 13 genes encoding canonical histone H3 proteins that differ from two H3.3 genes by four or five amino acids. H3K36 is conserved among all these histone proteins. Therefore, it is unknown how mutations at one allele of 15 histone H3 genes are linked to Tumorigenesis. We have shown that the levels of H3K36 di- and tri-methylation (H3K36me2/me3) are reduced dramatically in chondroblastomas and chondrocytes bearing the same the genetic mutation as chondroblastomas. Mechanistically, we show that H3.3K36M mutant proteins inhibit enzymatic activity of some, but all H3K36 methyltransferases. In addition, chondrocyte cells with H3.3K36M mutant proteins exhibit several hallmarks of cancer cells. Based on these studies, we propose that H3.3K36M mutant proteins alter epigenomes of specific progenitor cells, which in turn lead to cellular transformation and tumorigenesis.

Speaker Biography

Fang Dong is an Associate Research Scientist in Institute of Cancer Genetics of Columbia University. He has expertise in evaluation and passion in improving the health and wellbeing. His open and contextual evaluation model based on responsive constructivists creates new pathways for improving healthcare. He works under the Leadership of Dr. Zhiguo Zhang.

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