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Hypoxia drives transient site-specific copy gain and drug-resistant gene expression.

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Recommendations:

Very Good 29 May 2015

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NEW FINDING

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This article reports the surprising discovery that hypoxia can induce transient changes in gene copy number in normal and cancerous cells. This follows up on the authors' work that the histone H3K9/36 tri-demethylase, KDM4A, can induce copy number changes {1}. Here they show that hypoxia can induce the same changes in a KDM4A-dependent manner. These changes are rapid and transient, dependent on the cell replicating its DNA in S phase. Returning the cells to normoxic conditions results in the loss of the extra copy numbers. The gene amplifications are specific to certain chromosomal regions, although they do not perform a global gene analysis here. However, they correlate tumors with hypoxic gene expression signatures with amplification of the same specific regions, suggesting that hypoxia leads to copy number changes in actual tumors. While the physiological significance of these copy number changes are still not clear, the authors show that the 'drug resistance oncogene' CKS1B is one of the genes amplified by hypoxic conditions, potentially explaining how these copy number changes could affect tumor growth.

References

1. **KDM4A lysine demethylase induces site-specific copy gain and rereplication of regions amplified in tumors.**
Black JC, Manning AL, Van Rechem C, Kim J, Ladd B, Cho J, Pineda CM, Murphy N, Daniels DL, Montagna C, Lewis PW, Glass K, Allis CD, Dyson NJ, Getz G, Whetstine JR.
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Disclosures

None declared

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Abstract:

ABSTRACT

Copy number heterogeneity is a prominent feature within tumors. The molecular basis for this heterogeneity remains poorly characterized. Here, we demonstrate that hypoxia induces transient site-specific copy gains (TSSGs) in primary, nontransformed, and transformed human cells. Hypoxia-driven copy gains are not dependent on HIF1α or HIF2α; however, they are dependent on the KDM4A histone demethylase and are blocked by inhibition of KDM4A with a small molecule or the natural metabolite succinate. Furthermore, this response is conserved at a... more »
syntenic region in zebrafish cells. Regions with site-specific copy gain are also enriched for amplifications in hypoxic primary tumors. These tumors exhibited amplification and overexpression of the drug resistance gene CKS1B, which we recapitulated in hypoxic breast cancer cells. Our results demonstrate that hypoxia provides a biological stimulus to create transient site-specific copy alterations that could result in heterogeneity within tumors and cell populations. These findings have major implications in our understanding of copy number heterogeneity and the emergence of drug resistance genes in cancer.

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