Reprogramming of metabolism in tumors by co-alterations of proximal enzyme coding and cancer causing genes

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Aberrant metabolism is an emerging hallmark of cancer. Metabolic genes (MG) have been identified as oncogenes (OG) and tumor suppressor genes (TSG) or targets of oncogenic signaling. Cancer is a direct consequence of genomic aberrations, such as somatic copy number alterations (SCNA) that frequently occur in the genome across all cancer types affecting not only oncogenic genes, but also multiple passenger and potential co-driver genes. Besides this, it has been shown that gene order in eukaryotes is not random, but rather subjected to natural selection and hence, of functionality. In addition, cancer gene (CG) enriched regions in the genome can be under co-transcriptional control. The presented work aims at systematically exploring how proximity of MG and cancer causing genes (CG) in the genome can lead to metabolic remodeling. We observed that CG-MG pairs are unexpectedly often proximally positioned in the chromosome and share SCNA susceptible loci, thus being co-altered *i.e.* either co-deleted or co-amplified. We observed this across all cancer types we analyzed and hypothesize that such co-alteration events have a functional impact on oncogenic metabolism. However, the underlying challenge was to delineate cancer metabolism driving genes from passengers. To this end, an analysis and filtering pipeline was developed to identify metabolic cancer genes (MCG) from functionally relevant co-alteration events employing mutual information, network analysis and *a priori* knowledge of functionally relevant gene sets. Our cancer wide (from The Cancer Genome Atlas) genomic data driven approach revealed a hitherto unknown generic mechanism at a large scale elucidating metabolic reprogramming in cancer cells based on linear gene proximities and we identified over 100 new metabolic cancer genes very likely to be involved in reprogramming of cancer cell metabolism.

Reference

Sharma, A.K., Eils, R. and Konig, R. (2016) Copy Number Alterations in Enzyme-Coding and Cancer-Causing Genes Reprogram Tumor Metabolism, *Cancer research*, **76**, 4058-4067.