## 2017 Publications

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### Other publications


**Related Articles**

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**Acetylation Blocks cGAS Activity and Inhibits Self-DNA-Induced Autoimmunity.**

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**Acetylation Blocks cGAS Activity and Inhibits Self-DNA-Induced Autoimmunity.**
Abstract
The presence of DNA in the cytoplasm is normally a sign of microbial infections and is quickly detected by cyclic GMP-AMP synthase (cGAS) to elicit anti-infection immune responses. However, chronic activation of cGAS by self-DNA leads to severe autoimmune diseases for which no effective treatment is available yet. Here we report that acetylation inhibits cGAS activation and that the enforced acetylation of cGAS by aspirin robustly suppresses self-DNA-induced autoimmunity. We find that cGAS acetylation on either Lys384, Lys394, or Lys414 contributes to keeping cGAS inactive. cGAS is deacetylated in response to DNA challenges. Importantly, we show that aspirin can directly acetylate cGAS and efficiently inhibit cGAS-mediated immune responses. Finally, we demonstrate that aspirin can effectively suppress self-DNA-induced autoimmunity in Aicardi-Goutières syndrome (AGS) patient cells and in an AGS mouse model. Thus, our study reveals that acetylation contributes to cGAS activity regulation and provides a potential therapy for treating DNA-mediated autoimmune diseases.

PMID: 30799039 [PubMed - as supplied by publisher]

Extensive Heterogeneity and Intrinsic Variation in Spatial Genome Organization.

Abstract
Several general principles of global 3D genome organization have recently been established, including non-random positioning of chromosomes and genes in the cell nucleus, distinct chromatin compartments, and topologically associating domains (TADs). However, the extent and nature of cell-to-cell and cell-intrinsic variability in genome architecture are still poorly characterized. Here, we systematically probe heterogeneity in genome organization. High-throughput optical mapping of several hundred intra-chromosomal interactions in individual human fibroblasts demonstrates low association frequencies, which are determined by genomic distance, higher-order chromatin architecture, and chromatin environment. The structure of TADs is variable between individual cells, and inter-TAD associations are common. Furthermore, single-cell analysis reveals independent behavior of individual alleles in single nuclei. Our observations reveal extensive variability and heterogeneity in genome organization at the level of individual alleles and demonstrate the coexistence of a broad spectrum of genome configurations in a cell population.

PMID: 30799036 [PubMed - as supplied by publisher]

PPAR-independent action against metabolic syndrome development by fibrates is mediated by inhibition of STAT3 signalling.

Abstract
OBJECTIVES: Metabolic syndrome (MS) is the concurrence of at least three of five medical conditions: obesity, high blood pressure, insulin resistance, high serum triglyceride (TG) and low serum high-density lipoprotein levels. While fibrates are used to treat disorders other than the lowering serum TG, the mechanism by which fibrates decrease MS has not been established.

METHODS: In this study, wild-type and Ppara-null mice fed a medium-fat diet (MFD) were administered gemfibrozil and fenofibrate for 3 months respectively, to explore the effect and action mechanism.

KEY FINDINGS: In Ppara-null mice, MFD treatment increased body weight, adipose tissue, serum TG and impaired glucose tolerance. These phenotypes were attenuated in two groups treated with gemfibrozil and fenofibrate. The STAT3 pathway was activated in adipose and hepatic tissues in positive control, and inhibited in groups treated with gemfibrozil and fenofibrate. The above phenotypes and inflammation were not observed in any wild-type group. In 3T3-L1 adipogenic stem cells treated with high glucose, STAT3 knockdown greatly decreased the number of lipid droplets.

CONCLUSIONS: Low dose of clinical fibrates was effective against MS development independent of PPAR, and this action was mediated by STAT3 signalling inhibition in adipose tissue and, to a lesser extent, in hepatic tissues.
Capillary morphogenesis gene 2 maintains gastric cancer stem-like cell phenotype by activating a Wnt/-catenin pathway.

Oncogene. 2018 07;37(29):3953-3966


Abstract
A growing body of evidence shows that the development and progression of gastric cancer (GC) is mainly associated to the presence of gastric cancer stem-like cells (GCSLCs). However, it is unclear how GCSLC population is maintained. This study aimed to explore the role of capillary morphogenesis gene 2 (CMG2) in GCSLC maintenance and the relevance to GC progression. We found that CMG2 was highly expressed in GC tissues and the expression levels were associated with the invasion depth and lymph node metastasis of GC, and inversely correlated with the survival of GC patients. Sorted CMG2High GC cells preferentially clustered in CD44High stem-like cell population, which expressed high levels of stemness-related genes with increased capabilities of self-renewal and tumorigenicity. Depletion of CMG2 gene resulted in reduction of GCSLC population with attenuated stemness and decrease of invasive and metastatic capabilities with subdued epithelial-mesenchymal transition phenotype in GC cells. Mechanistically, CMG2 interacted with LRP6 in GCSLCs to activate a Wnt/-catenin pathway. Thus, our results demonstrate that CMG2 promotes GC progression by maintaining GCSLCs and can serve as a new prognostic indicator and a target for human GC therapy.

AXL/AKT axis mediated-resistance to BRAF inhibitor depends on PTEN status in melanoma.

Oncogene. 2018 06;37(24):3275-3289

Authors: Zuo Q, Liu J, Huang L, Qin Y, Hawley T, Seo C, Merlino G, Yu Y

Abstract
Multiple genetic mutations within melanoma not only cause lesion-specific responses to targeted therapy but also alter the molecular route of resistance to that therapy. Inactivation of PTEN occurs in up to 30% of melanomas, frequently with a concurrent activating BRAF mutation. PTEN loss regulates both acquired and intrinsic drug resistance. Here we show that AXL/AKT axis mediated-resistance to BRAF inhibitor (BRAFi) depends upon PTEN status in melanoma. Hyperactivation of both ERK and AKT pathways was associated with BRAFi resistance in melanoma with wildtype PTEN. The PTEN-impaired melanoma cells required only the ERK resistance mechanism. Moreover, we identified AXL as a key upstream effector of AKT pathway-associated resistance to BRAFi in melanoma with wildtype PTEN, but not in melanoma with impaired PTEN. Notably, we confirmed that blocking AXL by shRNA and a small molecular inhibitor could rescue the sensitivity of resistant melanoma cells with wildtype PTEN to BRAFi and inhibit their growth in vitro and in vivo. Our study has uncovered a mechanism by which PTEN status contributes to acquired resistance to BRAFi and offers a rational strategy to guide clinical testing in pre-identified subsets of patients who relapse during treatment with BRAFi. The identified protein AXL represents a promising therapeutic target for BRAF mutant melanoma patients with wildtype PTEN.

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