## Recent Publications by Members

### 2017 Publications

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### Other publications

**PubMed**


*Novel EBV LMP-2-affibody and affitoxin in molecular imaging and targeted therapy of nasopharyngeal carcinoma.*
Novel EBV LMP-2-affibody and affitoxin in molecular imaging and targeted therapy of nasopharyngeal carcinoma.

PLoS Pathog. 2020 Jan 06;16(1):e1008223


Abstract

Epstein-Barr virus (EBV) infection is closely linked to several human malignancies including endemic Burkitt's lymphoma, Hodgkin's lymphoma and nasopharyngeal carcinomas (NPC). Latent membrane protein 2 (LMP-2) of EBV plays a pivotal role in pathogenesis of EBV-related tumors and thus, is a potential target for diagnosis and targeted therapy of EBV LMP-2+ malignant cancers. Affibody molecules are developing as imaging probes and tumor-targeted delivery of small molecules. In this study, four EBV LMP-2-binding affibodies (ZEBV LMP-212, ZEBV LMP-2132, ZEBV LMP-2137, and ZEBV LMP-2142) were identified by screening a phage-displayed LMP-2 peptide library for molecular imaging and targeted therapy in EBV xenograft mice model. ZEBV LMP-2 affibody has high binding affinity for EBV LMP-2 and accumulates in mouse tumor derived from EBV LMP-2+ xenografts for 24 h after intravenous (IV) injection. Subsequent fusion of Pseudomonas exotoxin PE38KDEL to the ZEBV LMP-2 142 affibody led to production of Z142X affitoxin. This fused Z142X affitoxin exhibits high cytotoxicity specific for EBV+ cells in vitro and significant antitumor effect in mice bearing EBV+ tumor xenografts by IV injection. The data provide the proof of principle that EBV LMP-2-specific affibody molecules are useful for molecular imaging diagnosis and have potentials for targeted therapy of LMP-2-expressing EBV malignancies.

PMID: 31905218 [PubMed - as supplied by publisher]

Lifestyle Factors and Risk of Myeloproliferative Neoplasms in the NIH-AARP Diet and Health Study.

Int J Cancer. 2020 Jan 06;:


Abstract

The etiology of Philadelphia chromosome negative myeloproliferative neoplasms (MPN) is largely unknown. We assessed potential associations between lifestyle factors and MPN risk in the NIH-AARP Diet and Health Study. In this prospective cohort with 463,049 participants aged 50-71 years at baseline (1995-1996) and a median follow-up of 15.5 years, we identified 490 MPN cases, including 190 with polycythemia vera (PV) and 146 with essential thrombocythemia (ET). Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Smoking was not associated with MPN risk in the overall cohort, but analyses stratified by sex suggested that smoking increased the risk of MPN in women (former smoker vs. non-smokers, HR=1.43, 95% CI: 1.03-2.00, p=0.03; current smokers vs. non-smokers, HR=1.71, 95% CI: 1.08-2.71, p=0.02). Coffee consumption was inversely associated with the risk of PV (high vs. low intake, HR=0.53, 95% CI: 0.33-0.84, p-trend<0.01), but not the risk of ET or MPN overall. Further analysis revealed an inverse association between amount of caffeine intake and PV risk (high vs. low intake, HR=0.55, 95% CI: 0.39-0.79, p-trend<0.01). While the consumption of caffeinated coffee appeared to confer a protective effect against PV, the consumption of decaffeinated coffee did not. This large prospective study identified smoking as a risk factor for MPN in women and suggests that caffeine intake is associated with a lower risk of PV. This article is protected by copyright. All rights reserved.

PMID: 31904114 [PubMed - as supplied by publisher]

CXCR1- or CXCR2-modified CAR T cells co-opt IL-8 for maximal antitumor efficacy in solid tumors.

Nat Commun. 2019 09 05;10(1):4016


Abstract

Chimeric antigen receptor (CAR) T-cell therapy targeting solid tumors has stagnated as a result of tumor heterogeneity, immunosuppressive microenvironments, and inadequate intratumoral T cell trafficking and persistence. Early (3 days) intratumoral presentation of CAR T cells post-treatment is a superior predictor of survival than peripheral persistence. Therefore, we have co-opted IL-8 release from tumors to enhance intratumoral T-cell trafficking through a CAR design for maximal antitumor activity in solid tumors. Here, we demonstrate that IL-8 receptor, CXCR1 or CXCR2, modified CARs markedly enhance migration and persistence of T cells in the tumor, which induce complete tumor regression and long-lasting immunologic memory in pre-clinical models of aggressive tumors such as glioblastoma, ovarian and pancreatic cancer.
Dissecting genetic factors affecting phenylephrine infusion rates during anesthesia: a genome-wide association study employing EHR data.

BMC Med. 2019 08 28;17(1):168

Authors: Zhang Y, Poler SM, Li J, Abedi V, Pendergrass SA, Williams MS, Lee MTM

Abstract

BACKGROUND: The alpha-adrenergic agonist phenylephrine is often used to treat hypotension during anesthesia. In clinical situations, low blood pressure may require prompt intervention by intravenous bolus or infusion. Differences in responsiveness to phenylephrine treatment are commonly observed in clinical practice. Candidate gene studies indicate genetic variants may contribute to this variable response.

METHODS: Pharmacological and physiological data were retrospectively extracted from routine clinical anesthetic records. Response to phenylephrine boluses could not be reliably assessed, so infusion rates were used for analysis. Unsupervised k-means clustering was conducted on clean data containing 4130 patients based on phenylephrine infusion rate and blood pressure parameters, to identify potential phenotypic subtypes. Genome-wide association studies (GWAS) were performed against average infusion rates in two cohorts: phase I (n=1205) and phase II (n=329). Top genetic variants identified from the meta-analysis were further examined to see if they could differentiate subgroups identified by k-means clustering.

RESULTS: Three subgroups of patients with different response to phenylephrine were clustered and characterized: resistant (high infusion rate yet low mean systolic blood pressure (SBP)), intermediate (low infusion rate and low SBP), and sensitive (low infusion rate with high SBP). Differences among clusters were tabulated to assess for possible confounding influences. Comorbidity hierarchical clustering showed the resistant group had a higher prevalence of confounding factors than the intermediate and sensitive groups although overall prevalence is below 6%. Three loci with P<1×10^-6 were associated with phenylephrine infusion rate. Only rs11572377 with P=6.09×10^-7, a 3'UTR variant of EDN2, encoding a secretory vasoconstricting peptide, could significantly differentiate resistant from sensitive groups (P=0.015 and 0.018 for phase I and phase II) or resistant from pooled sensitive and intermediate groups (P=0.047 and 0.018).

CONCLUSIONS: Retrospective analysis of electronic anesthetic records data coupled with the genetic data identified genetic variants contributing to variable sensitivity to phenylephrine infusion during anesthesia. Although the identified top gene, EDN2, has robust biological relevance to vasoconstriction by binding to endothelin type A (ETA) receptors on arterial smooth muscle cells, further functional as well as replication studies are necessary to confirm this association.
Extensive Heterogeneity and Intrinsic Variation in Spatial Genome Organization.

Cell. 2019 03 07;176(6):1502-1515.e10

Authors: Finn EH, Pegoraro G, Brandão HB, Valton AL, Oomen ME, Dekker J, Mirny L, Misteli T

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 - indexed for MEDLINE]

Early T Follicular Helper Cell Responses and Germinal Center Reactions Are Associated with Viremia Control in Immunized Rhesus Macaques.


Abstract
T follicular helper (TFH) cells are fundamental in germinal center (GC) maturation and selection of antigen-specific B cells within secondary lymphoid organs. GC-resident TFH cells have been fully characterized in human immunodeficiency virus (HIV) infection. However, the role of GC TFH cells in GC B cell responses following various simian immunodeficiency virus (SIV) vaccine regimens in rhesus macaques (RMs) has not been fully investigated. We characterized GC TFH cells of RMs over the course of a mucosal/systemic vaccination regimen to elucidate GC formation and SIV humoral response generation. Animals were mucosally primed twice with replicating adenovirus type 5 host range mutant (Ad5hr)-SIV recombinants and systemically boosted with ALVAC-SIVM766Gag/Pro/gp120-TM and SIVM766&CG7V gD-gp120 proteins formulated in alum hydroxide (ALVAC/Env) or DNA encoding SIVenv/SIVGag/rhesus interleukin 12 (IL-12) plus SIVM766&CG7V gD-gp120 proteins formulated in alum phosphate (DNA&Env). Lymph nodes were biopsied in macaque subgroups prevaccination and at day 3, 7, or 14 after the 2nd Ad5hr-SIV prime and the 2nd vector/Env boost. Evaluations of GC TFH and GC B cell dynamics including correlation analyses supported a significant role for early GC TFH cells in providing B cell help during initial phases of GC formation. GC TFH responses at day 3 post-mucosal priming were consistent with generation of Env-specific memory B cells in GCs and elicitation of prolonged Env-specific humoral immunity in the rectal mucosa. GC Env-specific memory B cell responses elicited early post-systemic boosting correlated significantly with decreased viremia postinfection. Our results highlight the importance of early GC TFH cell responses for robust GC maturation and generation of long-lasting SIV-specific humoral responses at mucosal and systemic sites. Further investigation of GC TFH cell dynamics should facilitate development of an efficacious HIV vaccine.IMPORTANCE The modest HIV protection observed in the human RV144 vaccine trial associated antibody responses with vaccine efficacy. TF follicular helper (TFH) cells are CD4+ T cells that select antibody secreting cells with high antigenic affinity in germinal centers (GCs) within secondary lymphoid organs. To evaluate the role of TFH cells in eliciting prolonged virus-specific humoral responses, we vaccinated rhesus macaques with a combined mucosal prime/systemic boost regimen followed by repeated low-dose intrarectal challenges with SIV, mimicking human exposure to HIV-1. Although the vaccine regimen did not prevent SIV infection, decreased viremia was observed in the immunized macaques. Importantly, vaccine-induced TFH responses elicited at day 3 postimmunization and robust GC maturation were strongly associated. Further, early TFH-dependent SIV-specific B cell responses were also correlated with decreased viremia. Our findings highlight the contribution of early vaccine-induced GC TFH responses to elicitation of SIV-specific humoral immunity and implicate their participation in SIV control.

PMID: 30463978 [PubMed - indexed for MEDLINE]