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Herpes simplex encephalitis (HSE) is the most common infectious disease of the central nervous system worldwide. However, the pathogenesis of HSE is not clear. Research has shown that the immune response mediated by the toll-like receptor 3 (TLR3) signaling pathway is essential to protect the central nervous system against herpes simplex virus (HSV) infection. However, an excessive immune response may cause tissue damage accompanied by pathological changes. The aim of this study was to explore the molecular mechanism via which corilagin controls HSE through the TLR3 signaling pathway in vitro and in vivo. Cells and mice were pre-treated with polyriboinosinic polyribocytidylic acid poly(IC) or HSV type 1, and then treated with corilagin. After treatment, the mRNA and protein levels of TLR3, TLR-like receptor-associated interferon factor (TRIF), tumor necrosis factor (TNF) receptor type 1-associated DEATH domain protein (TRADD), TNF receptor-associated factor (TRAF) 3 and 6, nuclear factor-kappa-B (NF-B) essential modulator (NEMO), P38, and interferon regulatory factor 3 (IRF3) were decreased. Interleukin-6 (IL-6), TNF-, and type 1 interferon- were also decreased. When TLR3 expression was silenced or increased, corilagin still inhibited the expression of TLR3 and its downstream mediators. Hematoxylin-eosin (HE) staining and immunohistochemical examinations of mouse brain tissues revealed that corilagin lessened the degree of brain inflammation. Altogether, these results suggest that corilagin may regulate the immune response in HSE and relieve inflammatory injury by interfering with the TLR3 signaling pathway. PMCID PMC6497770 PMID 31080403 84Similar articles

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85Prognostic significance of IFITM1 expression and correlation with microvessel density and epithelial-mesenchymal transition signature in lung adenocarcinoma.

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We evaluated the relationship between interferon-induced transmembrane protein 1 (IFITM1) expression, epithelial-mesenchymal transition (EMT) signature and angiogenesis in lung adenocarcinoma. Additionally, we examined prognostic significance of IFITM1 according to pTNM stage to confirm that IFITM1 can serve as a complement to the pTNM stage. A total of 141 lung adenocarcinoma specimens were evaluated retrospectively by immunohistochemical staining for IFITM1, EMT markers (e-cadherin, -catenin, and vimentin), and CD31 to measure microvessel density. IFITM1was expressed in 46.8correlated with increased microvessel density (P=0.048). However, IFITM1 expression was not associated with three EMT markers. In a multivariate analysis, IFITM1 was an independent prognostic factor for overall survival in a multivariate analysis (hazard ratio 2.59, P=0.01). Online database with data from 720 lung adenocarcinoma patients also revealed a negative prognostic significance of IFITM1 (P¡0.001). Furthermore, high IFITM1 expression was significantly correlated with decreased OS rates in each pTNM stage. IFITM1 is significantly correlated with angiogenesis and it may be used as a useful additional prognostic marker to aid pTNM classification. Copyright 2019 Elsevier GmbH. All rights reserved. PMID 31079850 90Similar articles

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91Management of chronic myeloid leukemia during pregnancy a retrospective analysis at a single center.

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We analyzed the management and outcomes of pregnancies of patients with chronic myeloid leukemia at a single center over fifteen years. Among the 203 CML female patients, there were ten pregnancies in seven women, all of them not planned. In three cases, the chronic myeloid leukemia diagnosis was made during pregnancy. Five patients received tyrosine kinase inhibitors in the first weeks of pregnancy and the drug was interrupted until delivery. One patient lost complete cytogenetic response, and two patients lost the hematological response. A patient with a stable major molecular response had two successful pregnancies without loss of response. There were four premature births. There were no maternal adverse events, fetal malformation or death. All patients received Interferon-alpha during gestation, and two received hydroxyurea for a short period. Leukapheresis was performed in two patients for hyperleukocytosis control. One patient with sickle cell disease died from disease progression six months after delivery. CONCLUSIONS The tyrosine kinase inhibitors ministration should be interrupted during pregnancy. Patients should be advised to achieve a stable and deep molecular response if they plan to conceive, to avoid the risk of disease progression. Copyright 2019 Associao Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. All rights reserved. PMID 31079659 98Similar articles

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99Mutations in Hepatitis D Virus Allow It to Escape Detection by CD8+ T Cells and Evolve at the Population Level.

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BACKGROUND AIMS Hepatitis D virus (HDV) superinfection in patients with hepatitis B virus (HBV) is associated with rapid progression to liver cirrhosis and hepatocellular carcinoma. Treatment options are limited, and no vaccine is available. Although HDV-specific CD8+ T cells are thought to control the virus, little is known about which HDV epitopes are targeted by virus-specific CD8+ T cells or why these cells ultimately fail to control the infection. We aimed to define how HDV escapes the CD8+ T-cell-mediated response. METHODS We collected plasma and DNA samples from 104 patients with chronic HDV and HBV infection at medical centers in Europe and the Middle East, sequenced HDV, typed human leukocyte antigen (HLA) class I alleles from patients, and searched for polymorphisms in HDV RNA associated with specific HLA class I alleles. We predicted epitopes in HDV that would be recognized by CD8+ T cells and corresponded with the identified virus polymorphisms in patients with resolved (n = 12) or chronic (n = 13) HDV infection. RESULTS We identified 21 polymorphisms in HDV that were significantly associated with specific HLA class I alleles (P ¡ .005). Five of these polymorphisms were found to correspond to epitopes in HDV that are recognized by CD8+ T cells; we confirmed that CD8+ T cells in culture targeted these HDV epitopes. HDV variant peptides were only partially cross-recognized by CD8+ T cells isolated from patients, indicating that the virus had escaped detection by these cells. These newly identified HDV epitopes were restricted by relatively infrequent HLA class I alleles, and they bound most frequently to HLA-B. In contrast, frequent HLA class I alleles were not associated with HDV sequence polymorphisms. CONCLUSIONS We analyzed sequences of HDV RNA and HLA class I alleles that present epitope peptides to CD8+ T cells in patients with persistent HDV infection. We identified polymorphisms in the HDV proteome that associate with HLA class I alleles. Some variant peptides in epitopes from HDV were only partially recognized by CD8+ T cells isolated from patients; these could be mutations that allow HDV to escape the immune response, resulting in persistent infection. HDV escape from the immune response was associated with uncommon HLA class I alleles, indicating that HDV evolves, at the population level, to evade recognition by common HLA class I alleles. Copyright 2019 AGA Institute. Published by Elsevier Inc. All rights reserved. PMCID PMC6486497 Free PMC Article PMID 30768983 Indexed for MEDLINE 129Similar articles 130Icon for Elsevier Science 131Icon for PubMed Central

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132Design and Synthesis of A PD-1 Binding Peptide and Evaluation of Its Anti-Tumor Activity.

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Immune-checkpoint blockades, suchas PD-1 monoclonal antibodies, have shown new promising avenues to treat cancers. Failure responsesof many cancer patients to these agents have led to a massive need for alternative strategies to optimize tumor immunotherapy. Currently, new therapeutic developments involve peptide blocking strategies, as they have high stability and low immunogenicity. Here, we have designed and synthesized a new peptide FITC-YT-16 to target PD-1. We have studied FITC-YT-16 by various experiments, including Molecular Operating Environment MOE modeling, purification testing by HPLC and LC mass, peptidePD-1 conjugation and affinity by microscale thermophoresis (MST), and T cell immune-fluorescence imaging by fluorescence microscopy and flow cytometry. The peptide was tested for its ability to enhanceT cell activity against tumor cell lines, including TE-13, A549, and MDA-MB-231. Lastly, we assessed T cell cytotoxicity under peptide treatment. YT-16PD-1 interaction showed a high binding affinity as a low energy complex that was confirmed by MOE. Furthermore, the peptide purity and molecular weights were 90.96FITC-YT-16 interacted with PD-1 at a Kd value of 17.8 2.6 nM. T cell imaging and flow cytometry revealed high affinity of FITC-YT-16 to PD-1. Interestingly, FITC-YT-16 efficiently blocked PD-1 signaling pathways and promoted T cell inflammatory responses by elevating IL-2 and INF- levels. Moreover, FITC-YT-16 has the ability to activate T cell cytotoxicity. Therefore, FITC-YT-16 significantly enhanced T cell anti-tumor activity by blocking PD-1PD-L1 interactions. PMCID PMC6386944 Free PMC Article PMID 30699956 Indexed for MEDLINE 139Similar articles 140Icon for Multidisciplinary Digital Publishing Institute (MDPI) 141Icon for PubMed Central

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142Cytokine-induced memory-like natural killer cells have enhanced function, proliferation, and in vivo expansion against ovarian cancer cells.

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OBJECTIVE Natural killer (NK) cells are lymphocytes well suited for adoptive immunotherapy. Attempts with adoptive NK cell immunotherapy against ovarian cancer have proven unsuccessful, with the main limitations including failure to expand and diminished effector function. We investigated if incubation of NK cells with interleukin (IL)-12, IL-15, and IL-18 for 16h could produce cytokine-induced memory-like (CIML) NK cells capable of enhanced function against ovarian cancer. METHODS NK cells were preactivated briefly with IL-12, IL-15, and IL-18, rested, then placed against ovarian cancer targets to assess phenotype and function via flow cytometry. Real-time NK-cell-mediated tumor-killing was evaluated. Using ascites cells and cell-free ascites fluid, NK cell proliferation and function within the immunosuppressive microenvironment was evaluated in vitro. Finally, CIML NK cells were injected intraperitoneal (IP) into an in vivo xenogeneic mouse model of ovarian cancer. RESULTS CIML NK cells demonstrate enhanced cytokine (IFN-) production and NK-cell-mediated killing of ovarian cancer. NK cells treated overnight with cytokines led to robust activation characterized by temporal shedding of CD16, induction of CD25, and enhanced proliferation. CIML NK cells proliferate more with enhanced effector function compared to controls in an immunosuppressive microenvironment. Finally, human CIML NK cells exhibited potent antitumor effects within a xenogeneic mouse model of ovarian cancer. CONCLUSIONS CIML NK cells have enhanced functionality and persistence against ovarian cancer in vitro and in vivo, even when exposed to ascites fluid. These findings provide a strategy for NK cell-based immunotherapy to circumvent the immunosuppressive nature of ovarian cancer. Copyright 2019. Published by Elsevier Inc. PMCID PMC6430659 Available on 2020-04-01 PMID 30658847 Indexed for MEDLINE 153Similar articles 154Icon for Elsevier Science

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155Role of IL-10 in inhibiting protective immune responses against infection with heterologous Plasmodium parasites.

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Malaria is induced by infection with Plasmodium parasites, which are genetically diverse, and the immune response to Plasmodium infection has both allele-specific and cross-reactive components. To determine the role of the cross-reactive immune response in the protection and disease manifestation in heterologous Plasmodium infection, we used infection models of P. chabaudi chabaudi (Pcc) and P. berghei ANKA (PbA). CD4+ T cells primed with Pcc infection exhibited strong cross-reactivity to PbA antigens. We infected C57BL6 mice with Pcc and subsequently treated them with an anti-Plasmodium drug. The Pcc-primed mice exhibited reduced parasitemia and showed no signs of experimental cerebral malaria after infection with PbA. CD4+ T cells from the Pcc-primed mice produced high levels of IFN- and IL-10 in response to PbA early after PbA infection. The blockade of IL-10 signaling with anti-IL-10 receptor antibody increased the proportion of activated CD4+ and T cells and the IFN- production by CD4+ T cells in response to PbA antigens, while markedly reducing the levels of parasitemia. In contrast, IL-10 blockade did not have a significant effect on parasitemia levels in unprimed mice after PbA infection. These data suggest a potent regulatory role of IL-10 in the cross-reactive memory response to the infection with heterologous Plasmodium parasites leading to the inhibition of the protective immunity and pathogenesis. Copyright 2019 Elsevier B.V. All rights reserved. PMID 30639137 Indexed for MEDLINE 162Similar articles 163Icon for Elsevier Science

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164Prospects for the use of spherical gold nanoparticles in immunization.

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Recent years have seen extremely fast development of new viral nanovaccines and diagnostic agents using nanostructures prepared by biological and chemical synthesis. We used spherical gold nanoparticles (average diameter, 15 nm) as a platform for the antigen for swine transmissible gastroenteritis virus (TGEV). The literature data demonstrate that immunization of animals with the TGEV antigen coupled to gold nanoparticles (GNPs) not only activates antigen-presenting cells but also increases the proliferative activity of splenic lymphoid (antibody-forming) cells. The contents of -IFN, IL-1, and IL-6 in animals immunized with GNP-antigen conjugates were found to be higher than those in intact animals or in animals given the antigen alone. The increased concentration of IL-1 in the immunized animals directly correlated with the activity of macrophages and stimulated B cells, which produce this cytokine when activated. The increased concentration of IL-6 indicates that the injected preparations are stimulatory to cellular immunity. Immunization with the TGEV antigen conjugated to GNPs as a carrier activates the respiratory activity of lymphoid cells and peritoneal macrophages, which is directly related to their transforming activity and to the activation of antibody generation. Furthermore, the use of this conjugate allows marked improvement of the structure of the animals' immune organs and restores the morphological-functional state of these organs. The microanatomical changes (increased number of follicles) indicate the activation of the B-dependent zone of the spleen and, consequently, the development of a humoral-type immunological reaction. The degradative processes observed in the animals immunized with TGEV antigen alone are evidence of weak resistance to pathogen attack. These results can be used to develop vaccines against this infection by employing TGEV antigen coupled to gold nanoparticles as a carrier. PMID 30402771 Indexed for MEDLINE 173Similar articles 174Icon for Springer

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175Production of IL-35 by Bregs is mediated through binding of BATF-IRF-4-IRF-8 complex to il12a and ebi3 promoter elements.

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IL-10 and IL-35 suppress excessive immune responses and therapeutic strategies are being developed to increase their levels in autoimmune diseases. In this study, we sought to identify major cell types that produce both cytokines in-vivo and to characterize mechanisms that regulate their production. Experimental autoimmune uveitis (EAU) is a CNS autoimmune disease that serves as model of human uveitis. We induced EAU in C57BL6J mice and investigated whether T cells, B lymphocytes, or myeloid cells are the major producers of IL-10 or IL-35 in blood, lymph nodes (LNs), spleen, and at the site of ocular inflammation, the neuroretina. Analysis of these tissues identified B cells as the major producers of IL-10 and IL-35 in-vivo. Compared to regulatory T cells (Tregs), IL-10- or IL-35-producing regulatory B cells (Bregs) are substantially expanded in blood, LNs, spleen, and retina of mice with EAU. We performed EMSA and chromatin immunoprecipitation (ChIP) assays on activated B cells stimulated with IL-35 or TLR agonists. We found that BATF, IFN regulatory factor (IRF)-4, and IRF-8 transcription factors were recruited and bound to AP1-IRF-composite elements (AICEs) of il12a, ebi3, andor il10 loci, suggesting their involvement in regulating IL-10 and IL-35 transcriptional programs of B cells. Showing that B cells are major source of IL-10 and IL-35 in-vivo and identifying transcription factors that contribute to IL-10 and IL-35 expression in the activated B-cell, suggest that the BATFIRF-4IRF-8 axis can be exploited therapeutically to regulate physiological levels of IL-10IL-35-Bregs and that adoptive transfer of autologous Bregs might be an effective therapy for autoimmune and neurodegenerative diseases. 2018 Society for Leukocyte Biology. PMID 30117603 Indexed for MEDLINE 180Similar articles 181Icon for Wiley

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182Genome-Wide DNA Methylation Analysis in Systemic Sclerosis Reveals Hypomethylation of IFN-Associated Genes in CD4+ and CD8+ T Cells.

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Epigenetic modifications, including DNA methylation, play an important role in the pathogenesis of autoimmune diseases. In this study, we characterized the DNA methylome in primary T cells of patients with systemic sclerosis. Genome-wide DNA methylation assays of CD4+ and CD8+ T cells from 24 systemic sclerosis patients and 24 matched controls were conducted and differentially methylated regions were validated. In the discovery stage, we found that hypomethylation of genes involved in the type I IFN signaling pathway was significantly enriched in both CD4+ (P = 7.59 10-6) and CD8+ (P = 2.10 10-8) differentially methylated regions. In the validation stage, we confirmed these changes for five type I IFN-associated genes. In addition, protein levels of both type I IFN- (P ¡ 0.0001) and (P = 0.002) were significantly elevated in the sera of systemic sclerosis patients. Moreover, significant associations between type I IFN- protein levels with the DNA methylation status as well as the expression profiles of these IFN-associated genes were confirmed. In conclusion, the type I IFN pathway is dysfunctional at the epigenetic level in systemic sclerosis patients, indicating that hypomethylation and upregulation of type I IFN-associated genes might be critical in systemic sclerosis pathogenesis. Copyright 2017 The Authors. Published by Elsevier Inc. All rights reserved. PMID 29248544 Indexed for MEDLINE 200Similar articles 201Icon for Elsevier Science

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202AKT1 distinctively suppresses MyD88-depenedent and TRIF-dependent Toll-like receptor signaling in a kinase activity-independent manner.

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We found that AKT1, a primary effector molecule of PI3K-AKT signaling, distinctively suppressed Toll-like receptor (TLR)-mediated MyD88-dependent and TollIL-1R domain-containing adaptor inducing IFN- (TRIF)-dependent signaling by inhibiting NF-B activation and IRF3 activity independently of its kinase activity. In AKT1 knockout RAW264.7 cells, lipopolysaccharide (LPS)-induced transcription and protein production of cytokines including IL-1 and TNF- (regulated by the MyD88-dependent pathway), as well as IFN- and RANTES (C-C motif chemokine ligand 5 CCL-5; regulated by the TRIF-dependent pathways) was enhanced compared to wild type cells. In response to LPS stimulation, AKT1 knockout cells also exhibited enhanced NF-B and IFN- promoter activities, which were reduced to a level comparable to that in wild type cells by complementation with either AKT1 or its kinase-dead mutant (AKT1-KD). Expression of AKT1 or AKT1-KD similarly suppressed NF-B and IFN- promoter activities induced by LPS and other TLR ligands in wild type cells. Analysis of NF-B activation caused by transient expression of proteins involved in the MyD88-dependent pathway in TLR signaling revealed that AKT1 suppressed signaling that occurs between activation of IKK and that of NF-B. In contrast, AKT1 appeared to suppress the IFN- promoter through inhibition of IRF3 activity itself. These results demonstrate a novel, non-kinase function of AKT1 that inhibits TLR signaling, and suggest the multifunctional nature of AKT1. Copyright 2017 Elsevier Inc. All rights reserved. PMID 29242168 Indexed for MEDLINE 206Similar articles 207Icon for Elsevier Science

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