019 Serum RIP1 level as a severity-predictive marker for Stevens-Johnson syndrome and toxic epidermal necrolysis

ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening diseases, such as maculopapular exanthema (ME) and erythema multiforme (EM) at the early stage. Although keratinocytes have been suggested to die as apoptosis in SJS/TEN, our recent study revealed that necroptosis, programmed necrosis, also contribute to keratinocyte death in SJS/TEN. Necroptosis is mediated by receptor-interacting kinase-3 (RIK3) and mixed lineage kinase domain-like pseudokinase phosphorylation. We aim to investigate whether serum RIP1 levels serve as a predictive biomarker for SJS/TEN severity. The serum samples were obtained from patients with SJS/TEN (n=11), EM major (n=19), EM minor (n=5) and ME (n=6) in the acute phase. SJS/TEN group have significantly higher serum RIP1 levels than the other groups (EM major: P<0.002, EM minor: P<0.003, ME: P<0.003, healthy controls: P<0.002). Also in the EM major group, serum RIP1 levels were significantly higher than in the healthy controls (P<0.006). In addition, positive correlations were found between serum RIP1 levels and the frequency of keratinocyte death in histopathological examination, body temperature, mucosal involvement, and organ dysfunction. We also analyzed changes in serum RIP1 levels after initiation of treatment (S: n=4; EM: n=4) and after clinical recovery (S: n=1; EM: n=3). In all these samples, serum RIP1 levels decreased after treatment. We showed the clinical usefulness of serum RIP1 levels as a differential or prognostic marker for ME, EM or SJS/TEN. By predicting of the severity at the early stage, we can start appropriate treatment earlier.

020 Profile of BP180 and BP230-specific IgG autoantibodies in bullous pemphigoid

ABSTRACT

Background: Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by autoantibodies against BP180 and BP230. There is emerging evidence that IgG autoantibodies against BP230 play an important role in the pathogenesis of BP. Objective: To determine the rate of anti-BP230 IgG and anti-BP230 IgG in BP, and to evaluate their diagnostic relevance in BP sera. Methods: We collected serum samples from 156 patients who met the clinical and immunologic, and histologic features consistent with BP. In addition, 10 control individuals were included for comparison. We used commercially available IgG enzyme-immunosorbent assay (ELISA) to detect IgG and IgE ELISAs for both BP180 and BP230. A receiver operating characteristic (ROC) curve was used to evaluate the ability of the ELISA to detect specific IgG and IgE antibodies in sera. Results: The results of this study indicated that most BP patients exhibit elevated IgG levels in the serum. IgG autoantibodies to both BP180 and BP230 can be detected in BP sera. The results of total IgG and anti-BP10 IgG ELISAs are well correlated. In BP patients, the positivity rate of anti-BP180 IgG is higher than anti-BP180 IgE. IgG anti-BP230 autoantibodies seemed to be pathogenic in BP.

021 Nanoparticle vaccine of cervical cancer based E7-HSP110 activate the exclusive killing-tumor response of CD8+ T cells in mice

ABSTRACT

HPV16 E7 protein has been recognized as a target in the design of therapeutic vaccines for cervical cancer. However, many epitope vaccines have been limited in practical application due to design defects. It is still necessary to explore new vaccine forms to further enhance its immunogenicity to HPV16 related tumors. In this study, we aimed to design novel self-assembled nanoparticle HPV16 vaccine through combining RGD-GCG-K and fusion double expression plasmid RRES2-3:E7-HSP110-1E0 (RGD-GCG-K,RRES2-3:E7-HSP110-1E0). The nanoparticles were prepared and identified by gel retardation, transmission electron microscopy and DNase I protection assays. Flow cytometry, ex vivo specific cytotoxicity of CTL-lactate dehydrogenase release analysis to evaluate the vaccinated immune responses. Immunization of TC-1 tumor-bearing mice with nanoparticles generated a larger pool of E7-specific CD8+ T cells with increased effector functions than the control groups. The vaccine immunization of TC-1 tumor-bearing mice with nanoparticles generated a larger pool of CD8+ T cells with increased effector functions than the control groups. The in vivo tumor protective effectiveness of nanoparticle was investigated in the prophylactic and therapeutic mouse models. Ultimately, the nanoparticles vaccine targeted for HPV16 E7 onconegates by significantly inhibited the growth of subcutaneous TC-1 tumor. The vaccine form designed in this study not only provides a potential choice for the development of new HPV vaccine, but also provides a new idea for specific immunotherapy of cervical cancer. However, many epitope vaccines have been limited in practical application due to design defects. It is still necessary to explore new vaccine forms to further enhance its immunogenicity to HPV16 related tumors. In this study, we aimed to design novel self-assembled nanoparticle HPV16 vaccine through combining RGD-GCG-K and fusion double expression plasmid RRES2-3:E7-HSP110-1E0 (RGD-GCG-K,RRES2-3:E7-HSP110-1E0). The nanoparticles were prepared and identified by gel retardation, transmission electron microscopy and DNase I protection assays. Flow cytometry, ex vivo specific cytotoxicity of CTL-lactate dehydrogenase release analysis to evaluate the vaccinated immune responses. Immunization of TC-1 tumor-bearing mice with nanoparticles generated a larger pool of E7-specific CD8+ T cells with increased effector functions than the control groups. The vaccine immunization of TC-1 tumor-bearing mice with nanoparticles generated a larger pool of CD8+ T cells with increased effector functions than the control groups. The in vivo tumor protective effectiveness of nanoparticle was investigated in the prophylactic and therapeutic mouse models. Ultimately, the nanoparticles vaccine targeted for HPV16 E7 onconegates by significantly inhibited the growth of subcutaneous TC-1 tumor. The vaccine form designed in this study not only provides a potential choice for the development of new HPV vaccine, but also provides a new idea for specific immunotherapy of cervical cancer.

022 Diet-induced obesity predisposes anti-PD-1 antibody-treated mice to iniquimod-induced psoriasis: dermatitis via immune-related adverse events in cancer patients treated with anti-PD-1

ABSTRACT

Immune checkpoint inhibitors, including anti-PD-1, have led to tremendous progress in cancer treatment. However, severe immune-related adverse events (irAEs) occur in some cancer patients receiving anti-PD-1 treatment. Given that obesity is an exacerbating factor for psoriasis, we hypothesized that obese mice have more exacerbated immune-related psoriasis dermatitis (PD) than lean mice. To investigate anti-PD-1. Obese mice were obtained by feeding C57BL/6 mice with a Western diet (WD) (moderate levels of fat and high levels of simple sugars) while lean mice were fed with a control diet. After feeding for 12 weeks, WD mice weighed 30% more than CD-fed mice. Both groups underwent topical a 5-day IMQ treatment course to induce PD. Compared with lean mice, obese mice had higher baseline expression of poracoid-associated cytokines such as IL-17A (44-fold, P<0.007), IL-23 (2.6-fold, P=0.047), and 1000Ab (39-fold, P=0.002) and higher PD-1 expression (48% vs. 26%, P=0.046 on y5 low T cells, which are major producers of IL-17A in murine PD. After anti-PD-1 treatment, obese mice had an exaggerated skin response to IMQ compared to lean mice (ear thickness change on day 5: 94% vs. 87%, P=0.0001). Our results have clinical implications in that obesity may be a risk factor for exacerbation of psoriasis-like dermatitis during anti-PD-1 treatment. Furthermore, they provide a mechanistic basis for this known complication of checkpoint inhibitor therapy because of the greater baseline expression of PD-1 on IL-17A-producing, y5-low T cells in WD-fed, obese mice.

023 Global knockout of immunomodulatory indolamine 2,3-dioxygenase has no effect on psoriiform lesions in the imiquimod-induced mouse model of psoriasis

ABSTRACT

Indoleamine 2,3-dioxygenase (IDO) is a cytoxic autoimmune enzyme that degrades tryptophan, resulting in tryptophan depletion and the accumulation of metabolites. The expression/activity of IDO in various cells, such as macrophages, dendritic cells, and T cells, has been demonstrated to block T cell responses in a number of situations, including towards allergenic fungi and graft/transplants. IDO induces immune suppression through two nonmutually exclusive mechanisms: (1) IDO degrades tryptophan into kynurenine, thus depleting the microenvironment of this essential amino acid and "starving" immune cells, and (2) IDO-generated kynurenine is actively immune suppressive through mechanisms including the induction of regulatory T cells (Treg) through binding to the aryl hydrocarbon receptor. We hypothesized that IDO knockout mice would exhibit a hyperactive immune response because of decreased Treg function and therefore an exacerbation of the psoriiform phenotype in the imiquimod-induced mouse model of psoriasis, an immune-mediated skin disease. Littermate wild-type and IDO knockout mice were treated with imiquimod, and ear edema, the severity of skin lesions, and the thickness of the epidermis were monitored. Unexpectedly, imiquimod-treated IDO knockout and wild-type mice showed similar ear edema, psoriasis area and severity index (PASI) scores, and epidermal thickness, indicating no effect of IDO gene loss on the skin's response to imiquimod. While these data may suggest a lack of involvement of IDO and Tregs in skin inflammation, other possible mechanisms, such as compensatory changes or the possibility that imiquimod already maximally suppressed Treg function, must also be considered.

024 Differentiation of acute graft-versus-host disease from drug reaction in skin by a novel tissue-based biomarker assay

ABSTRACT

Differentiation of acute graft-versus-host disease from drug reaction in skin by a novel tissue-based biomarker assay

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Acute graft-versus-host disease (GVHD), a serious complication of allogeneic hematopoietic stem cell transplantation (HCT), often involves the skin. Since clinical and microscopic features of GVHD can mimic those of certain drug eruptions, accurate diagnosis can be challenging. Currently, no ancillary testing is available to improve diagnostic certainty. We aimed to develop a tissue-based molecular assay and clinical-molecular fusion model to improve differentiation of GVHD from drug reactions following HCT. We queried our institution's HCT database (2010-2016) for skin biopsy specimens showing vascular interface changes attributable to GVHD or drug reaction, as classified by retrospective review of clinical records. We found 2454 specimens (1984 with tissue-based biomarkers, 470 with serum-based biomarkers, RNAseq) on archived skin biopsy specimens, we designed and tested a quantitative RT-PCR-based biomarker assay and generated clinical-molecular fusion diagnostic models. Of 62 putative tissue-based biomarkers, 26 were included in the assay. Significant differences in gene expression (M1A, M1DA, OAS, LMJIA, GSTM5, and SPPI) were detected between cases of GVHD (n=67) and post-HCT drug reaction with vacuolar interface changes (n=17; p<0.05). An optimal fusion model, incorporating quantitative expression of M1A, M1DA, OAS, LMJIA, GSTM5, and SPPI, was constructed (ROC AUC: 0.89). This novel tissue-based diagnostic clinical-molecular fusion model appeared to distinguish GVHD from drug reactions in this retrospective cohort. Multicenter validation studies are required.