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Original Article

Hybridoma-derived monoclonal antibodies targeting a viscumin epitope: a novel approach for detection and potential therapeutic applications

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Abstract: Mistletoe extracts contain the ribosome inactivating protein viscumin, which exhibits effectiveness in alternative therapies but also presents considerable toxicity risks. Hence, specific and sensitive diagnostics for identifying viscumin exposure should be developed. This study aimed to develop monoclonal antibodies (mAbs) to viscumin and to test their protective capacity against its cytotoxic effects. A peptide epitope, representing A-chain of viscumin of 9 amino acids, was synthesized and conjugated to Bovine Serum Albumin (BSA) for the immunization of BALB/c mice. Spleen cells from immunized mice were fused with SP2/0 myeloma cells to obtain hybridomas. The generated mAbs for viscumin were selected through ELISA and further characterized. The cytotoxicity of viscumin against Hep-G2 cells was conducted with the SRB assay, which revealed a reduction in cell viability, respectively: about 80% at 2.5 µg/mL, 64% at 5 µg/mL, and 46% at 10 µg/mL. Interestingly, it was observed that the mAbs significantly mitigated the cytotoxic activity of viscumin, causing the viability of about 86% at all tested concentrations. Hence, they showed potential for mAbs in developing sensitive diagnostic assays and therapeutic strategies to counteract the toxic effects of viscumin. Further mAb variants' characterization, epitope mapping, and determination of the affinity should be conducted to improve both diagnostic and therapeutic avenues of viscumin-induced toxicity.

Keywords: Hybridoma, monoclonal antibody, viscumin, myeloma, cell culture, SRB assay

Introduction

Mistletoe extracts, derived from Viscum album and several other species, have become increasingly popular in complementary and alternative therapy, even with their presence of toxic compounds such as the ribosome-inactivating proteins (RIPs) viscumin and mistletoe lectins (MLs) [1, 2]. Despite some in vitro studies suggesting potential therapeutic benefits [3], the therapeutic efficacy of these mistletoe extracts is disputed, with documented extreme adverse events such as anaphylaxis, allergic reaction, and cases of lymphoma following use of mistletoe preparations [4, 5]. Inadvertent consumption, particularly in children, is a significant concern [5]. As such, the development of reliable methodologies for diagnosing exposure to viscumin is imperative, particularly in cases of suspected toxicity or adverse reaction to mistletoe preparations.

Current methodologies for diagnosing viscumin exposure fall short. Certain tests can detect mistletoe lectins but lack the desired specificity for viscumin alone [6]. Production of monoclonal antibodies (mAbs) specific for viscumin is a new direction for developing diagnostics and possibly therapeutic interventions. With high specificity and with a high yield, mAbs could become ideal reagents for immunoassays and a range of additional applications [7].

The purpose of this investigation is to produce mAbs specific for a synthetic peptide epitope derived from the A chain of viscumin. It is predicted that such mAbs will have specific and selective binding for viscumin, allowing for its detection. In providing a basis for developing a sensitive and specific assay for viscumin, this work could have important implications for public health and therapeutic management of mistletoe toxicity in a clinical environment.

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Materials and method

Peptide design and conjugation

Multiple sequence alignment of four AB-type protein toxin sequences, sourced from NCBI in FASTA format, revealed a potential 9-mer epitope candidate. The C-terminal 9-mer of Viscumin's catalytic chain, QQTTGEEYF, was selected due to its minimal interference and synthesized by BIOMATIK [8]. To enhance its immunostimulatory potential, the peptide (QQTTGEEYF) was conjugated to bovine serum albumin (BSA) using the glutaraldehyde method. Specifically, 6 mg of BSA and 6 mg of the peptide were combined in 3 ml of pH 7.4 phosphate buffer, homogenized, and filtered (0.45 μm). Subsequently, 1 ml of 20 mM glutaraldehyde was added incrementally and stirred gently for one hour. To prevent microbial contamination, the solution was filtered again (0.2 μm) and dialyzed overnight in 4 liters of pH 7.5 phosphate buffer [9].

Immunization

In this study, two groups of 6- to 8-week-old female BALB/c mice were immunized to compare immune responses. Group 1 received four biweekly injections (20 μg of an epitope-BSA conjugate) via subcutaneous and intraperitoneal routes, while Group 2 received 20 μg of the epitope alone. The first injection included Complete Freund's adjuvant (Sigma-Aldrich), followed by three with Incomplete Freund's adjuvant. Before the final injection, blood was drawn from the eye vein, and serum was analyzed. ELISA results showed strong immunoreactivity to the immunogen. Three days prior to spleen isolation, a fifth injection (without adjuvant) was administered via the tail vein.

Cell fusion and screening of positive clones

Splenocytes were mixed with SP2/0 myeloma cells with the use of a 50% solution of 4000 molecular weight molecular weight polyethylene glycol (PEG) 4000, acting as a fusing reagent [10], following protocols developed by Kohler and Milstein. 1:5 fusion ratio, consisting of splenocytes and myeloma cells, was utilized [11]. Hybridoma cells produced thereafter were then cultured in 96-well plates with DMEM-HAT selection medium supplemented with 20% fetal serum. Hybridoma colonies developed over a period of 7 to 10 days, and efficiency in fusion was determined through a count of colonies developed. Colonies in plates were then screened for monoclonal antibody (mAbs) production and for colony size using the Enzyme-Linked Immunosorbent Assay (ELISA) for overall evaluation. Microscopical examination confirmed positive wells and mAbs-producing wells, and cells in mAbs-producing wells were then passaged in 12-well plates for expansion. After expansion, HAT medium was replaced with HT medium (Sigma-Aldrich) for a period of two weeks for selection of hybrids.

Cloning and propagation of hybridoma cells

Indirect Enzyme-Linked Immunosorbent Assay (ELISA) was employed to identify positive clones and quantify the extent of antibody secretion.

The positive wells were subjected to a series of three subcloning procedures, each facilitated by the technique of limiting dilution. Following a period of two weeks, the supernatant derived from the clones was subjected to an Enzyme-Linked Immunosorbent Assay (ELISA) to evaluate the production of monoclonal antibodies.

96-well plates were coated with Viscumin (10 mg/mL) and incubated overnight at 4°C. Non-specific binding was blocked with 5% non-fat dry milk in PBST for 1 hour at 37°C, followed by three washes. The plates were then incubated with hybridoma cell supernatant and goat anti-mouse IgG-HRP conjugate, each for 1 hour at 37°C with washes in between. After a final wash, OPD was added for color development. The reaction was stopped with 2 M H_2SO_4 and the optical density was measured at 450 nm.

Cells were harvested, resuspended in a freezing medium, and stored at a controlled cooling rate in an isopropanol cell cooler before being transferred to a liquid nitrogen tank for long-term storage.

Monoclonal antibody characterization via SRB assay

This experiment examined the specificity and structural stability of monoclonal antibodies targeting viscumin toxin using the SRB assay. Hep-G2 cells in 96-well plates were treated with mistletoe extract containing viscumin at 2.5, 5, and 10 μg concentrations. Two groups

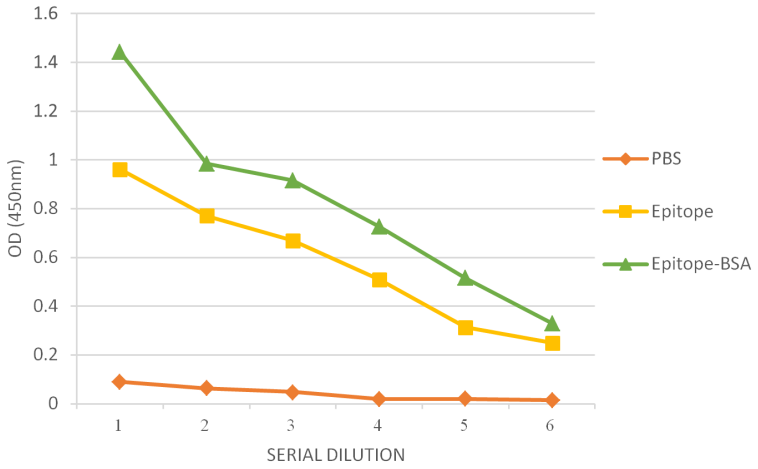

Figure 1. The vertical axis represents the absorbance at 450 nm, while the horizontal axis illustrates the dilution trend ranging from 1:100 to 1:3200. PBS: Mice that received an injection of PBS, serving as the control group. Epitope: Mice that were immunized with a non-conjugated epitope. Epitope-BSA: Mice that were immunized with an epitope conjugated to bovine serum albumin (BSA).

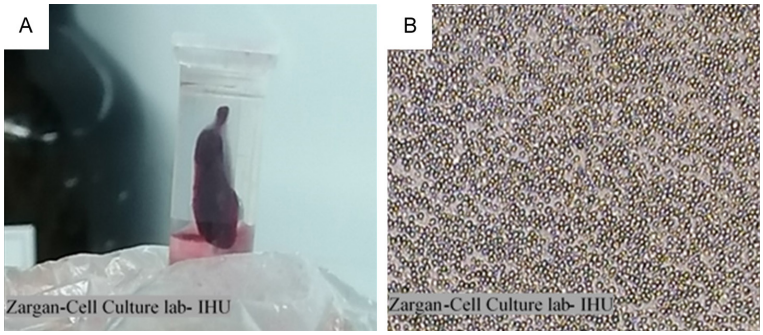

Figure 2. Splenocyte isolation from immunized mouse. A. Isolated spleen from an immunized mouse. B. Isolated splenocytes from the spleen, visualized at 40× magnification using a Zeiss Axiovert 25 Inverted Phase Contrast Fluorescence Microscope.

were established: wells with anti-viscumin epitope antibodies and control wells without. Mistletoe extract was added alongside 2 × 10^4 cells per well, followed by incubation at 37°C. Cells were then fixed by removing the medium and adding 0.5 mL of 5% trichloroacetic acid (TCA), chilled at 4°C for 10 minutes. After four washes, cells were dried and stained with 0.04% sulforhodamine B (SRB) for one hour at room temperature. Unbound dye was cleared with 1% acetic acid (v/v) and water, then 50 mL of 10 mM Tris base (pH 10.5) was added to dissolve the protein-bound dye. Optical density was measured at 490-530 nm.

Results

Immunization and antibody titration

Following the preparation of the antigen and the administration of five injection, a blood sample was procured from the murine subjects through an ocular approach. Subsequently, an ELISA was conducted on the sera. A statistical analysis of the results demonstrated that antibody production in both groups, immunized with epitope-BSA and epitope alone, was significantly different compared to the controls as seen in **Figure 1**.

Cell fusion and screening of positive wells

Once antibody production was confirmed via ELISA, the selected mouse was euthanized and its spleen was isolated under sterile conditions, as shown in **Figure 2**. Subsequently, splenocytes were isolated and fused with myeloma cells. These fused cells were then cultured in a medium supplemented with Hypoxanthine-Aminopterin-Thymidine (HAT). Microscopic monitoring was conducted immediately after fusion, two days post-fusion, five days pot-fusion and ten days post-fusion, as depicted in **Figure 3**. Once the hybridoma cells achieved an appropriate confluence, the production of antibodies was assessed. This was done by conducting an ELISA on the supernatant. The results confirmed the cells' capability to produce antibodies (**Table 1**). The valuable clones generated through cell fusion resulted in the selection of clone A4 for subsequent applications.

Cloning and propagation of hybridoma cells

Following the selection of cells, a series of limit dilutions were performed on the most promis-

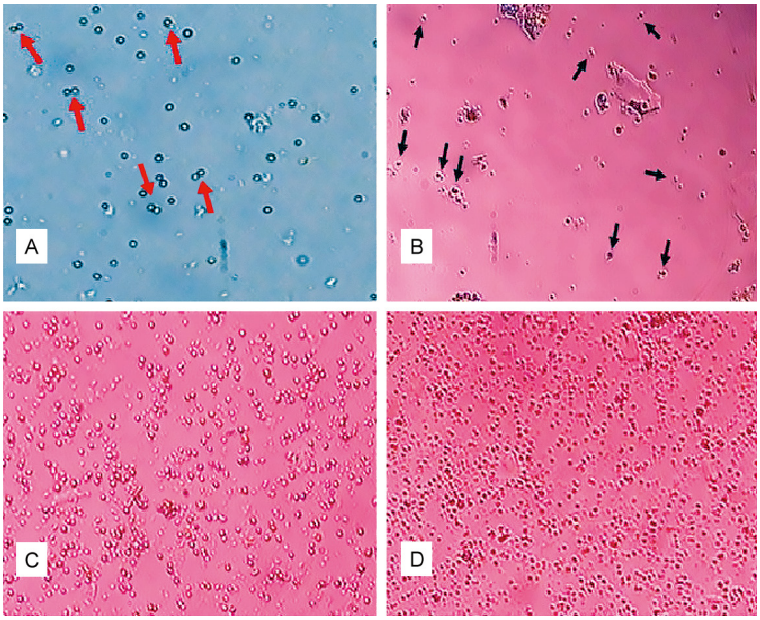

Figure 3. Hybridoma formation post-cell fusion. A. Immediately post-fusion, the fused cells are indicated by red arrows. B. Two days post-fusion the fused cells are indicated by black arrows. C. Five days post-fusion. D. Ten days post-fusion, hybridoma cells are the only ones that have demonstrated growth (40×. Zeiss Axiovert 25 Inverted Phase Contrast Fluorescence Microscope).

Table 1. ELISA screening of antibody-producing hybridoma cells

Clone name	F5	A4	H5	B8
ELISA OD	0.598	1.43	1.089	0.983

ing wells. After three rounds of limit dilution, we were confident that a single cell had been accurately isolated. Assuming the doubling time of hybridoma cells is about 18 hours, the proliferation of the cell lines was calculated using the formula ($2^{x/18}$), with 'x' characterizing the time duration in hours up to day 10 post-first 18 hours, where the estimated cell count reached an approximately limiting dilution of about 8100 cells. Such a result, therefore, confirms the consistency and reproducibility of the experimental protocol used. Subsequent to the proliferation of cells and the attainment of an appropriate confluence, an Enzyme-Linked Immunosorbent Assay (ELISA) was conducted on the supernatant of the hybridoma. The clones were then transferred to a 24-well plate. After a period of two weeks, another ELISA was conducted on the supernatant of the hybridoma that had been cultivated in the 24-well plate. The results confirmed the reliability of these cells for the production of monoclonal antibodies.

Monoclonal antibody characterization

The effect of viscumin toxin on Hep-G2 cells was assessed by the sulforhodamine B (SRB) assay (**Figure 4A**). Results show a dose-dependent decrease in cell viability. Exposure to viscumin at 2.5, 5, and 10 µg/mL produced survival rates of 80%, 64%, and 46%, respectively, demonstrating a very potent cytotoxic effect. A one-way ANOVA revealed a statistically significant difference in cell viability between the groups ($P < 0.001$). Conversely, the presence of the anti-viscumin monoclonal antibody effectively neutralized the cytotoxic effects of viscumin on Hep-G2 cells (**Figure 4B**). Cell viability remained consistently high (~86%) across all tested viscumin concentrations (2.5-10 µg/mL), indicating substantial protection conferred by the antibody. A one-way ANOVA revealed a statistically significant difference in cell viability only between the control group (100%) and all the viscumin + antibody groups (86%, $P < 0.001$). There was no significant difference in cell viability between the different viscumin concentrations in the presence of the antibody ($P > 0.05$).

Discussion

Viscumin, a type 2 ribosome-inactivating protein (RIP) derived from mistletoe, functions similarly to ricin and abrin by disrupting protein synthesis through the removal of adenine from ribosomes. It consists of an enzymatic A-chain and a B-chain responsible for cell binding; however, viscumin is significantly less cytotoxic than ricin and exhibits distinct cellular interactions. Specifically, viscumin binds to the cell surface periphery, in contrast to ricin, which clusters near the cell body. Although low pH restricts direct entry into the cytosol for ricin, abrin, and viscumin, these proteins can enter endocytic vesicles and subsequently reach the

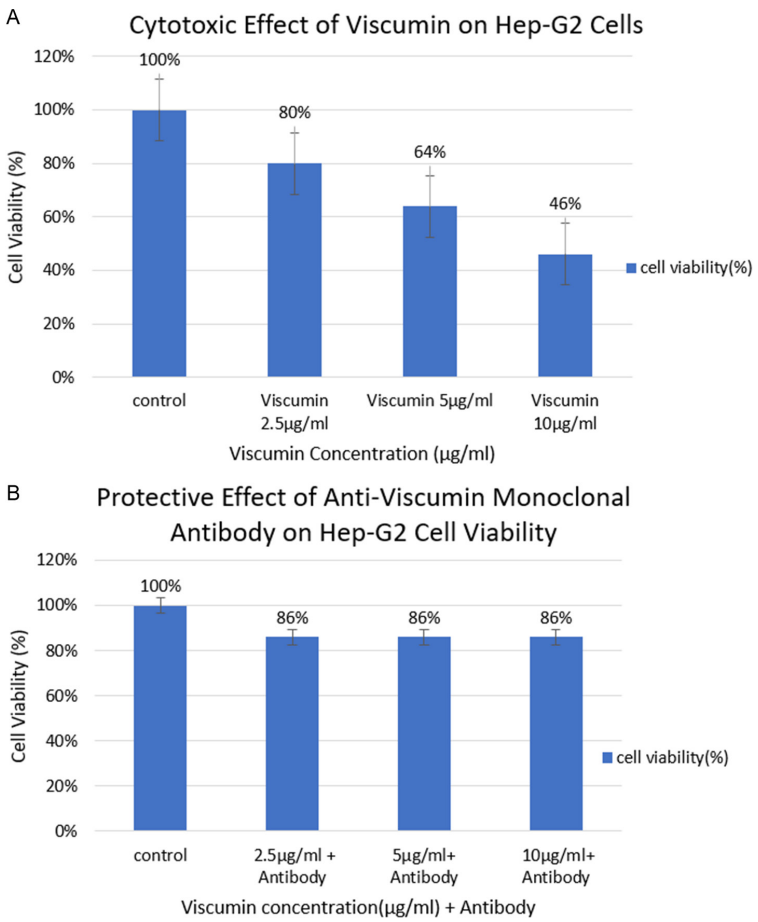

Figure 4. A. Cytotoxic Effect of Viscumin on Hep-G2 Cells. Viscumin exposure decreases cell viability, as measured by the SRB assay, in a dose-dependent manner. Data are presented as mean ± standard deviation (n=3). One-way ANOVA revealed a significant difference between groups ($P < 0.001$). B. Protective Effect of Anti-Viscumin Monoclonal Antibody on Hep-G2 Cell Viability. Anti-viscumin antibody maintained ~86% Hep-G2 cell viability (SRB assay) across all viscumin concentrations (2.5-10 µg/mL), unlike viscumin-only treated cells. ANOVA: significant difference between control (100%) and all antibody-treated groups ($P < 0.001$), but not between antibody-treated groups ($P > 0.05$).

cytosol upon pH normalization. These variations in binding, cytotoxicity, and intracellular trafficking emphasize the unique cellular interactions of viscumin compared to other RIPs [12, 13].

The study followed the vaccination protocol involving both intraperitoneal (IP) and subcutaneous (SC) administration routes Similar to that carried out by Malekie [14]. The antibody production obtained thus supported this route which was universally used due to its ability to stimulate several lymph nodes, thereby enhancing immune response [15].

In the present study, we demonstrate that the BSA-conjugated epitope and the epitope alone substantially stimulated the mice immune system, resulting in a strong increase in antibody production in comparison with the control group. The finding contradicts the commonly accepted hypothesis that small molecules, often defined as haptens because of their small size, do not induce an immune response [16, 17].

Short peptides, even those under 10 amino acids, can trigger an immune response in mouse models by driving adaptive immunity through epitope recognition and T-cell activation via MHC presentation [18, 19]. These interactions underpin effective antigen presentation, proving that brief peptide sequences can elicit robust immune responses [20]. Moreover, their immunogenicity can be improved by certain sequences or modifications, which are useful in the design of vaccines. Besides, even short peptides could also serve as good B cell epitopes to induce antibody production, which is very important for the induction of immunity [21]. Thus, small peptides that can interact with both T and B cells are of interest in immunological applications. Mice that had been immunized with epitope-BSA were deliberately chosen for analysis in the scope of this research. This decision was based on the observed fact that these mice had demonstrated a significantly increased rate of antibody production. A highly pronounced increase in antibody synthesis left them much more fit for the purposes of this study.

In this study, myeloma cells and splenocytes were fused using polyethylene glycol (PEG), consistent with methods reported by Antipova and Tonevitsky [13, 22, 23].

PEG acts as a dehydrating agent; it removes water molecules from the cell surface and thus brings cell membranes closer together, which finally induces cell agglutination and results in the clumping of cells and the establishment of cell to cell contacts [24]. PEG also facilitates the fusion of both plasma and intracellular membranes by altering the structural and dielectric properties of the cell membranes. This process causes subtle changes in lipid packing in the bilayer leaflets and thus promotes membrane fusion [25]. The fused cells were grown on a feeder layer made up of a mixture of normal murine splenocytes and murine peritoneal cells. This contrasts with the approach taken by Neal et al., where the MRC-5 cell line was used as the feeder layer [26]. Despite these differences in methodology, both experiments were successful. In the present study, we used limit dilution techniques with the intention of obtaining isolated single cells, and ELISA was then utilized in order to detect the production of antibodies. These techniques have been used by many researchers for the purpose of obtaining a unique hybridoma clone and simultaneously proving the production of antibodies [27, 28].

Castellettie and co-authors suggested that monoclonal antibodies, produced by the hybridoma technology, specifically recognize linear epitopes [29]. However, our results establish that these antibodies, besides their linear epitope recognition capabilities, can also identify the native protein structure in the Mistletoe plant extract. These results concur with those obtained by Neal's studies [26]. Furthermore, this observation aligns with broader research on monoclonal antibodies against other RIPs. Notably, monoclonal antibodies against ricin and abrin have also demonstrated the ability to target both linear and conformational epitopes [30, 31]. For instance, studies have shown that antibodies like 4C13 against ricin recognize linear epitopes, while others target spatial conformation epitopes [32, 33]. Similarly, antibodies against abrin, such as D6F10, have been shown to have well-delineated neutralizing epitopes, demonstrating the versatility of monoclonal antibodies against RIPs, a property also seen in our viscumin antibodies [31].

The SRB assay results (**Figure 4A**) indicate a clear dose-dependent decrease in the Hep-G2 cell viability following exposure to viscumin. This is consistent with the known cytotoxic mechanisms of type II ribosome-inactivating proteins such as viscumin: RIPs target ribosomes-in particular, the ribosomal RNA 28s, to inhibit protein synthesis, and cell death occurs [34]. For instance, the reduction of cell viability from 80 to 46% shows that viscumin has considerable potency against the Hep-G2 cell line. This dose-dependent response is consistent with past reports on the effect of mistletoe extracts and purified viscumin on different cancer cell lines, including Hep-G2 [35].

On the contrary, the anti-viscumin monoclonal antibody reduces the cytotoxicity of viscumin (**Figure 4B**). In the presence of the antibody, cell viability remained remarkably constant at ~86% over the whole concentration range of viscumin tested (2.5-10 μg/mL), indicating that high levels of effector activity are established. Although not conferring total protection, their presence would suggest an appreciable improvement in cell survival relative to viscumin treatment alone. This study raises hypotheses regarding the antibody's protective mechanism, which may include: (i) binding to viscumin to obstruct its interaction with cell receptors, thereby preventing entry; (ii) attaching to viscumin to interfere with its ribosomal targeting; or (iii) entering cells alongside viscumin and modifying its processing to cease the inhibition of protein synthesis. Yet, with ~86% cell viability compared to 100% in controls, the protection isn't complete. This could reflect an insufficient antibody dose or a less-than-optimal affinity for viscumin, leaving some toxin active.

We evaluated the antibody's effect in vitro on Hep-G2 cells. Limited by access to other cell lines, we recommend future studies test it across a wider range and in animal models to clarify its mechanism and efficacy. Our findings suggest it could quickly detect viscumin in mistletoe users, paving the way for faster diagnostics and therapies.

Disclosure of conflict of interest

None.

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