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APPLICATION OF COBRA VENOM FACTORS IN LIFE SCIENCES

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Abstract: Complement is an important part of the immune system and plays an important role in the body's natural defense and immune regulation. Excessive activation of complement can cause inflammation and tissue damage. In particular, excessive activation of the alternative complement pathway plays an important role in the occurrence and development of a series of diseases and symptoms. Role. Cobra venom factor, a specific activating protein of the complement alternative pathway isolated from cobra venom, has played an important role in complement-related research use. Here is a review of the application of cobra venom factors in life sciences.
Keywords: Cobra venom factor; Complement; Complement alternative pathway; Endothelial cells; Inflammation

1 APPLICATION OF CVF IN THE STUDY OF THE REGULATORY MECHANISM OF THE ALTERNATIVE COMPLEMENT PATHWAY

Complement is an important part of the immune system and plays an important role in the body's natural defense and immune regulation. [1-2]. complement system By Limited protein decomposition system composed of more than 30 protein components system, its activation is 3 ways: Classical pathway, bypass pathway and coagulation Setin pathway. Normal activation of complement helps to perform its physiological functions, But overactivation can cause inflammation and tissue damage [2-4], especially the excessive activation of the alternative complement pathway, is responsible for the occurrence of a series of diseases and symptoms. played an important role in the development of [5-6]. In exploring and revealing the regulatory mechanism of complement alternative pathway activation and the role of complement in related symptoms and pathological injuries In research on the pathological effects of cobra venom, an egg derived from cobra venom White molecules played an extremely important role.
already In the early 20th century, it was discovered that cobra venom can inhibit serum complement. 20th Century It was only after the 1960s that cobra venom factors with anti-complement activity were isolated from cobra venom. (cobra venom factor, CVF) [7-8]. in subsequent 30 Over the years, from the distribution Highly similar protein molecules have been isolated from the venom of cobras from different regions, all using CVF this name [9-14]. to different sources CVF Studies on the physical and chemical properties and structure of [15], CVF By An acidic glycoprotein molecule composed of three polypeptide chains covalently bonded, with a relative molecular mass of generally 1.4 × 10 5 ~1.56 × 10 5, among which The alpha chain is approximately 6.85 × 10 4, the β chain is approximately 4.85 × 10 4, γ chain is approximately 3.2 × 10 4. from certain sources CVF of gamma chain in SDS Electrophoresis shows microscopic heterogeneity, showing 3 to 5 very close bands, possibly due to Caused by the unevenness of the C- terminal. CVF and complement components C3 is highly homologous in structure and function [16]. CVF In serum, it can interact with complement B factors combine to form complex CVFB, in which B factor is D Recognized and enzymatically cleaved by factors to form CVFB. CVFB have C3/C5 convertase activity and is related to endogenous C3/C5 convertase compared to CVFBb Very stable and resistant to complement alternative pathway regulatory proteins H factor sum I inactivation of factors, Therefore, it has a long half-life and can be continuously activated C3 and C5, ultimately leading to depletion of alternative complement pathway activity [16].
It is based on CVF Specificity and efficiency in activating the alternative complement pathway sex and related to the high level of complement alternative pathway activation pathway under pathological or physiological conditions.
The alternative complement pathway is complement The oldest of the 3 activation pathways [17], which plays an extremely important role in resisting the invasion of foreign pathogens. However, in the history of complement system research, the understanding and elucidation of the alternative pathway was later than that of the classical pathway. And in this recognition Cheng Zhong, CVF It played an important role. complement alternative pathway C3/ C5 conversion The formation of enzymes is critical to the function of this pathway. With the help of CVF, enabling the bypass pathway Have a deeper understanding of the structural biology and enzymatic properties of C3/C5 convertase [18-19]. and advance One step development CVFB (CVFBb) and endogenous Comparative study of the functional domains and enzymatic properties of C3/C5 convertase can not only deepen the understanding of complement alternative pathways knowledge and understanding of activation regulatory mechanisms and will likely provide complement Regulatory intervention and research on new anti-complement drugs provide new strategies and effective targets.

2 APPLICATION OF CVF IN PATHOLOGICAL RESEARCH ON COMPLEMENT-RELATED DISEASES

Complement is an important part of the immune system. It can be activated by antigen- antibody complexes or microorganisms. It clears immune complexes through lysis, opsonization, phagocytosis and activation of inflammatory responses, and exhibits the biological functions of complement. [1-4]. However, in recent years, with the development of life science research In-depth, more and more evidence shows that complement plays an important role in a series of diseases and symptoms [2,5-6,20-23]. autoimmune diseases, Inflammation, ischemia-reperfusion injury, acute lung injury, blood system abnormalities, Neurodegenerative diseases, infections, tumors, atherosclerosis, etc. Closely related to excessive activation of complement [24].

based on CVF Specific activation of the complement alternative pathway, which can be exploited CVF prepares animal models that remove complement and conducts research on related pathological mechanisms. study [16]. In such animal models, complement components C3, C5 and attack membrane complex formation subsequent components C6~C9 are consumed by activation. Pass By using this decomplementation model, a series of complementation Studies on the correlation with related diseases and symptoms reveal the role of complement in specific Role in identifying disease symptoms and pathological lesions [16]. With the development of complement pathology With in-depth research and understanding of the role of psychology, as a successful and high-level A highly specialized research tool, CVF will continue to play a role in this type of research important role.

On the other hand, you can use CVF specifically activates the complement alternative pathway, Study the effects of complement alternative pathway activation products on relevant target cells and target tissues role and impact on health. Using this strategy, we successfully demonstrated the effects of complement alternative pathway activation products on microvascular endothelial cells and platelets. Inflammatory activation and its effects on related inflammation, platelets, and coagulation function in rats and mice [25-30]. Based on the important role that complement alternative pathway activation plays in many diseases, CVF as complement The study of inflammatory response, coagulation and fibrinolytic function regulation by bypass activators is helpful for further understanding the mechanisms of the occurrence and development of inflammation. important meaning and value.

3 APPLICATION OF CVF IN ORGAN TRANSPLANTATION RESEARCH

Organ transplantation is an effective way to save the lives of patients with organ failure means, but the increasingly prominent donor shortage has seriously hindered the The development of organ transplantation has caused many patients to die while waiting. based on This situation, in 20th Century After the 1990s, there was an upsurge in xenogeneic organ transplantation research. In xenogeneic organ transplantation, the relationship between donor and recipient There are large species differences, and hyperacute rejection will occur after organ transplantation. (hyperacute rejection, HAR). This kind of HAR is stored by Natural antibody- and complement-mediated immunity against xenogeneic vascular endothelial cells Rejection, which usually occurs within minutes or hours after transplantation occur, resulting in a series of irreversible histopathological damage and functional impairment of the graft. can lose [31-32]. Therefore, to successfully carry out xenogeneic organ transplantation, we must first overcome HAR. In the course of this research, it was because CVF The characteristics of specifically acting on complement and consuming complement make it become overcome HAR Powerful tool to enable xenotransplantation research Encouraging progress has been made [33-36]. At the same time, by overcoming HAR Studies of delayed xenograft rejection that occurred after This greatly promoted the development of xenotransplantation immunology. That's exactly CVF Application in xenotransplantation research promotes the development of complementary supplementation based on inhibition of Research on body-activated xenogeneic transgenic organ transplantation makes xenogeneic organ transplantation Plants are getting closer and closer to practical applications.

With the increasing popularity of organ transplantation and the increasing understanding of transplantation immunology, Continuous in-depth research has led to the discovery in recent years that complement activation products pass through Endothelial cells and regulatory platelets, granulocytes, monocytes and lymphocytes Cell positioning, activation and effector functions are widely involved in homologous organ Acute rejection and chronic rejection after organ transplantation [37-38]. By regulating complement, inducing immune tolerance can reduce rejection reactions. Respond to secondary inflammatory damage, reduce graft damage, and prolong transplantation plant survival [39-40]. Based on this research strategy, CVF can play an important role in homogeneous organ transplantation research.

4 APPLICATION OF CVF IN ANTI-TUMOR RESEARCH

Increasing evidence shows that there is a complex relationship between complement and tumors, and that complement plays a double-edged role in the occurrence and development of tumors. [2,4,41-43]. However, there are still uncertainties in tumor killing strategies based on complement-mediated cytotoxicity. [44], Therefore, further research and revelation of the role and mechanism of complement in tumor development will help formulate new anti-tumor strategies and the development of new anti-tumor drugs. Specific as complement alternative pathway activator, CVF The application may mainly lie in two aspects. First, it is used to study the impact of complement on the microenvironmental mechanism of tumor occurrence and development under pathophysiological conditions. [45-46]; The second is based on complement-mediated cytotoxicity. CVF is cross-linked with tumor-specific monoclonal

antibodies, Through the targeting guidance of monoclonal antibodies, the CVF Targeted on the surface of specific tumor cells, using CVF Forming C3/C5 convertase CVFBb Continuous activation of the complement alternative pathway produces large amounts of membrane attack complexes (MAC), thereby causing damage to tumor cells [47-48]. The success of this strategy is related to the expression of complement regulatory proteins on the membrane surface of tumor target cells. CD46, CD55, CD59 related to the situation. In addition, complement alternative pathway activation on or near the tumor tissue surface may cause inflammation initiation and amplification, contributing to immune killer cell targeting of solid tumor tissue. Infiltrate or promote the diffusion of drugs in the tumor, which may Treatment provides benefits, but given the double-edged nature of complement activation effects, this This possible benefit needs to be carefully evaluated.

5 APPLICATION OF CVF AS MOLECULAR PROBE IN DIAGNOSIS OR DETECTION

CVF Characteristics of specific activation of the complement alternative pathway enable it to act as Highly specific and sensitive molecules for related diagnostic or detection purposes probe.

paroxysmal nocturnal hemoglobinuria (paroxysmal nocturnal hemoglobinuria, PNH) It is an acquired hemolytic disease caused by gene mutations in hematopoietic stem cells. [49]. patients due to hematopoietic stem cells PIG-A gene mutation, Causes defects in ankyrin synthesis, Complement regulatory proteins CD 55 and The loss of cell membrane proteins, including CD 59, causes blood cells to show resistance to complement activation. sensitivity [50]. Generally used clinically Ham test, sugar water test, Snake venom factor hemolysis test and microcomplement sensitivity test as PNH Diagnostic specific complement hemolysis test items [51]. In recent years, the flow of Cytometry becomes the test PNH the mainstream method, and as the method Improved, the sensitivity and accuracy of its detection are significantly improved [52], but its testing costs are correspondingly higher. use CVF complement activating PNH Hemolysis test has high specificity and its target is missing CD 59 red blood cells, the detection cost is low, and the requirements for instruments and equipment are not high. based on CVF developing PNH Diagnostic kits still have great promotion and use value in primary hospitals or underdeveloped areas.

use CVF and B Characteristics of specific binding of factors, in specific can be used to detect complement in experimental systems B factor sum D factor activity. Mice are commonly used experimental animals, but when using standard When the complement hemolysis test was used to measure serum complement alternative pathway activity, its The hemolysis efficiency is low and requires a large amount of serum, which makes it difficult to In studies related to mice as experimental materials, it is basically impossible to measure complement activity[53]. And use CVF It can better realize the supplementation of mouse serum body beside road activity of Measurement Certainly. right KM, BALB/c, C57BL/6 Serum complement alternative pathway assays of 3 commonly used strains of mice showed that utilizing CVF Can significantly improve the sensitivity of measuring complement alternative pathway activity degree, significantly reducing the amount of serum, enabling the determination of mouse serum paracomplement changes in road activity become a reality, thus enabling us to overcome the challenges that we could only rely on in the past ELISA Determination of mouse serum complement component content but unable to determine activity limitations [53].

6 PROSPECTS FOR THE DEVELOPMENT OF CVF AS AN ANTI-COMPLEMENT DRUG

Activation of complement is a double-edged sword, and its overactivation may directly Or indirectly cause potential danger to the body. Activation of the complement alternative pathway in The initiation, amplification, and effector phases of inflammation play important roles. Complement activation products activate endothelial cells, platelets, neutrophils Cells closely related to inflammation, such as cells and macrophages, produce important inflammatory effect [2], and is closely related to abnormalities in coagulation and fibrinolytic system functions [4,29-30]

because CVF The anti-complement effect is through activation of the alternative pathway It is realized by consuming complement. This essential characteristic determines its function. The high risk nature of clinical therapeutic drug use. Therefore, foreign scholars set Designed a human complement C3 and CVF hybrid molecules, through genes The humanized hybrid molecule obtained through engineering expression is named HC 3-1496. Its remarkable feature is that it can activate C3, while not will act on C5, thereby avoiding the activation effects of C5 and subsequent components answer [54]. The anti-complement effect of this molecule has been tested in various animal models Verification results show that it is safe and effective [55]. HC 3-1496 The design strategy is based on CVF Development of new anti-complement drugs to provide new ideas.

To sum up, CVF Its structure and function determine its importance Its application value has been around or based on for nearly half a century CVF carry out Related research has had a profound impact on related fields of life sciences impact on the complement system and the pathogenesis of human-related diseases As the understanding of the relationship continues to deepen and expand, highly specific complement pathway activator protein CVF will surely have more and more extensive and important applications.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

REFERENCES

[1] Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. Cell Res, 2010, 20: 34-50

[2] Merle SH, Noah R, R, Halbwachs-Mecarelli L, L, et al. Complement system part II: role in immunity. Front Immunol, 2015, 6: 257

[3] Wagner E, Frank MM. Therapeutic potential of complement modulation. Nat Rev Drug Discov, 2010, 9: 43-56

[4] Ricklin D, Hajishengallis G, Yang K, et al. Complement: a key system for immune surveillance and homeostasis. Nat Immunol, 2010, 11: 785-97

[5] Thurman JM, Holers VM. The central role of the alternative complement pathway in human disease. J Immunol, 2006, 176: 1305-10

[6] Holers VM. The spectrum of complement alternative pathway-mediated diseases. Immunol Rev, 2008, 223: 300-16

[7] Ballow M, Cochrane CG. Two anticomplement factors in cobra venom: hemolysis of guinea pig erythrocytes by one of them. J Immunol, 1969, 103: 944-52

[8] Müller-Eberhard HJ, Fjellstrom KE. Isolation of the anticopmlementary protein from cobra venom and its mode of action on C3. J Immunol, 1971, 107: 1666-72

[9] Pepys MB, Tompkins C, Smith AD. An improved method for the isolation from Naja naja venom of cobra factor (CoF) free of phospholipase A. J Immunol Methods, 1979,30: 105-17

[10] von Zabern I, Hinsch B, Przyklenk H, et al. Comparison of Naja n. naja and Naja h. haje cobra-venom factors: correlation between binding affinity for the fifth component of complement and mediation of its cleavage. Immunobiology, 1980, 157: 499-514

[11] Eggertsen G, Lind P, Sjöquist J. Molecular characterization of the complement activating protein in the venom of the indian cobra (Naja n. siamensis). Mol Immunol, 1981, 18: 125-33

[12] Takahashi H, Hayashi K. Purification and characterzation of anticomplement factor (cobra venom factor) from the Naja naja atra venom. Biochim Biophys Acta, 1982, 701: 102-10

[13] Vogel CW, Müller-Eberhard HJ. Cobra venom factor: improved method for purification and biochemical characterization. J Immunol Methods, 1984, 73: 203-20

[14] Sun QY, Lu QM, Wang WY, et al. A highly active anticomplement factor from the venom of Naja kaouthia. Acta Biochem Biophy Sin, 2001, 33: 483-8

[15] Vogel CW, Bredehorst R, Fritzinger DC, et al. Structure and function of cobra venom factor, the complement-activating protein in cobra venom. Adv Exp Med Biol, 1996, 391: 97-114

[16] Vogel CW, Fritzinger DC. Cobra venom factor: structure, function, and humanization for therapeutic complement depletion. Toxicon, 2010, 56: 1198-222

[17] Liszewski MK, Farries TC, Lublin DM, et al. Control of the complement system. Adv Immunol, 1996, 61: 201-83

[18] Janssen BJ, Gomes L, Koning RI, et al. Insights into complement convertase formation based on the structure of the factor B-cobra venom factor complex. EMBO J, 2009, 28: 2469-78

[19] Laursen NS, Andersen KR, Braren I, et al. Substrate recognition by complement convertases revealed in the C5-cobra venom factor complex. EMBO J, 2011, 30: 606- 16

[20] Botto M, Kirschfink M, Macor P, et al. Complement in human diseases: lessons from complement deficiencies. Mol Immunol, 2009, 46: 2774-83

[21] Takano T, Elimam H, Cybulsky AV. Complement - mediated cellular injury. Semin Nephrol, 2013, 33: 586- 601

[22] Meri S. Complement activation in diseases presenting with thrombotic microangiopathy. Eur J Intern Med, 2013, 24: 496-502

[23] Song WC. Crosstalk between complement and toll-like receptors. Toxicol Pathol, 2012, 40: 174-82

[24] Ricklin D, Lambris JD. Progress and trends in complement therapeutics. Adv Exp Med Biol, 2013, 735: 1-22

[25] Wang Cai'e, Sun Qianyun, Li Min, wait. Snake venom anti-complement protein atrase B inhibition Platelet aggregation induced by complement activation. Chinese Pharmacological Bulletin, 2 009, 25: 1205-9

[26] Li Min, Shen Liangxian, Zhang Xiangyan, wait. Two anti-complement proteins cause lipopolysaccharide Comparative study on the protective effect of acute lung injury. Chinese Pharmacological Bulletin, 2012, 28: 521-6

[27] Sun Qianyun, Li Min, Ye Qiaoling, wait. Activation of the complement alternative pathway leads to endothelial cell activation and damage. Chinese Pharmacological Bulletin, 2012, 28: 925-9

[28] Li Hongling, Sun Qianyun, Li Min, wait. Complement alternative pathway activation products stimulate endothelium cellular NF -κB, p38 MAPK, JAK 2 pathway activation and inhibitors intervention research. Chinese Journal of Cell Biology, 201 3, 35: 836-41

[29] Li Min, Sun Qianyun, Zhao Qiong, wait. Excessive activation of complement alternative pathway affects coagulation in vivo blood function. Chinese Pharmacological Bulletin, 2014, 30: 39-44

[30] Lu Qingyu, Li Min, Sun Qianyun. Activation of complement alternative pathway induces endothelial cell fibrinolysis Research on expression changes and intervention of coagulation-related molecules. Chinese Pharmacological Bulletin, 2015, 31: 1142-6

[31] O'Connell PJ, Cunningham A, d'Apice AJ. Xenotrans- plantation: its problems and potential as a clinical procedure. Transplant Rev, 2000, 14: 18-40
[32] Cooper DK, Ekser B, Tector AJ. Immunobiological barriers to xenotransplantation. Int J Surg, 2015 [Epub ahead of print]
[33] Leventhal JR, Dalma s so AP, Cromwell JW, et al. Prolongation of cardiac xenograft survival by depletion of complement. Transplantation, 1993, 55: 857-65
[34] Kobayashi T, Taniguchi S, Neethling FA, et al. Delayed xenograft rejection of pig-to-baboon cardiac transplants after cobra venom factor therapy. Transplantation, 1997, 64: 1255-61
[35] Sun QY, Chen G, Guo H, et al. Prolonged cardiac xenograft survival in guinea pig-to-rat model by a highly active cobra venom factor. Toxicon, 2003, 42: 257-62
[36] Chen G, Sun QY, Wang XM, et al. Improved suppression of circulation complement dose not block acute vascular rejection of pig-to-rhesus monkey cardiac transplants. Xenotransplantation, 2004, 11: 123-32
[37] Wood KJ, Goto R. Mechanisms of rejection: current perspectives. Transplantation, 2012, 93: 1-10
[38] Valenzuela NM, McNamara JT, Reed EF. Antibody- mediated graft injury: complement-dependent and complement-independent mechanisms. Curr Opin Organ Transplant, 2014, 19: 33-40
[39] Baldwin III WM, Samaniego M, Qian ZP, et al. Complement as a mediator of allograft injury: an inflammatory view. Transplant Rev, 2000, 14: 41-51
[40] Chen S, Zhong S, Xiang Y, et al. Complement inhibition enables renal allograft accommodation and long-term engraftment in presensitized nonhuman primates. Am J Transplant, 2011, 11: 2057-66
[41] Rutkowski MJ, Sughrue ME, Kane AJ, et al. Cancer and the complement cascade. Mol Cancer Res, 2010, 8: 1453-65
[42] Ricklin D, Lambris JD. Complement in immune and inflammatory disorders: pathophysiological mechanisms. J Immunol, 2013, 190: 3831-8
[43] Markiewski MM, Lambris JD. Is complement good or bad for cancer patients?A new perspective on an old dilemma. Trends Immunol, 2009, 30: 286-92
[44] Stevenson GT. Three major uncertainties in the antibody therapy of cancer. Haematologica, 2014, 99: 1538-46
[45] Nitta H, Murakami Y, Wada Y, et al. Cancer cells release anaphylatoxin C5a from C5 by serine protease to enhance invasiveness. Oncol Rep, 2014, 32: 1715-9
[46] Downs-Canner S, Magge D, Ravindranathan R, et al. Complement inhibition: a novel form of immunotherapy for colon cancer. Ann Surg Oncol, 2015 [Epub ahead of print]
[47] Vogel CW, Müller-Eberhard HJ. Induction of immune cytolysis: tumor-cell killing by complement is initiated by covalent complex of monoclonal antibody and stable C3/ C5 convertase. Proc Natl Acad Sci USA, 1981, 78: 7707-11
[48] Juhl H, Sievers M, BaltzerK, et al. A monoclonal antibody- cobra venom factor conjugate increases the tumor-specific uptake of a 99mTc-labeled anti-carcinoembryonic antigen antibody by a two-step approach. Cancer Res, 1995, 55: 5749s-55s
[49] Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood, 2014, 124: 2804-11
[50] DeZ ern AE, Brod sky RA. Paroxysmal nocturnal hemoglobinuria: a complement-mediated hemolytic anemia. Hematol Oncol Clin NorthAm, 2015, 29: 479-94
[51] Red blood cell diseases (anemia) group of the Hematology Branch of the Chinese Medical Association. Paroxysmal Chinese expert consensus on diagnosis and treatment of nocturnal hemoglobinuria. China Journal of Hematology, 2013, 34: 276-9
[52] Preis M, Lowrey CH. Laboratory tests for paroxysmal nocturnal hemoglobinuria. Am J Hematol, 2014, 89: 339-41
[53] Sun Qianyun, Ye Qiaoling, Yan Yinping. Mouse serum complement alternative pathway hemolysis New methods for activity determination. Chinese Pharmacological Bulletin, 2011, 27: 1619-22
[54] Vogel CW, Finnegan PW, Fritzinger DC. Humanized cobra venom factor: structure, activity, and therapeutic efficacy in preclinical disease models. Mol Immunol, 2014, 61: 191-203
[55] Vogel CW, FritzingerDC, Gorsuch WB, et al. Complement depletion with humanised cobra venom factor: efficacy in preclinical models of vascular diseases. Thromb Haemost, 2015, 113: 548-52