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Review article

Drug therapy for chronic subdural hematoma: Bench to bedside

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ABSTRACT

Chronic subdural hematoma (CSDH) is a common neurosurgical condition. Currently, surgery is the most effective medical intervention for treatment of this disorder. Because CSDH is an inflammatory angiogenic disease involving multifactorial mechanisms, a better understanding of CSDH pathogenesis should facilitate clinical management. Therefore, the purpose of this review is to describe recent progress in elucidation of molecular mechanisms causing CSDH and to summarize the body of knowledge gained from past drug treatment studies. Because hematoma fluid and outer membrane characteristics may be linked to pathology, they could serve as disease biomarkers. Moreover, past drug treatment studies have shown that such biomarkers may mutually synergize to initiate and promote CSDH progression. These findings suggest that modulation of biomarker expression or function using drug therapy may benefit CSDH patients.

1. Introduction

Chronic subdural hematoma (CSDH) is frequently encountered in neurosurgical practices [1,2]. Although surgery is currently the most effective treatment, the high risk of post-surgical complications and associated high medical costs are challenges that patients face. Fortunately, over the past 100 years, the progression of surgical treatment methodology has evolved from decompressive surgery to a minimally invasive surgical approach [3]. With early CSDH diagnosis, patients may recover without surgery but must undergo frequent follow-up. However, only a very small percentage of patients undergo hematoma resorption without surgery; the majority of cases will eventually require surgery within a specific time frame to achieve effective treatment outcomes. Moreover, because many patients experience postoperative CSDH recurrence, adjuvant drug therapies are an active research area and new drugs are urgently needed to cure patients without surgery and reduce recurrence risk.

In 1962, Ambrosetto first report use corticoids treat the patients with CSDH [4] which prompted clinicians to attempt drug therapies for CSDH. After a half-century of drug research, coupled with concurrent studies of CSDH pathophysiological characteristics, CSDH drug treatment clinical trials have made some progress. Currently, CSDH is defined as an inflammatory angiogenic disease. CSDH development involves multifactorial mechanisms including proliferation and rupture of pathological blood vessels in the hematoma outer membrane, release of inflammatory mediators and abnormalities of the coagulation system [1]. Discovery of drugs that can modulate CSDH pathological mechanisms could achieve effective control over CSDH development, decrease postoperative recurrence or may even cure CSDH.

2. Potential therapeutic targets for CSDH

The study of disease requires a classic animal model. At present, many animal models of CSDH, but they are not fully suited to CSDH natural pathological development process [14]. Therefore, the mechanism of CSDH is more based on the clinical patients of hematoma membrane, hematoma fluid and body fluid samples carried out.

3. Pathological angiogenesis

Pathological vascularization of hematoma outer plays the key role in the development of CSDH. Past studies reported that hematoma outer vascular lack of normal smooth muscle cells, and found that vascular endothelium connection loose, basement membrane and vascular peripheral cell loss, resulting in increased vascular permeability of the capsule, blood components and exudate repeatedly into the hematoma cavity, absorption is less than its exudation or leakage, resulting in subdural hematoma volume

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increases [5–7]; and most of the hematoma intima by composed of flat fibroblasts, during which the lack of blood vessels, which speculated hematoma cavity bleeding and exudation from the hematoma outer membrane [8]. Moreover, abnormal expression of vasoproliferative proteins is present in hematoma outer also report the result [9–12] (Table 1).

These factors all play an important role in the proliferation of blood vessels. Moreover, VEGF (vascular endothelial growth factor), COX-2 (cyclooxygenase-2), PIGF (placental growth factor), sVEGFR-1 (soluble vascular endothelial growth factor receptor), TGF-β1 (transforming growth factor-β1), bFGF (basic fibroblast growth factor) and PDGF (platelet-derived growth factor) concentrations in CSDH hematoma fluid have also been observed to be significantly higher than in patient peripheral blood or cerebrospinal fluid [9,10,13–18]. These findings collectively suggest that the pathological progression of CSDH is tightly linked to the proliferation of blood vessels. In the early stages of CSDH, the neovascularization of the capsule is still immature and red blood cells leak from the vascular space into the hematoma cavity. With maturation of the hematoma capsule, leakage is reduced and the hematoma gradually stabilizes. Notably, during the CSDH maturation process, the VEGF concentration changes in step with changes observed using diagnostic imaging techniques. For example, Weigel et al., found that computed tomography (CT) imaging and VEGF concentration of hematoma fluid in CSDHs are closely related [19], while Hua et al. reported similar results using magnetic resonance imaging (MRI) [20].

4. Inflammation

Inflammatory mediators play an important role in the pathologic progression of CSDH. A variety of inflammation-related factors, such as interleukins, have been detected in the outer membrane of hematomas at significantly higher concentrations than in peripheral blood and cerebrospinal fluid [18,21–25] (Table 1). Such mediators cause specific inflammation that results in progression from subdural effusion to subdural hematoma, even though inflammatory chemokines, such as angiogenesis inhibitors, normally act to inhibit abnormal proliferation [23]. It should be noted here that local inflammatory immune response imbalances, especially common in the elderly, can subvert normal control mechanisms and lead to CSDH formation [26]. In addition, several studies suggest that inflammation is responsible for both early stage capillary bleeding, as well as for angiogenesis that appears late in the course of CSDH to initiate development of a vascular network [13]. Both disease stages could therefore be exploited using drug therapy to block the pathological process of hematoma development.

5. Abnormal coagulation

Coagulation dysfunction has also been postulated to play an important role in CSDH. First, previous studies have shown that expression of plasminogen activator in endothelial cells of the cap-

Table 1
Potential therapeutic targets of CSDH based on the sample of patients.

Biomarker		Mechanism	Refs.
Hematoma fluid	Outer membranes		
	Ras, Ras-GAP, c-Raf, MEK, ERK, eNOS and p-ERK	Pathological vascular	[12]
VEGF	VEGF and HIF-1a	Pathological vascular	[9]
COX-2	COX-2	Pathological vascular	[10]
PIGF and sVEGFR-1		Pathological vascular	[14]
VEGF	VEGF, ANG-1 and ANG-2	Pathological vascular	[11]
VEGF		Pathological vascular	[15]
VEGF and bFGF		Pathological vascular	[16]
VEGF, bFGF and PDGF		Pathological vascular	[17]
	MMP-1, MMP-2, MMP-9, TIMP-1 and TIMP-2	Pathological vascular	[52]
MMP-2, MMP-9		Pathological vascular	[20]
	PI3-kinase, Akt, eNOS and VE-cadherin	Pathological vascular	[26]
VEGF, bFGF and IL-6		Pathological vascular/ Inflammation	[13]
ERK, p-ERK, p38, p-p38, JNK and p-JNK		Pathological vascular/ Inflammation	[53]
CCL2, CXCL8/IL8, CXCL9 and CXCL10		Inflammation	[21]
IL-10		Inflammation	[22]
TNF-α, IL-6 and IL-8		Inflammation	[23]
IL-4, IL-5, IL-10, IL-1RA and IL-13		Inflammation	[24]
	JAK1, STAT1 and STAT3	Inflammation	[25]
Eotaxin-3/CCL26 and TGF-β1	Smad	Pathological vascular / Inflammation	[18]
	IL-6, STAT3, JAK2, SOCS3 and PIAS3	Inflammation	[54]
	t-PA	Abnormal coagulation	[27]
Prekallikrein, HMW-kininogen, bradykinin, plasminogen, FDP, t-PA, a2 PI; PT; APIT; AT III		Abnormal coagulation	[28]

CSDH: Chronic subdural hematoma; Ras: Rat sarcoma; Ras-GAP: Rat sarcoma GTPase activating protein; c-Raf: Raf-1 proto-oncogene, serine/threonine kinase; MEK: MAPK kinase; ERK: Extracellular signal-regulated kinase; eNOS: Endothelial nitric oxide synthase; p-ERK: phosphorylated extracellular signal-regulated kinase, VEGF: Vascular endothelial growth factor; HIF-1a: Hypoxia-inducible factor-1; COX-2: cyclo-oxygenase 2; PIGF: Placental growth factor; sVEGFR-1: vascular endothelial growth factor receptor-1; ANG-1: Angiopoietin-1; ANG-2: Angiopoietin-1; bFGF: basic fibroblast growth factor; PDGF: Platelet derived growth factor; MMP-1: Matrix metalloproteinases-1; MMP-2: Matrix metalloproteinases-1; MMP-9: Matrix metalloproteinases-9; TIMP-1: Tissue inhibitor of metalloproteinases-1; TIMP-2: tissue inhibitor of metalloproteinases-1; PI3-kinase: phosphoinositide 3-kinase; Akt: rAC-alpha serine/threonine-protein kinase; VE-cadherin: Vascular endothelial-cadherin; JNK: Jun N-terminal kinase; p-JNK: p-Jun N-terminal kinase; CCL2: C chemokine ligand -2; CXCL8: C-X-C motif ligand 8; CXCL9: C-X-C motif ligand 9; CXCL10: C-X-C motif ligand 10; TNF-α: Tumor necrosis factor-α; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; IL-13: Interleukin-4; IL-1RA: Interleukin-1 receptor antagonist; JAK1: Janus kinase 1; JAK1: Janus kinase 2; SOCS3: Suppressor of cytokine signalin 3; PIAS3: Protein inhibitor of activated Stat3; STAT1: Signal transducer and activator of transcription 1; STAT3: Signal transducer and activator of transcription 1; TGF-β1: Transforming growth factor β; Smad: Sma- and mad-related protein; t-PA: tissue plasminogen activator; FDP: Fibrin/fibrinogen degradation products; t-PA: tissue-type plasminogen activator; a2 PI: a2 plasmin inhibitor; PT: Prothrombin time; APIT: Activated partial thromboplastin time; AT III: Antithrombin III.

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