Advances in diagnosis, treatments, and molecular mechanistic studies of traumatic brain injury

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1. Introduction

Traumatic brain injury (TBI), also known as intracranial injury, occurs when an external force damages the brain. TBI can be classified by severity (mild, moderate, or severe), mechanism (closed or penetrating head injury), or other characteristics (1). TBI is a main cause of death and disability around the world especially in soldiers, children, and young men. Males suffer TBIs more frequently than females. Each year about 1.7 million Americans are saved in emergency rooms after suffering a TBI of some severity; of these, 52,000 die of TBI and other secondary injuries and another 275,000 are hospitalized and survive (2). Neurological damage from TBI does not only occur at the moment of focal impact upon the head but also involves secondary injury over the ensuing hours and days. This injury, which includes changes in cerebral blood flow and intracranial pressure, leads to substantial damage following the original injury. Besides cell death, a series of physiological changes including diffuse axonal injury (DAI), micrangium damage, and diffuse neuronal injury can also occur on a microscopic scale in the cerebral parenchyma following trauma and lead to subsequent morbidity. Clinical symptoms of these physiological changes include loss of consciousness, dizziness, headaches, inattention, and hypomnesia (3).

Currently, patients with moderate to severe trauma will in all probability receive treatment in an intensive care unit after a neurosurgical procedure (4). Treatment depends on the patient’s stage of recovery. In the acute stage, the primary objective of the surgeon is to stabilize the patient and do one's best to prevent further damage because slight damage can worsen the primary injury caused by trauma (4). Rehabilitation is the primary treatment for interim and latter stages of recovery (4). Prognosis worsens with the severity of injury. Permanent disability is considered to occur in 10% of mild injuries, 66% of moderate injuries, and 100% of severe injuries (5). Most patients in a coma or with a subarachnoid hemorrhage or DAI are considered...
to have a bad prognosis (6–8). Thus, there is an urgent need for novel therapies, medicines, biomarkers to predict prognosis, and treatment alternatives.

This review begins by briefly discussing advances in clinical diagnosis and management of TBI. This review then focuses on studies of the biomechanics of and rehabilitation from TBI. This review then summarizes the potential usefulness of alternative treatments of TBI. This review concludes by offering ideas on the direction for future research into TBI treatments and their clinical use.

2. Clinical diagnosis and treatment

TBI has been studied since 1650–1550 BC and there are methods of assessing and managing the progression of TBI, but its prognosis remains, so more effective forms of clinical treatment of TBI should be sought (9).

2.1. Novel methods of assessing TBI

Formalin-fixed, paraffin-embedded archival tissue (PEAT) specimens were obtained from a total of 95 primary ALM (42 males and 53 females, mean age T)

2.1.1. Imaging of structural abnormalities

Concussion, based on the current definition, is a symptom of TBI. Concussions were conventionally considered to be simply physiological injuries, caused by a metabolic disorder of the brain as a result of alternations in ionic gradients, a disruption of sodium, potassium, and calcium channels, an imbalance in neurotransmitters, and inflammation (10). This standpoint has been substantiated by a series of metabolic and functional imaging studies in humans (11,12) and animals (10). Nevertheless, studies of the usefulness of advanced structural neuroimaging methods, such as susceptibility weighted imaging and diffusion tensor imaging, have revealed subtle structural abnormalities in white matter and brain microvasculature in a significant proportion of patients with a TBI, and especially in patients with severe TBI (11–13).

Histopathological results from patients with a TBI who subsequently died from their injuries suggested that DAI is a key pathologic cause of TBI (14,15). Advanced neuroimaging studies, and especially those involving diffusion tensor imaging (DTI), support this contention. DTI is used to test the diffusion of water along the axis of white matter tracts and can discern the interruption of water diffusion within 2 weeks of persistent TBI in people with a normal MRI scan (16,17). Although DTI results are potential biomarkers of TBI, studies of DTI differ in their description of changes in diffusion, facilities use different imaging protocols, facilities use different methods of quality assurance and methods of analysis, and facilities have failed to provide sufficient normative data. These problems need to be resolved.

A diffuse microhemorrhage (DM) is another physiological cause of TBI. DM has long been considered to be a physiological cause of severe TBI, but abnormalities in cerebrovascular reactivity and cerebral blood flow have also been found in mild TBI, and especially in people who have suffered multifocal mild TBIs and who have enduring post-concussive symptoms (18,19) Data from neuroimaging studies (20) using T2*-weighted gradient echo imaging, which is sensitive to DM, found DM in deep white matter in 23 of 98 patients who suffered a TBI.

Other abnormalities indicative of TBI have been identified by computed tomography (CT) and high-resolution magnetic resonance imaging (MRI). These abnormalities include focal contusions, traumatic subarachnoid haemorrhage, and extra-axial hematomas. MRI is clearly much more sensitive than CT at verifying the presence of subtle abnormalities. A multicenter study of 98 patients revealed that 27 (28%) had an aberrant MRI scan an average of 12 days after injury (20). In that study, a subarachnoid haemorrhage confirmed by a CT scan and multiple foci of hemorrhagic axonal injury identified by MRI were related to more severe disability three months after TBI (20).

After TBI, functional magnetic resonance imaging (fMRI) has revealed changes in dynamic functional connectivity and the pattern of brain activity in a resting state as well as changes in cognitive test results. Changes in test results and fMRI results in a resting state have been noted even when patients perform well on cognitive tests and are allowed to return to regular activities (11,12,21).

Quantitative electroencephalogram has been used to identify a physiological disorder after TBI and provide evidence of enduring neuronal malfunction at a certain point after clinical symptoms disappear (22). Although these advanced methods of imaging and electroencephalography seem to be more sensitive than current methods of clinical diagnosis, they still are mainly in the research stage.

2.1.2. Biomarkers

The diagnosis of TBI can be difficult if the injury is not witnessed, no evidence of a wound exists, a CT scan is normal, or if the diagnosis was delayed for 24 hours or longer. To aid in the diagnosis of TBI and decrease the dependency on self-reports, biomarkers of TBI in the blood, saliva, urine, and cerebrospinal fluid (CSF) have attracted the attention of researchers (23). Serum is the most often researched biomarker reservoir (24). The most extensively researched biomarkers in the blood are glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1). A receiver operating characteristic (ROC) analysis has indicated that the area under the curve is greater than 0.87 for
both GFAP and UCHL1 (25). The high sensitivity and specificity of these biomarkers mean that they can distinguish between individuals who have suffered a TBI and healthy people (0.87, 95% CI 0.83-0.90, and 0.91, 95% CI 0.88-0.94, for GFAP and UCHL1, respectively) and differentiate between individuals who have suffered a TBI and who have an abnormal CT scan and those who have a normal CT scan (0.71, 95% CI 0.64-0.78, and 0.88, 95% CI 0.84-0.93, for GFAP and UCHL1, respectively) (25,26). However, GFAP and UCHL1 do not have sufficient sensitivity and specificity to predict the prognosis for a complicated TBI (25). Biomarkers were detected in professional hockey players before the season and again after a TBI, and these players had increased concentrations of microtubule-stabilized tau protein in the blood after a TBI (27). The range of this rise in the concentration of tau protein is associated with the duration of post-concussive symptoms. Despite advances in animal models and human studies and evidence that biomarkers can potentially facilitate the diagnosis of TBI, further confirmation is needed. Given the variety of pathological mechanisms involved in TBI, a set of biomarkers with sufficient sensitivity and specificity needs to be developed for general clinical use (25).

2.2. Clinical treatment

During TBI, a few cells in the brain are directly mechanically damaged, but more cells are injured as a result of trauma-induced biochemical changes, which is what is referred to as secondary injury. Based on guidance from the Mayo Clinic (28), the following medications may be used to prevent secondary injury to the brain immediately after a trauma.

Diuretics, which are a group of substances that promote the production of urine, are used to treat heart failure, liver cirrhosis, hypertension, water poisoning, certain kidney diseases, and TBI (29). Drugs such as high ceiling/loop diuretics, thiazides, carbonic anhydrase inhibitors, potassium-sparing diuretics, calcium-sparing diuretics, and osmotic diuretics decrease the amount of fluid in tissues and increase micturition (30-32). Diuretics, given intravenously to people who have suffered a TBI, help decrease pressure inside the brain. However, they have serious side effects, such as hypovolemia, hypokalemia, hyperkalemia, hyponatremia, metabolic alkalosis, and metabolic acidosis (33).

Anticonvulsants, also known as anti-epileptic drugs or anti-seizure drugs, are a diverse group of pharmacological agents used to treat epileptic seizures. People who have suffered a moderate to severe TBI are at risk of having seizures during the first week after injury. An anti-seizure drug may be given during the first week to avoid any additional brain damage that might be caused by a seizure. Additional anti-seizure medication is used only if seizures occur (34,35). Numerous studies have indicated that phenytoin (PHT) can be used to prevent seizures soon after TBI, but other anti-seizure drugs such as levetiracetam (LEV) are also being used in clinical practice. PHT has its drawbacks, such as cognitive side effects and effects on physical recovery (36). Over the past few years, certain new drugs such as zonisamide and vigabatrin have been used clinically in the US, the UK, Australia, and Japan for both adjunctive therapy and monotherapy for partial seizures (simple, complex, and secondarily generalized), generalized seizures (tonic, tonic-clonic, and atypical absence), and combined seizures (37-39).

Coma-inducing medication is sometimes used by doctors to induce a temporary coma (a deep state of unconsciousness) (40). Because the metabolism of the brain has been significantly altered during a TBI and areas of the brain may lack a sufficient blood flow, coma-inducing drugs are used to profoundly inactivate the brain so that it consumes less oxygen (41). This is especially helpful if blood vessels, stressed by elevated pressure in the brain, are unable to carry the normal amount of nutrients and oxygen to brain cells (42). Although coma-inducing medications protect the brain, the brain as a whole is, by definition, not receiving the blood it needs.

3. Studies of mechanisms

3.1. Signaling pathways

Recent clinical therapies cause various adverse reactions and have not yielded satisfactory results (43,44). Thus, a great deal of work needs to be done to explore the molecular mechanisms of TBI and develop more targeted therapies.

An obvious inflammatory response occurs following a TBI. In the immediate phase following the primary trauma, the inflammatory reaction aggravates cell damage and worsens prognosis (45). The nuclear factor kappa B (NF-κB) signaling pathway has long been considered to be an inflammation-related signaling pathway, mainly based on the function of NF-κB in the expression of proinflammatory genes including cytokines, chemokines, and adhesion molecules (46). NF-κB is also considered to play a significant part in the regulation of apoptosis (47). Several studies at different facilities have found that NF-κB, as a downstream element of a series of receptors such as toll-like receptor 4 (TLR-4) and tumor necrosis factor receptor-associated factor 6 (TRAF6), is activated in specimens of animal or human brains (48-50). Thus, NF-κB is considered to be a target by which to decrease inflammation and apoptosis after TBI. Several research teams are developing various NF-κB inhibitors, such as SN50, nerve growth factors, and pituitary adenylate cyclase-activating polypeptide (PACAP), to suppress

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the up-regulation of NF-κB in brain tissue (47,50,51).

Glycogen synthase kinase 3 beta (GSK-3β) is one of the most important downstream elements of NF-κB (52), so several research teams have focused on changes in its expression and its potential as a target for TBI treatment. An animal model indicated that GSK-3β is involved in neuronal survival after TBI (53). Lin et al. found that transfection of GSK-3β small-interfering RNA increased cell survival in Sprague-Dawley rats (54).

In the inflammatory response after TBI, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is found to be activated and to increase cell apoptosis in the cortical pericontusional zone (55). The same research team also reported that recombinant human erythropoietin (rhEPO) increased the level of p-JAK2 and p-STAT3 expression, decreasing apoptosis and promoting cell survival.

As TBI progresses, reactive oxygen species (ROS) are produced in brain tissue and lead to cellular apoptosis (56). The nuclear factor (erythroid-derived 2)-like 2 (NFE2L2 or Nrf2) signaling pathway regulates the level of expression of antioxidant proteins that protect against oxidative injury induced by trauma and inflammation, and this pathway has increasingly attracted attention in studies of the molecular mechanism of ROS in TBI (57). In rat and mouse experiments, activation of the Nrf2 pathway has been found to inhibit ROS-induced damage in brain tissue (58).

Catenin beta 1 (β-catenin) is a dual function protein, regulating the coordination of cell-cell adhesion and gene transcription (59). β-catenin was found to increase in astrocytes in gliogenesis after TBI in the adult brain and it was found to be involved in neuronal survival (60). Several substances have been found to activate the β-catenin pathway to alleviate cell injury. Up-regulation of serum- and glucocorticoid-regulated kinase (SGK) was reported to protect against neuronal apoptosis via the β-catenin signaling pathway (61). Interestingly, in this study the β-catenin signaling pathway was activated by GSK-3β, which indicates that there may be a signaling pathway in TBI. In addition, up-regulation of survivin, a key component in the β-catenin pathway, was found to promote neurogenesis following TBI (62).

Many other signaling pathways have also been investigated, such as the Notch pathway, PTEN pathway, ERK pathway, and p38MAPK pathway. These pathways may be a novel target for new TBI therapies (63-66).

3.2. Microenvironment

The cell microenvironment consists of elements that directly affect conditions around a cell or a cell cluster, and these elements play a direct or indirect role in affecting cell behavior biophysically or biochemically (67). The cell microenvironment consists of (i) an extracellular matrix (ECM), (ii) cytokines, hormones, and other bioactive materials around cells produced from autocrine, endocrine, and paracrine secretions, (iii) exosomes between cells, and (iv) mechanical forces created by the movement of tissue or the movement of physiological fluids such as blood.

Neuro-inflammation represents an important pathological process in secondary injury after TBI (68). Resident astrocytes and microglia are usually the initial cells that promote an inflammatory cascade following tissue injury, and bioactive proteins associated with the activation of these cells are often used as biomarkers of TBI (69,70). Astroglisis, an abnormal increase in the number of astrocytes due to the destruction of nearby neurons, has been defined in the context of both neuroprotection and neurodegeneration (71,72). Activated astrocytes are able to secrete pro-inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs) that degrade the extracellular matrix and lead to further disintegration of the blood-brain barrier (73,74). However, astrocytes are also able to secrete molecules that promote repair and regeneration after central nervous system (CNS) damage (75,76).

Exosomes are cell-derived vesicles that exist in a number of biological fluids such as blood and urine and in used cell culture medium (77). Exosomes interact with the plasma membrane of a target cell by ligand-to-receptor binding, fusion, internalization, or a combination of these actions. If the exosomes fuse with recipient cells, they can transfer their cargo, including bioactive lipids, cytokines, growth factors, receptors, and hereditary material, to the addressee cell (78). In a study, TBI-derived exosomes induced the emergence of pro-inflammatory cytokines, including IL-1β. IL-1β is produced primarily by microglia and acts as a pro-inflammatory pyrogen, up-regulating expression of other cytokines, proteases, and MMPs (79). Previous studies reported that specific microRNAs are associated with the progression of neurological disorders, leading to the initiation and progression of complications associated with a TBI (80). MicroRNAs delivered by exosomes produced by injured brain cells do present an advantage since they are sensitive, clinically accessible biomarkers that can improve the diagnosis of TBI and that can function as prognostic markers after treatment.

Mechanotransduction refers to the various mechanisms by which cells translate a mechanical stimulus into an electro-chemical signal (81). The role of pathological cellular mechanotransduction in brain tissue remains unclear. However, several studies have indicated that it may be an initiator of TBI. In an in vitro study, quick deformation of three-dimensional collagen gels led to a decrease in embedded neuronal viability when the collagen concentration increased, indicating the potential impact of cell-ECM interactions on injury (82). Another study suggested that ECM influences axonal injury by activating Rho signaling pathways; up-regulation of RhoA was accompanied by fluid percussion brain injury (83).
3.3. Stem cells

Among acute neuropathological conditions, TBI is one of the major causes of death and disability around the world (84). Cell transplantation may be a therapy for TBI. Whether the production of new neurons leads to a recovery of function, axonal sprouting, synaptic plasticity, or neosynaptogenesis is unknown. The rate at which these new neurons are generated and the rate of functional recovery are known to be very low after TBI (85).

Studies initially focused on neuronal restoration after TBI. One year after transplantation of neural precursor cells (NPCs) into the striatum of mice, the mice had improved long-term survival and improved motor functions without tumor formation (86). Fetus-derived immortalized neural stem cells (NSCs) were transplanted into the injured cortex, leading to recovery of motor function but no cognitive improvement (87). After these NSCs were transplanted into the hippocampus, cognitive improvement was noted but there was no improvement in motor function (88).

A clinical study transplanted bone marrow mononuclear cells in 10 children (from age 5 to 14) with a Glasgow Coma Scale score of 5 to 8 (89). In both studies, the NSCs moved from the site of implantation to the site of the injury. In addition, the experimental group displayed improved recovery in comparison to the control group. At that point, IMRI revealed improved activity at the site of the injury, positron emission tomography (PET) revealed that patients were improving, somatosensory evoked potentials (SEP) revealed slight improvement until six months after transplantation, and Disability Rating Scale (DRS) scores quickly rose six months after transplantation.

A clinical study transplanted bone marrow mononuclear cells in 10 children (from age 5 to 14) with a Glasgow Coma Scale score of 5 to 8 (90). This study noted no adverse effects during the six months after transplantation. These children were also evaluated with the Pediatric Logistic Organ Dysfunction (PELOD) test, and no adverse effects on white matter, gray matter, or cerebrospinal fluid (CSF) were noted.

The main obstacle to stem cell transplantation in TBI is the recovery of motor function and cognition. However, recovery depends on the injured area where stem cells are implanted (91). After stem cells are implanted into the hippocampus, for example, these implanted cells are more apt to survive than when they are implanted into various areas of the neocortex. In addition, different types of progenitor or stem cells seem to perform various functions after transplantation. Mesenchymal stem cells (MSCs) are used for neurotrophic support, progenitor oligodendrocytes are used to establish remyelination in white matter, and neural progenitor cells play a role in cell replacement.

4. Alternative and complementary medicine

Although conventional medications have been widely used in the clinical treatment of TBI, mounting evidence suggests that conventional medications for treatment of TBI have a number of drawbacks. Anti-convulsants induce amnesia, ataxia, and diplopia, anti-depressants induce blurred vision, confusion, and dizziness, and anti-psychotics induce headaches. Thus, complementary and alternative medicine, such as traditional Chinese medicine, may need to supplement treatments for TBI (92). Alternative medicine is any practice, approach, or medication that is thought to have the healing effects of medicine but that does not originate from evidence gathered using the scientific method (93). This form of medicine includes a large number of health care practices, products, and therapies. Complementary medicine is a form of alternative medicine used in combination with conventional medicine in the belief, albeit not proven using the scientific method, that it complements the treatment (94). Complementary and alternative medicine is referred to as CAM. Traditional Chinese medicine (TCM) is one type of CAM, and TCM stems from medical practices with common concepts that have developed in China for more than 2,000 years. TCM includes various herbal medicines, acupuncture, massage, exercise, and diet therapy (95). In experimental and clinical studies, animals and patients were given different CAM after TBI to assist in recovery when conventional medicine was unable to improve the condition of or prognosis for the control group (96). Both TCM (Table 1) and its bioactive components (Table 2) are being studied at the experimental or clinical level. However, most of these studies involve experiments in animal models.

Neuroprotection after TBI is key. Several TCMs display anti-inflammatory and/or anti-oxidant action. A Xingnaojing injection was found to have a protective effect in rats with a TBI. It may have a protective effect by alleviating brain edema and inhibiting the production of reactive oxygen species (ROS) in rats (97). Manasamitra vatakam was also reported to prevent brain damage from TBI-induced neurotoxicity by increasing superoxide dismutase (SOD) and 70 kilodalton heat shock proteins (HSP70) in rats (98). Studies of a Qingkailing injection and early treatment with MLC601 suggested that these TCMs reduce TBI-induced brain damage by blocking mitochondria-mediated signaling pathways in rats (99,100). Following primary trauma, the inflammatory response promotes neural cell damage and worsens prognosis, so studies have focused on the anti-inflammatory action of TCMs. In a rat model, a modified Shengyu decoction (MSD) was reported to be a potential therapy for TBI because it decreased the inflammatory response after TBI. MSD inhibits the inflammatory reaction by decreasing the levels of TNF-α, IL-1β, GFAP-, and Iba1-positive cells and by increasing the level of IL-10 (101). Another important aspect after TBI is neurogenesis. In addition to its anti-apoptotic action, MLC601 was also reported...
to promote motor recovery in an animal model (100). A Xingnaojing injection and MLC901 were reported to improve nerve impairment and recovery of cognitive function by increasing S100 calcium-binding protein beta (S100B) and neuron-specific enolase (NSE) in rats (97,102). Qin-Nao-Yi-Zhi-Fang was found to counteract glutamate excitotoxicity after TBI by inhibiting nitric oxide (103). In addition, the effects of Ginseng total saponins and MSD on neurogenesis have been studied. These TCMs may improve neurorestoration in an animal model of TBI animal model by increasing the nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), neural cell adhesion molecule (NCAM), and neural stem/progenitor cells (NSCs) (104,105). Several clinical studies have treated TBI with TCM. A rhubarb extract was reported to be able to decrease patients' body temperature, intracranial pressure, and hemorrhaging in the digestive tract, but the mechanism of this action remains unclear (106). Panax notoginseng saponin may have neuroprotective action by attenuating edema and hematoma (107).

Bioactive components of TCMs have also been studied as treatments for TBI over the years. Osthole, Panax ginseng saponin, and MSD on neurogenesis have been studied. These TCMs may improve neurorestoration in an animal model of TBI animal model by increasing the nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), neural cell adhesion molecule (NCAM), and neural stem/progenitor cells (NSCs) (104,105). Several clinical studies have treated TBI with TCM. A rhubarb extract was reported to be able to decrease patients' body temperature, intracranial pressure, and hemorrhaging in the digestive tract, but the mechanism of this action remains unclear (106). Panax notoginseng saponin may have neuroprotective action by attenuating edema and hematoma (107).
mediated signaling pathways and inhibiting ROS release in rats (108). Curculigoside, a component of Curculigo orchioides Gaertn., was found to reduce neuronal cell loss by blocking mitochondria-mediated signaling pathways and inhibiting ROS production in cortex neurons (109). Two research teams reported that ginsenoside Rhβ1 and Z-ligustilide, respectively extracted from Panax ginseng and Angelica sinensis, were able to reduce neurological deficits, cerebral edema, and disruption of the blood-brain barrier in rats by inhibit mitochondria-mediated and p53 signaling pathways (110,111). Curcumin was found to suppress the inflammatory response after TBI by inhibiting the TLR4/MyD88/NF-κB signaling pathway in mice (112). Chen et al. reported that salvianolic acid B, the most abundant component in Salvia miltiorrhiza Bunge, inhibits the inflammatory reaction by decreasing TNF-α and IL-1β and by increasing IL-10 and TGF-β1 in mice (113). Triptolide, a major bioactive compound in Tripterygium wilfordii Hook. f., was found to attenuate the inflammatory response by decreasing TNF-α, IL-1, IL-4, IL-6, IL-8, IL-17, and IL-23 in rat models (114).

Although a number of studies have examined TCM treatments for TBI, their molecular mechanisms have not been clearly indicated and there are few data from clinical studies of the components of TCMs in particular.

5. Conclusion

TBI is one of the leading causes of death and disability worldwide and it has attracted considerable attention from doctors and researchers. More accurate methods of diagnosis and more effective treatments are urgently needed in clinical practice. New methods of imaging and novel biomarkers were developed to provide more accurate results, but drug development is quite slow because it needs to be based on in-depth knowledge of the molecular mechanisms of TBI. Thus, researchers have extensively explored intracellular signaling pathways and the extracellular microenvironment (Figure 1). Their results may leads to new therapies to...
treat TBI. Due to the relatively high cost of novel drug development and how long that development takes, larger numbers of laboratories and pharmaceutical manufacturers are using the original ingredients in TCMs or isolating their bioactive components to develop drugs. Great progress has been made in experimental and clinical studies, but there is still a vast gap between TCM development and its clinical use worldwide.

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(Received May 13, 2015; Revised June 8, 2015; Accepted June 16, 2015)