Review article

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The primary, secondary, and tertiary brain injury

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Abstract

Traumatic brain injury (TBI) is one of the most prevalent causes of morbidity and mortality all over the world. The knowledge and understanding of pathophysiology of TBI are the priority as a basic to develop therapeutic opportunities and allow improvement of outcome for TBI patients. In TBI, primary damage occurs at the time of impact and the damage is preventable but not treatable. The process will continue caused following trauma due to complicating processes. Secondary brain insults have been found in many patients of severe TBI. This insult continues, which involves complex molecular and genes cascades, and is not fully understood. Chronic microglia activation and epigenetic mechanism were potential entry point in third brain damage processes. We suggest that treatment of tertiary insults might be ameliorate chronic complication of severe TBI patients.

Key words: Primary, secondary, tertiary brain injury, TBI.

Introduction

Traumatic brain injury (TBI) represents a major contributor to mortality, disability, and health cost expenditure around the world. TBI remains one of the most important medical problems in modern society. The pathomechanism process in TBI is extremely complex that involves a broad spectrum of cellular and molecular pathways. In general, TBI is divided into two discrete stages, primary and secondary injury. The primary brain injury is an irreversible process as the physical damage to parenchyma that occurs at the moment of impact. This can involve contusion and laceration, diffuse axonal injury, brain swelling and intracranial hemorrhage, and invariably results in immediate cell death. (1) The secondary brain injury is the result of a complex process that involves cascades of biochemical processes initiated at the time of injury that may endure hours and days. The delayed phase, which is called tertiary brain injury, caused by chronic microglia activation, epigenetic mechanism and alteration regulation in gen level, and often will lead the progression of neurodegeneration and delayed cell death. (1,2)

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The primary brain injury

The primary brain injury is caused at the moment of the injury. In the treatment terms, the first stage damage is preventable but not treatable. The primary damage occurs at the time of impact and includes contusion, lacerations, and diffuse axonal injury as a result of shearing, tearing or stretching. The biomechanics of primary injury are linked to the respond of the soft tissue of scalp, bone, blood vessels, axons, nerve cells, and glia of the brain .The type and severity of the resulting injury depends upon the nature of the initiating force, as well as the site, direction, and magnitude of the force. TBI is triggered by an external mechanical impact to the head. With direct impact local causes TBI through a combination of two injury mechanisms such as contact and inertial forces. Biome-

chanical theories have historically described 2 inertial phenomena: linear acceleration and rotational head movement. It is thought that linear acceleration forces lead to superficial mechanism of brain lesions, whereas rotational movements may explain deeper cerebral lesions and the concussion. (3,4)

Contact forces prevent the head from moving after the first impact. Inertial forces set the head in acceleration (translation or rotational or both) with and without a contact impact. The two main scheme of TBI are focal and diffuse injuries. Contact impact causes focal injuries such as injury to the scalp tissue, skull fractures, extradural hematomas, coup contusion, and subdural hematomas. Intracranial pressure (ICP) changes and brain motion due to translation acceleration have been linked to focal injuries such as contrecoup contusion, intracerebral and subdural hematomas. Rotational acceleration as an notable factor of the insult mechanism produces gliding concussion and diffuse axonal injury. This later form of injury is identified by the presence of axonal retraction balls and microglia cluster in white matter. It has been held to represent tearing of axons with extrusion of axoplasm from the torn end. While this is an attractive explanation, it is probably an oversimplification because similar axonal retraction balls can be observed in condition in which the axons have not been torn. (5-10)

The first injury of TBI is characterized by direct tissue damage and impaired regulation of the cerebral blood flow (CBF) and metabolism (**Figure 1**). This "ischemia-like" pattern leads accumulation of lactic acid due to anaerobic glycolysis, increases the permeability of membrane and successive edema formation. The anaerobic process causes depletion of adenosine triphosphate (ATP), and failure of energy dependent membrane ion pumps occurs. (11,12) The primary insult also results in an immediate disturbance of the cerebral circulation, resulting in cerebral ischemia and contributes significantly to about 90% of deaths after closed TBI. The physiological response to injury includes a tremendous surge of arterial hypertension, and it has been postulated by Kontos and his colleagues that this event triggers off the arachidonic acid cascade resulting in the formation of singlet oxygen and other free radicals, thromboxane, prostacyclin, and the leukotrienes. These agents will in turn cause alterations in the caliber of cerebral vessel, their endothelial surface, and areas of intravascular stasis resulting in multifocal cerebral ischemia. (8,13)

Proposed injury factors have included produce of membrane breakdown such as free fatty acids, platelet activating factors, and free radicals as well as change in certain cations, serotonin, catecholamine, endogenous opiates, and neurotoxic excitatory amino acids such as aspartate and glutamate. (14,15). These changes develop immediately in cerebral ischemia, which accompanies synaptic paralysis and temporary cardio-pulmonary dysfunction. In animal studies, the initial release of the excitatory amino acid glutamate, which is modulated by constitutive nitrous oxide (cNO) free radicals, has been reported increase intracellular Ca^{2+} ion levels in injured brain tissue. (14) Ischaemia brain damage is perpetuated by factors such as hypotension, hypoxia, ICP, edema, focal tissue compression, damage to microvasculature, and in late phases, vasospasm in the remaining vessels. (16)

TBI begins with high energy acceleration or deceleration of the brain within the cranium or with penetration of the brain. Focal injuries tend to occur at the site of impact, with focal neurologic deficits referable to those areas. The orbito frontal and anterior temporal lobes are characteristic and are most commonly affected because of the location of the brain in relation to the irregular surface of the skull base. As cranial trauma tends to occur in an anteroposterior direction, the brain moves in similar fashion and is injured as it transverses over the skull base. The diffuse shearing of axons as a result of sudden deceleration or rotational forces may occur in the cerebral white matter, gray-white junction, corpus callosum, and brain stem, causing no lateralizing neurologic deficits such as encephalopathy, or focal deficits such as cranial neuropathies. (17)

The neuronal damage and cell loss have been documented in brain regions such as the cerebral cortex, hippocampus, thalamus and substantia nigra during the first few hours following experimental and clinical TBI. Consequently, brain function is rapidly disrupted at the site of injury and in the distal regions interconnected through white matter tracts, leading to likely deficits in higher cognitive and vital sensory-motor functions. In the animal model, the cortical neurons and neurons of the hippocampal CA 3 region and hilus of the dentate gyrus show the earliest evidence of TBI-induced degeneration. Notwithstanding the pathomechanisms underlying post traumatic neuronal cell death are not well understood, the development of sophisticated neuropathological, immunohistochemical, and the molecular strategy for animal model study and clinical of TBI have enable researchers to begin to deep explore the cellular and genomic cascades that mediate cell insult and death in hu-

mans following TBI. (18,19)

The secondary brain injury

Superimposed on trauma-induced mechanical injury, ”secondary” or delayed neuronal damage develops over a period of hours or days after the initial trauma. (5) Although the forces initiating the primary injury generally take less than 100 milliseconds to occur, the resulting pathophysiological events are much more prolonged and progressive and may ultimately be the deciding factors in the patient’s recovery. Evidence of secondary brain injury has been found at autopsy in 70-90% of all fatal TBI patients. (20) Frequently, these patients deteriorate clinically over following several hours and days, and at least 25% of these patients die. (21) For patients who survive the initial injury, morbidity and mortality will be determined by secondary injury processes. Despite numerous efforts to pharmacologically intervene in secondary injury, none have demonstrated clinical efficacy. These secondary damage events are thought to account for the development of many of the neurological deficits observe after TBI, and their delay nature suggest that there is a window for the therapeutic intervention to prevent progressive tissue damage and improve functional recovery after injury. Clearly, there is ample opportunity to improve the care of these patients, and much of the promise lies on the cellular and molecular strategy. (3,6)

The secondary brain injury is caused by a dynamic interplay between ischemia, inflammation, and cytotoxic processes. (16,21) (**Figure 1**) Studies with micro dialysis techniques have shown that one of the most significant factors causing secondary brain injury is the excessive release of excitotoxins such as glutamate and aspartate that occurs at the time of the primary brain injury. (16)

The key point is characterized by terminal membrane depolarization along with excessive release of excitatory neurotransmitters, activation of N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylioxasole-4-propionic acid/kainic acid (AMPA/KA), and voltage-dependent Ca^{2+} and Na^{+} channels. The consecutive Ca^{2+} and Na^{+} influx lead to self-digesting intracellular processes. Ca^{2+} activates lipid peroxidases, proteases and phospholipases, which in turn increase the intracellular concentration of free fatty acids and free radicals. (11) Pathological elevation in intracellular Ca^{2+} after TBI can precipitate an attack on the lipid bilayer cell membrane via the activation of calcium-dependent phospholipase and generations of reactive oxygen species (ROS). Although glutamate binds to all excitatory amino acids (EAA) receptor. The first type of glutamate receptor binds NMDA and is know as NMDA receptor. The second type of glutamate receptor binds excitatory ligand AMPA/KA and the third type of glutamate receptor is metabotropic receptor, unlike ionotropic receptors, is associated with the activation of an intracellular second messenger. (7)

The primary pathophysiological event in ischemia is mitochondrial dysfunction. (23) Recently TBI studies have shown the importance of mitochondria and cellular energy levels, specifically ATP, in determination of normal cellular function as well as cellular survival. Cell death has been thought to occur by one of separate processes, necrosis and apoptosis. In both pathways mitochondria have a paramount role. (21)

Morphologically, necrosis is characterized by cell swelling, damage to cytoplasmic organelles, randomized deoxyribonucleic acid (DNA) fragmentation leading to DNA smear following gel electrophoresis, membrane lysis with release of cellular contents, and stimulation of inflammatory mechanism. Cells undergoing apoptosis display different characteristic morphological and bio-chemical features from necrosis, including cell shrinkage, formation of apoptotic bodies, condensation of chromatin, nuclear fragmentation, and extensive inter nucleosome DNA fragmentation. (18)

Apoptotic neural death involves intracellular (i.e., mitochondria) and extracellular (i.e., Fas/Fas-ligand mediated pathways). (24) The consequence of mitochondria permeability transition pore (MPTP) opening is the process of apoptosis. When the MPTP is open cytochrome-C and other pro-apoptotic molecules are released from the mitochondria membrane to the cytosol. The caspase cascade is then activated, and the apoptosis process is triggered. (21,24) Apoptosis represents the primary mechanism of cell death and is regarded as the morphological of programmed cell death (PCD). (18) PCD has been confirmed as a major cause of post-traumatic neuronal cell death and is associated with poorer prognosis in patients after TBI. Morphologically defined PCD includes apoptosis, autophagy, paraptosis, calcium-dependent death, and oncosis. The cell death mechanism that mediate the specific PCD process include, among many others, caspases and pro-apoptotic members of the Bcl-2 family (apoptosis), c-Jun N-terminal kinase (JNK), autophagy related gene (ATG), extracellular signal-regulated kinase-2 (ERK-2), poly (ADP-ribose) polymerase (PARP), apoptosis inducing factor (AIF), calpains and cathepsis (calcium-dependent death). (25)

The initial moments after TBI can be categorized

in two concurrent phases as follows: 1) metabolic crisis and 2) excitotoxicity. In response to direct tissue injury, the cerebral metabolism is deranged, leading to the accumulation of lactic acid due to anaerobic glycolysis and edema formation. (26,27) Brain edema formation frequently occurs after TBI. The current classification of brain edema relates to the structural damage or water and osmotic imbalance induced by the primary and secondary brain injury. (11)

In the most cases of TBI, brain edema progress is associated with vasogenic brain edema. The vasogenic brain edema is caused by mechanical or autodigestive disruption or functional breakdown of the endothelial cell layer of brain vessel. Disintegration of the cerebral vascular extracellular (interstitial) brain compartments with ensuring water accumulation. Anatomically, this pathology increases the volume of the extracellular space. The main pathophysiological change of brain edema is interstitial edema with blood brain barrier (BBB) dysfunction. At the later stage, vasogenic brain edema promote cellular or cytotoxic edema. (14)

The cytotoxic brain edema is characterized by intracellular water accumulation of neurons, astrocytes, and microglia irrespective of the integrity of vascular endothelial wall. This pathology is caused by an increased cell membrane permeability for ions, ionic pump failure due to energy depletion, and cellular reabsorption of osmotically active solutes. (11) The areas of the brain with an impaired BBB and ischemia can cause cytotoxic brain injury as well. Neurons and glial cell are particularly susceptible to cytotoxic cell injury. Cytotoxic edema, if widespread, can be associated with increase ICPs, impeded CBF, and ischemia, yet not independently with permanent neurological impairment. (3)

The development of neuroinflammation that follows TBI involves a complex process of cumulative changes that occur within brain. (1) In the brain, local and systemic inflammation work in concert to contribute to secondary brain injury. Although the brain has been considered to be an "immunologically privilege" site, an immense body or recent data suggest that there is a marked local inflammatory response to injury, and that selected aspects of this response amplify secondary damage. (24,26)

The microglia are the primary innate immune cells in the brain. The microglia represent the first line of defense following TBI, when they become overactivated or reactive they can induce detrimental neurotoxic effects by releasing multiple cytotoxic substances, including pro-inflammatory cytokines. (6) Human and animal studies indicate that microglia are chronically activated for weeks, months, and even years after the initial brain trauma, and may contribute to chronic neurodegeneration and related neurological deficits following injury. (6,28,29)

The inflammatory response to TBI starts at the point of injury, with tissue damage leading to the release of danger-associated molecular patterns (DAMPs) such as high mobility group box-1 (HMGB-1), ATP, heat shock, and S100 proteins. Circulating DAMPs are bound by pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) on myeloid and dendritic cells, and receptors of advanced glycosylation end-products (RAGE). Ligand recognition by these PRRs trigger the production of pro-inflammatory cytokine either through direct intracellular transduction, or by oligomerization to form inflammasome. The predominant consequence of tissue injury, DAMPs release and inflammasome activation in marked increase in synthesis of pro-inflammatory cytokine such as interleukin-1β (Il-1β), Il-6, Il-18 and tumour necrosis factor-α (TNF-α), accompanied by a counter-regulatory rise in levels of anti-inflammatory cytokines including Il-10 and transforming growth factor-β1 (TGF-β1). (6,30)

The significant function of TNF-α as mediator intracerebral inflammation has been highlighted by evidence from studies in the early 1990s. These studies demonstrated that the TNF-α can induce cerebral inflammation, cellular neurotoxicity, breakdown of the BBB, and intracranial leukocyte recruitment in various experimental setting. (20)

A potent mediator of intracranial inflammation and BBB damage is also represented by the pro-inflammatory cytokine Il-1. While Il-1α represents the mainly membrane bound form, and Il-1β is the secreted molecule which is largely responsible for Il-1-induced neurotoxicity. (20) As in of TNF-α, Il-1 might be involved in modulating the apoptosis process after TBI, and might be play a significant task in the neuronal survival as some studies suggest. The responsibility of Il-6 is more ambiguous as it has both pro- and anti-inflammatory actions. Il-6 levels in plasma and cerebro spinal fluid (CSF) increase after severe TBI. (21,31)

The concept of "dual role" of inflammation in TBI, it explains that many of formerly designated pro-inflammatory mediators have shown to possess potential effects in mediating deleterious as well as repair processes in the central nervous system (CNS). (20) In animal studies provided evidence that mice with a genetic deficiency of TNF and

members of TNF family, such as lymphotoxin (formerly designated as TNF-β) as well as the deficiency of TNF receptors have a worse outcome and a higher mortality than their wild-type littermates in the later period after injury. (20,32) It should be noted that most of the TBI study suggested involvement of cytokines in mediation of neurotoxic effects, while some CNS injury studies reported the participation of cytokines in neuronal survival and neuroprotection. (7)

The tertiary brain injury

The tertiary stage of TBI is due to the persistent inflammation and epigenetic changes, which cause a blockade of oligodendrocyte maturation, impaired neurogenesis, impaired axonal growth, or altered synaptogenesis. In chronic condition after injury, the presentation might be as sensitization to cognitive dysfunction, cell loss and seizures during subsequent inflammation. (33)

The chronic microglia activation can serve as a regenerating source of inflammation. The ongoing inflammation associates with the degree of white matter tract damage as a result of pararel underlying process, such as an abnormal protein deposition acting as a DAMP, or a consequence of failure to deactivate following acute injury or microgliosis. (30)

DAMPs released by injured neurons after TBI interact with toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) on activated microglia and trigger a vicious self-perpetuating cycle of damaging events that lead prolonged and dysregulated microglia activation that drives pathogenic processes and neurodegeneration. (6,34) TLRs are family of PRRs. TLRs are a class of proteins that are the important factors in the innate immune system, including cytokine release after activation DAMPs molecules. TLRs activation reprograms the adult neuroimmune response, sensitizing it to adult brain inflammation and injury, accelerating age-related cognitive decline and increasing susceptibility to seizure. (33)

Chronic microglia activation has been implicated directly in neurotoxicity by ROS production via nicotinamide adenosine dinucleotide hydrogen (NADPH) oxidase and pro-inflammatory cytokines such as TNF-α, indeed microglia activation has itself been demonstrated to drive hyperphosphorylation and aggregation of tau protein, further complicating the relationship between proteinopathy and inflammation. Increased levels of pro-inflammatory cytokines including Il-1β, Il-6, Il-18, and TNF-α persist, and associate with outcome in a dose-dependent manner, CSF Il-1β levels are predictive of development of post-traumatic epilepsy. (30,34) (**Figure 1**)

There is increasing evidence showing that TBI is associated with neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS). Rudelli, et al reported a case of classic AD pathology in a 38-year-old severe TBI, both tau pathologies and amyloid beta (Aβ) deposits were identified in survivors of single TBI. (35-38) Aβ1-42 has also been observed in the CSF of severe TBI patients and is thought to be directly related to the increased level of cerebral Aβ and neuronal amyloidogenic amyloid precursor protein (APP) level after TBI. (35,39-43) Aβ deposits not only commonly found in the brains of elderly patients who died from AD, but has also been found in one-third of TBI patients, some of whom are children. It is also known that people who experience such a TBI have a 400% increased risk of developing AD. (44) Recent studies employing transgenic mice engineered to overexpress human APP 2-fold failed to produce amyloid plaques or altered behavioral outcome. Young PD-APP mice has been shown to induce marked ipsilateral hippocampal atrophy with diminished Aβ-PP deposition during aging. (5)

In contrast to AD, studies attempting to correlate TBI and MS, another neurodegenerative, demyelinating disease of the CNS, are limited. Goldacre (45) and Kurland (46) found the evidence of association between TBI and the development of MS. However, risk analysis using Taiwan's National Health Insurance Research Database, indicated higher risk of incidence of MS in patients with a history of TBI compared to non TBI control group. (35,45-47) PD is a neurodegenerative disorder, which affects the dopaminergic neurons of the substantia nigra. PD-associated mitochondria dysfunction and pathology was observed after mild to moderate TBI and trichloroethylene (TCE) exposure in rats. (35,48) Also, TBI was reported to cause the nigrostriatal dopaminergic neurodegeneration in a rat model of lateral fluid percussion injury (LFPI) suggesting that TBI is a risk factor of PD development. (49)

Apolipoprotein E4 (ApoE4) allele has been shown to be a strong risk factor for AD may play direct assignment in Aβ deposits in vivo. The ApoE gene is located on chromosome 19 and important genetic polymorphisms for this gene exist including allele E2, E3, and E4. (24) Individuals who possess the E4 allele are at 2-6 fold increased risk of developing AD. (24) A significant genetic association of ApoE polymorphism with outcome after

TBI has recently been reported by Teasdale, et al, who showed that patients with ApoE4 are more than twice, as likely those without ApoE4, to have an unfavorable outcome 6 months after TBI. (18,50) Recently, Teasdale and colleagues reported that the frequency of ApoE4 in individual with Aβ deposits following TBI is higher than in most studies of AD, suggesting a genetic susceptibility to the effects of clinical TBI. (24,50,51)

The study of genes that influence outcome following TBI is still in its early stages. Evidence has been rapidly accumulated in the literature, particularly in the last decade, identifying genetic polymorphisms associated with the pathophysiology and outcome following TBI. (52) The genes associated with these polymorphisms play multifactorial parts in regulating the brain's response to injury and include both anti- and pro-inflammatory cytokines, DNA repair enzymes, signalling molecules, and neurotrophins. These variations are a result of alterations in the DNA sequence within a given gene and are referred to as genetic polymorphisms. Polymorphisms can arise from insertions or deletions of short lengths of DNA within a particular gene, interfering with the normal function of the gene, or at a single nucleotide (G, A, T, or C). When a single nucleotide is responsible for the modification in the DNA, it is referred to as a single nucleotide polymorphism (SNP). SNPs are the most common type of genetic variation, occurring once every 100-300 nucleotides, amounting to approximately 10 million in the human genome. (52-55)

Evidence from recent studies support the involvement of epigenetic mechanisms in the post-injured brain. (56) Epigenetic refer to functional changes to the genome that alter gene expression, but do not change the underlying DNA sequence. Epigenetic modifications include enzymatic regulation of transcription by the modification of permissive tags (acetylation, methylation) on histone or DNA or via microRNA (miRNA)-mediated regulation of translation. In human beings, acetylation regulates transcription of up to 5% of the genome, and every human gene can be regulated by at least one miRNA. (33,57-62)

DNA methylation in mammalian cells refers to the addition of a methyl group from S-adenosyl methionine (SAM) to the 5th carbon atom of cytosine forming 5-methylcytosine (5-mc). The reaction is catalyzed by the family of DNA methyltransferases (DNMTs). The opposing mechanism of demethylation is carried out by a set of enzymes, which maintain the homeostasis of DNA methylation in concert with DNMTs. Methylation primarily occurs at cytosine residues with adjoining guanosine, commonly referred to as cystidine phosphate guanosine (CpG) sites. (63-66)

Few studies have directly investigated the charge of epigenetic modification. One study, in which DNA methylation changes were examined early following contusion TBI in rats revealed that global hypomethylation was seen early (day 1 post injury) in regions of widespread necrosis, and slightly delayed in more peripheral regions (day 2 post injury). Further analysis showed that hypomethylation occurred mainly in activated microglia, suggesting hypomethylation defines a sub-population of microglia involved in the early processes following TBI. By a specific gene locus, insulin-like growth factor-1 (IGF-1) in the hippocampus, it was found that TBI associated with DNA hypermethylation at one region within the gene (exon 5 and upstream), and DNA hypomethylation at another (downstream of exon 5). The temporal epigenetic changes correlated with the expression of IGF-1 and the splice variant, IGF-1B, which have been shown to play prominent neuroprotective actions in brain's endogenous response following TBI. (56,67-71)

The principal component of chromatin other than DNA is the histone proteins, which forms chromatin architecture along with DNA. Histones possess highly basic amino acids that protrude from the histones, commonly referred to as histone tails. Histone tails undergo various post-translational modifications (PTMs), manifesting in altered sculpting of nucleosomes affecting internucleosomal interactions. (63)

During the acute and secondary phases of brain injury there is substantial loss of acetylation and methylation tags and considerable variation in miRNA expression. Reduced acetylation is associated with cognitive decline, which is accelerated after brain injury. A recent study has demonstrated that low-level radiation exposure in mice would increase concentration of miRNA-21, and oncomiRNA that stimulated cell growth and proliferation. Another miRNA, miRNA-107 might contribute to the pathogenesis of AD and reduced after TBI, ischemia, and hypoxia. Together, these findings suggested that changes in epigenetic processes, which could disrupt neurodevelopment, might also persist and caused tertiary brain damage. (59-62) (**Figure 1**)

Conclusion

The pathomechanism processes in TBI are dynamic and extremely complex that involve a broad spectrum of cellular and molecular pathways. The

primary TBI is characterized by direct tissue damage and impaired CBF and metabolism. In consequence of this insult, a cascade of ischemia, cytotoxic, and inflammatory processes are initiated, leading to secondary TBI. Chronic activation of microglia and epigenetic changes are the key role of tertiary TBI mechanisms.

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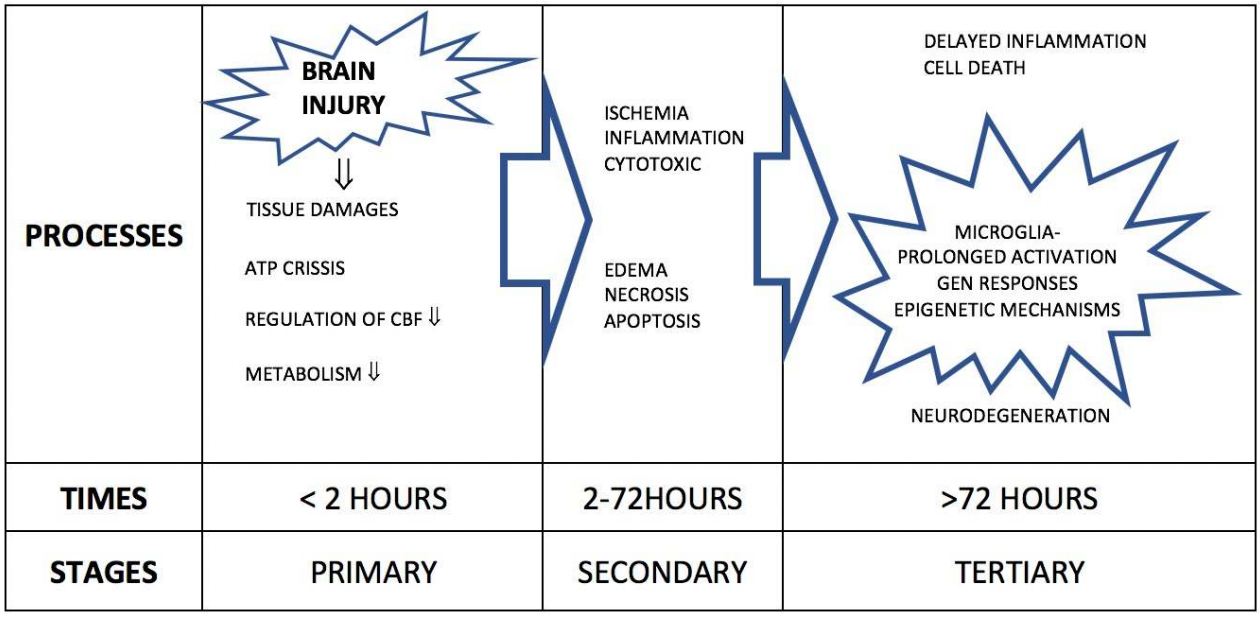
Figure 1. Stages, times, and processes of TBI



Legend: TBI=traumatic brain injury; ATP=adenosine triphosphate; CBF=cerebral blood flow.

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