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Review

Genetic Contributions to Recovery following Brain Trauma: A Narrative Review

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Abstract

Traumatic brain injury (TBI) is a frequently encountered form of injury that can have lifelong implications. Despite advances in prevention, diagnosis, monitoring, and treatment, the degree of recovery can vary widely between patients. Much of this is explained by differences in severity of impact and patient-specific comorbidities; however, even among nearly identical patients, stark disparities can arise. Researchers have looked to genetics in recent years as a means of explaining this phenomenon. It has been hypothesized that individual genetic factors can influence initial inflammatory responses, recovery mechanisms, and overall prognoses. In this review, we focus on cytokine polymorphisms, mitochondrial DNA (mtDNA) haplotypes, immune cells, and gene therapy given their associated influx of novel research and magnitude of potential. This discussion is prefaced by a thorough background on TBI pathophysiology to better understand where each mechanism fits within the disease process. Cytokine polymorphisms causing unfavorable regulation of genes encoding IL-1β, IL-RA, and TNF-α have been linked to poor TBI outcomes like disability and death. mtDNA haplotype H has been correlated with deleterious effects on TBI recovery time, whereas haplotypes K, T, and J have been depicted as protective with faster recovery times. Immune cell genetics such as microglial differentially expressed genes (DEGs), monocyte receptor genes, and regulatory factors can be both detrimental and beneficial to TBI recovery. Gene therapy in the form of gene modification, inactivation, and editing show promise in improving post-TBI memory, cognition, and neuromotor function. Limitations of this study include a large proportion of cited literature being focused on pre-clinical murine models. Nevertheless, favorable evidence on the role of genetics in TBI recovery continues to grow. We aim for this work to inform interested parties on the current landscape of research, highlight promising targets for gene therapy, and galvanize translation of findings into clinical trials.

Keywords: traumatic brain injury; recovery genetics; pathophysiology; cytokine polymorphism; mitochondrial DNA; gene therapy

1. Introduction

Neurotrauma, or traumatic brain injury (TBI), is a major public health concern that affects millions of individuals worldwide each year. In the United States alone, it is estimated that over 2.8 million people sustain neurotrauma annually, with around 50,000 deaths and over 280,000 hospitalizations resulting from these injuries [1]. The most common causes of neurotrauma include falls, motor vehicle accidents, and violence. Despite advances in treatment protocols, neurotrauma often leads to long-term physical, cognitive, and emotional deficits that can greatly impact the quality of life of those affected. The management of neurotrauma requires a multidisciplinary approach, including early diagnosis, prompt treatment, and ongoing rehabilitation to optimize functional recovery.

The diagnosis and management of neurotrauma is complex and requires a coordinated effort from a variety of medical professionals, including neurologists, neurosurgeons, rehabilitation specialists, and neuropsychologists [2]. The severity of TBI is typically classified according to the Glasgow Coma Scale (GCS), which assesses the patient's level of consciousness, motor function, and verbal response. Mild TBI (mTBI), also known as concussion, is the most common form of TBI and accounts for approximately 75% of all cases [3]. In contrast, moderate to severe TBI is characterized by prolonged loss of consciousness, post-traumatic amnesia, and neurological deficits [1]. The management of TBI is aimed at minimizing secondary brain injury, which can occur due to cerebral edema, hypoxia, and ischemia, among other factors [4,5]. Treatment may include surgery to remove blood clots or relieve intracranial pressure, medications to control seizures or reduce inflammation, and rehabilitation to help patients recover physical and cognitive function [4].

While the outcomes of neurotrauma can vary widely, recent research has highlighted the important role of genetics in determining the degree and rate of recovery following brain injury [6,7]. Specifically, pro- and anti-inflammatory cytokines have been shown to play a critical role in the inflammatory response that occurs after TBI, which can have

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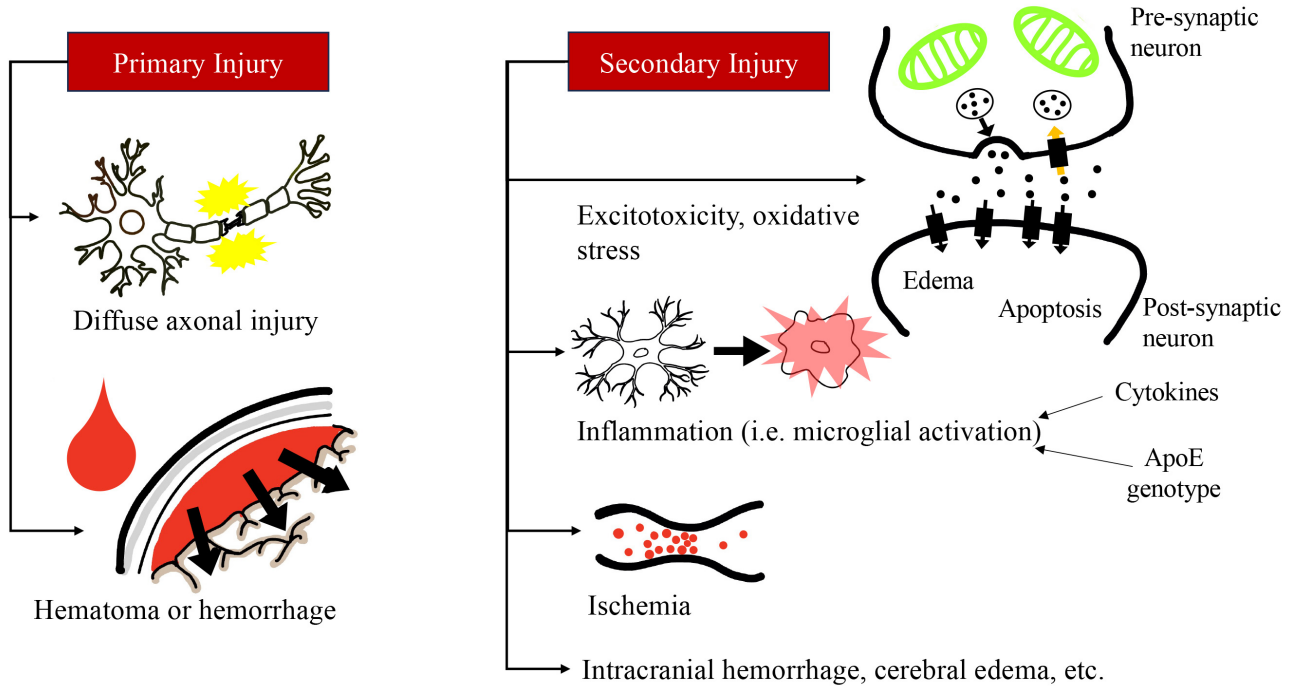

Fig. 1. Traumatic brain injury pathophysiology. Main pathophysiological mechanisms underlying traumatic brain injury, including primary and secondary mechanisms of injury. Primary and secondary mechanisms of injury are further broken down into their various subtypes. ApoE, apolipoprotein E.

a significant impact on the degree of brain damage and functional outcomes [8,9]. Cytokines are small proteins that are produced by immune cells and play a crucial role in regulating the immune response. Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), are upregulated in response to brain injury and can lead to secondary tissue damage [10,11]. In contrast, anti-inflammatory cytokines, such as interleukin-10 (IL-10), have a protective effect and can help reduce inflammation and promote tissue repair [12].

In addition to cytokines, certain repair mechanisms and genes have also been implicated in the recovery process following TBI [10,13,14]. For example, the brain-derived neurotrophic factor (*BDNF*) gene regulates the corresponding BDNF protein which plays a critical role in neuronal regeneration and synaptic plasticity and has been shown to be upregulated after TBI [15,16]. Other genes involved in the repair and regeneration of neural tissue include growth factors, such as insulin-like growth factor-1 (*IGF-1*), and transcription factors [17]. Understanding the genetic contributions to recovery following TBI can help identify new therapeutic targets and improve treatment outcomes for those affected by these injuries.

The purpose of this review paper is to summarize current research on the genetic contributions to recovery following brain trauma, with a particular focus on the role of cytokines and repair mechanisms. This work will synthesize current knowledge, highlighting key findings and identifying gaps in understanding. Additionally, potential future directions for research and clinical practice, including the development of personalized treatment approaches based on individual genetic profiles will be discussed.

2. Pathophysiology of Traumatic Brain Injury

TBI occurs when an external force causes two stages of cerebral injury, primary and secondary injury (Fig. 1). The primary injury occurs at the time of mechanical trauma through irreversible localized loss of brain tissue and injury of microvascular structures, diminishing cerebral blood flow regulation and metabolism [18,19]. Depending on the severity of impact, this initial injury triggers a cascade of pathophysiological effects that causes injuries beyond the site of primary damage, leading to further neurological dysfunction. These secondary injuries include inflammation, cerebral edema, excitotoxicity, oxidative stress, ischemia, intracranial hemorrhages and gliosis. Secondary injury pathways can evolve over hours to days, persist after TBI, and be explained by pathogenetic mechanisms.

2.1 Inflammation

Acute focal inflammation emerges within minutes of brain injury and disruption of the blood-brain barrier and is mainly characterized by the release of damage-associated molecular patterns, vasodilation, infiltration of leukocytes and release of inflammatory mediators, like chemokines, proteases, cytokines and reactive oxygen species (ROS), by

activated astrocytes and microglia. In animal models, inflammatory mediators were significant contributors to disseminated brain inflammation after TBI, which may be caused by TBI-induced transcription changes [20]. Arenson *et al*. [21] demonstrated extensive reorganization of gene coexpression patterns in hippocampal cells in 24-hour (acute) post-mild TBI animals. Mild TBI cell clusters were found to have a larger number of differentially expressed genes (DEGs) in astrocytes than other cell types. In contrast, lineage-specific transcriptome analysis 7-days following (subacute) severe TBI showed significantly more upregulation in gene expression of DEGs in microglia compared to astrocytes. Additionally, many of the top DEGs in both microglia and astrocytes were in the type I interferon signaling pathway, potentially a key contributor to neurodegenerative pathology [22,23].

Pathology and imaging studies have shown chronic, global activation of microglia in post-TBI patients, which may underlie secondary neurodegenerative pathologies like dementia, Parkinson's disease and chronic traumatic encephalopathy [24]. Todd *et al*. [22] found that the top DEGs in subacute TBI microglia were also found in microglial in the setting of neurodegeneration (*Lgals3bp*, *Clec7a*, and *Lpl*). The role of microglia in post-TBI inflammation was further characterized by Witcher *et al*. [25], who demonstrated microglia-dependent increases in expression of inflammation, interferon and chemokine-related genes over time. Acute TBI transcriptional responses were largely microglia-independent, while the immune processes that are thought to underlie subacute and chronic TBI injuries were microglial-dependent. Notably, Alzheimer's disease mouse models have implicated reactive microglia in the spread of phosphorylated Tau [20]. Therefore, injury-induced gene expression may contribute to the acute and chronic global immune responses in patients with TBI and the evolution of secondary pathologies like neurodegeneration.

2.2 Cerebral Edema

Post-TBI damage to cerebral vascular structures directly decreases blood flow and, subsequently, oxygen to the surrounding tissues [18]. Anaerobic glycolysis follows, leading to an increase in lactic acid and the failure of ATP-dependent mechanisms such as ion pumps [18,19]. The disruption in ion homeostasis leads to an intracellular accumulation of sodium and water that causes cytotoxic edema. Oxidative stress and mitochondrial dysfunction further contribute to the development of cytotoxic edema. Damage to the cerebral blood vessels also triggers an inflammatory response, including the activation of the membrane attack complex, that attacks the endothelial cells and disrupts the blood brain barrier [26]. The increased vascular permeability leads to extravasation of fluid into the extracellular space, otherwise known as vasogenic edema. Studies on rat models of TBI have found that the membrane protein aquaporin 4 (AQP4) may mediate edema formation, with AQP4 gene expression upregulated in cytotoxic edema and downregulated in vasogenic edema [24].

2.3 Excitotoxicity

TBI induces excitotoxicity through the excessive release and impaired uptake of glutamate. Mitochondrial calcium overload, triggered by N-methyl-D-aspartate (NMDA) receptor activation, leads to free radical generation, and mitochondrial membrane damage, ultimately causing apoptotic or necrotic neuronal cell death [19]. Astrocytes normally clear extracellular glutamate via excitatory amino acid transporters such as glutamate-aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1), but their expression is reduced after injury, likely worsened by inflammation-induced nuclear factor-κB (NF-κB) signaling [27]. This impairs glutamate buffering, exacerbating excitotoxicity. Variability in genes regulating glutamate signaling, such as GLT-1 transporters, may influence individual susceptibility to excitotoxic damage after TBI.

2.4 Genetic Predispositions

The severity of the primary injury combined with certain genetic predispositions can impact a patient's recovery from TBI. Individuals with apolipoprotein E (APOE) 4 isoform have a high risk of developing post-traumatic cognitive impairments and Alzheimer's disease due to reduced effectiveness in clearing amyloid-beta protein from the brain, further contributing to inflammation and oxidative stress [28,29]. APOE4 mice with repeated mild TBI showed more inflammation, neurodegeneration, and activated microglia, and less BDNF than APOE3 mice [30]. Following TBI, increased BDNF signaling has been associated with reduced inflammation and edema, and the effects of BDNF may depend on age. A study on severe TBI found younger patients with hypothesized no-risk *BDNF* alleles had higher probabilities of survival compared to older patients with the same alleles [31,32]. Therefore, genetic variations of BDNF, glial cell line-derived neurotrophic factor, and their receptors likely contribute to differences in an individuals' susceptibility to secondary TBI injury.

3. Role of Cytokine Polymorphisms

Cytokine polymorphisms are best defined by looking at its individual parts. Polymorphisms are similar but distinct entities from mutations in that both can represent variations in genetic sequences between different individuals of the same species. However, polymorphisms represent common changes while mutations represent rare variants that little to no other population members possess [33]. Polymorphisms can range from single nucleotide variations to clusters of nucleotides that repeat throughout the genome [34]. This, when combined with the previously described cytokines, best defines cytokine polymorphisms as common variants in genetic sequences that encode for proteins involved in intercellular signaling.

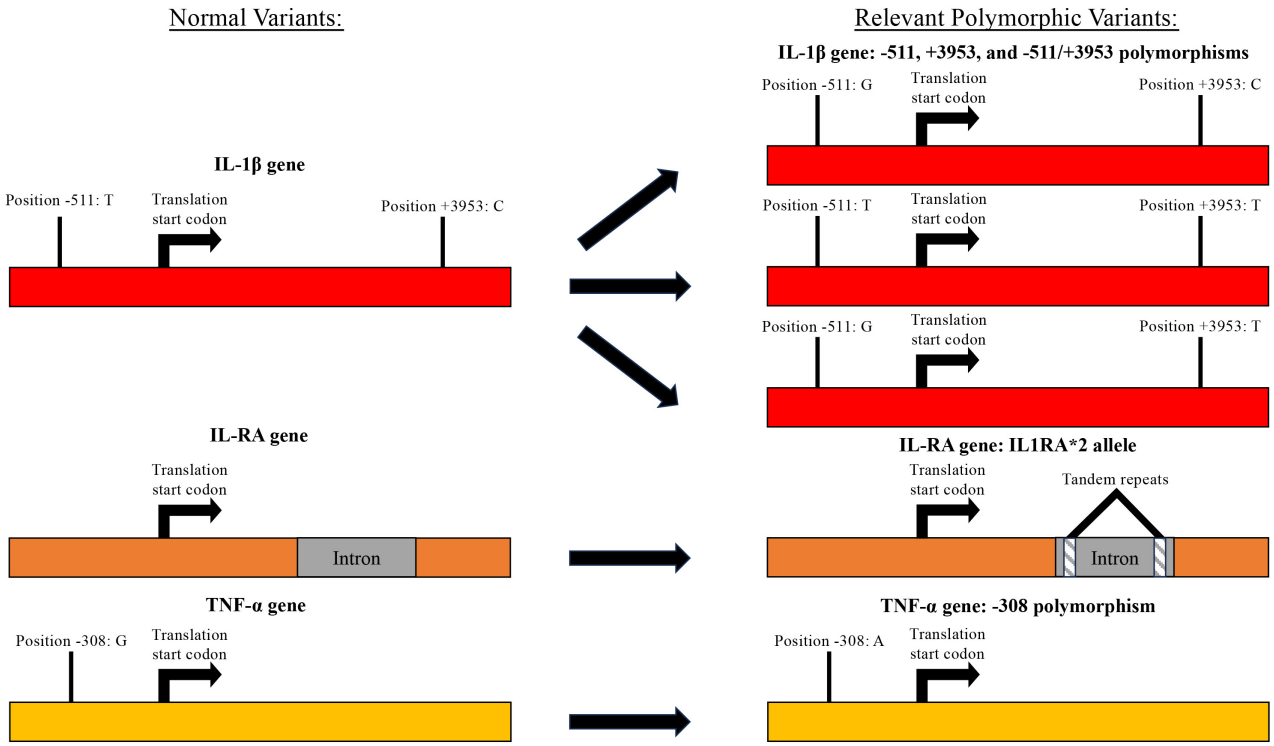

Fig. 2. Relevant cytokine polymorphisms and associated normal genes. Visualization of critical cytokine genes and associated polymorphisms linked to worsened traumatic brain injury outcomes. Positive (+) and negative (-) positions are relative to translation start codons. Note that image sizes and distances are not to scale. *IL-1β*, interleukin-1 beta; *IL-RA*, interleukin-receptor antagonist; *TNF-α*, tumor necrosis factor-alpha; T, thymine; C, cytosine; G, guanine.

The role of cytokine polymorphisms was first described more than two decades prior in an attempt to better understand the pathophysiology of diseases affected by cytokines and/or identify potential new targets for therapeutics [34]. Since this time, statistically significant associations have been drawn between cytokine polymorphisms and susceptibility to a variety of pathologies including but not limited to adverse drug reactions, infectious disease, cardiovascular disease, autoimmune disease, neurodegenerative disease, psychiatric disease and cancer [35–45]. A common theme connecting these disease processes is inflammation–a direct sequelae of altered cytokine function. It has therefore been suggested that developing targeted therapy towards modulating these cytokines may not only prevent the onset of these disease processes but also improve their response to treatment [35,36,39,40,42,45].

The potential role of cytokine polymorphisms modulating inflammation associated with TBI has inspired subsequent study. Work on this subject first focused around alterations in genes encoding interleukin-1 alpha (IL-1α) and IL-6 with later works including study of IL-1β, IL receptor antagonist (IL-RA), TNF-α, transforming growth factor-beta (TGF-β) and lectin pathway proteins [46–48]. The most recent review articles about cytokine polymorphisms and TBI were published in 2021 with no similar publication types since. At the time, Gomez *et al.* [46] examined seven studies spanning over the past 20 years and found conflicting data regarding the association or lack thereof between *IL-6* polymorphisms and TBI [49–51]. They found similar lack of associations involving lectin pathway polymorphisms and TBI; however, they did highlight literature reporting associations between IL-1β and TNF-α polymorphism and TBI [46,51–53]. Zeiler *et al.* [47] shortly followed with a review involving nine studies of cytokine polymorphisms over a similar time frame. It should be noted that five of these nine articles overlapped with those analyzed by Gomez *et al.* [46,47,50,51,53–55]. Zeiler *et al.* [47] provided more context on some of the published results by not only reporting lack of clear association between *IL-1α* polymorphisms and TBI but also highlighting poorer TBI outcomes in patients with certain *IL-1β*, *IL-RA*, and *TNF-α* polymorphisms [51,53–56]. They echoed Gomez *et al.* [46] regarding the lack of clear consensus when describing the association or lack thereof between *IL-6* polymorphisms and TBI outcomes [47,49,50].

Surveying the current literature using techniques similar to those of the studies mentioned above reveals no additional publications regarding cytokine polymorphisms and TBI. With this in mind, focus will be placed on polymorphisms involving *IL-1β*, *IL-RA* and *TNF-α* given their demonstrated associations with TBI [51,53,56] (Fig. 2). The *IL-1β* polymorphisms described specifically refer to

Table 1. Characteristics of studies discussing mtDNA haplotypes.

Study title	Author	Publication year	Other characteristics	Reference number in manuscript
Mitochondrial DNA and traumatic brain injury	Bulstrode *et al.*	2014	n = 880 included TBI patients *Study type*: Prospective cohort study *Outcomes*: structured questionnaire + GOS score	[60]
Mitochondrial polymorphisms impact outcomes after severe traumatic brain injury	Conley *et al.*	2014	n = initially 136 TBI patients expanded to 336 patients *Study type*: Prospective study *Outcomes*: GOS, NRS, DRS at 3 months, 6 months, 12 months	[61]

mtDNA, mitochondrial DNA; TBI, traumatic brain injury; GOS, Glasgow Outcome Scale; NRS, Neurobehavioral Rating Scale; DRS, Disability Rating Scale.

the –511 and +3953 positions within the gene, which are occupied by guanine (G) and thymine (T) nucleotides (versus T and cytosine (C) nucleotides in others), respectively. Uzan *et al.* [53] reports correlation between these polymorphisms and higher rates of persistent vegetative state, severe disability and death post-TBI, suggesting these genetic variations may have potentiated IL-1β's positive effect on intercellular adhesion molecule-1 production (and subsequent inflammation). The *IL-RA* polymorphism described specifically refer to *IL1RA*2* allele of the gene, where each patient has two copies of tandem repeats within the intron. Hadjigeorgiou *et al.* [56] reports correlation between this polymorphism and higher rates of intracranial hemorrhage six months after TBI, suggesting this genetic variant may limit the negative effect IL-RA normally has on IL-1 function and its associated inflammatory properties. The *TNF-α* polymorphism described specifically refers to the –308 position within the gene, which is occupied by an adenine (A) nucleotide (versus a G nucleotides in others). Waters *et al.* [51] reports correlation between this polymorphism and higher rates of persistent vegetative state, severe disability and death six months post-TBI, suggesting this variant may have increased production of TNF-α and potentiated its known role in initiating intracranial inflammatory responses.

Although these associations were statistically significant, the limited amount of studies with supporting data should be increased. Additional large sample studies from a variety of medical centers with diverse patient panels can improve the external validity of these results. If this data is obtained and aligns with previous findings, we also recommend research into possible gene editing therapy to both resolve these polymorphisms and improve TBI outcomes.

4. Role of Mitochondrial DNA Haplotypes

Mitochondrial DNA (mtDNA) is the circular double stranded DNA found inside the mitochondria of eukaryotic cells. It was first discovered by Margit and Sylvan Nass in 1963 and is mostly inherited in a maternal fashion due to the increased concentration of mtDNA found in egg follicles compared to sperm [57]. The role of mtDNA has largely been focused on its responsibility for the metabolic functions and energy production of cells; however, emerging literature focused on animal and human studies show how mtDNA dysfunction can lead to advanced age, disease progression, and neurodegenerative diseases [48]. Despite these advances in research, there have been limited studies focused on mtDNA haplotypes and their role in TBI recovery. Here we explore the role of mtDNA haplotypes in TBI and discuss research efforts that have been made to further understand their function in TBI and TBI recovery.

There are 37 total genes contained within mtDNA. Thirteen of those genes are located on one polypeptide which is responsible for cellular energy through oxidative phosphorylation [48,57]. In TBI, the decreased oxygen supply to the injured brain results in increased anaerobic metabolism which is the direct result of mitochondrial damage. The consequences of this include an overproduction of ROS, excitotoxicity, increased lactic acid levels, and calcium overload [48,58]. Because of its proximity to the electron transport chain, mtDNA is susceptible to ROS which can introduce mutations within mtDNA. Due to the lack of robust repair mechanisms in the mitochondria, the mutations accumulate and become fixed over several generations due to mtDNA maternal inheritance [59]. These variations are haplotype groups and allow researchers to understand how the mitochondrial mutations can affect disease progression and aging overtime.

Mitochondrial haplotype groups or haplogroups are defined as a population that shares the same mtDNA sequence or similar mutations and polymorphisms. They are labeled A-Z with some haplogroups showing increased susceptibility to disease, while other haplogroups showing protective measures against disease [48,59,60]. After conducting a review of the literature, there were two notable studies that discussed the role of haplogroups in TBI recovery (Table 1, Ref. [60,61]).

Conley *et al*. [61] in 2014 looked at how mitochondrial polymorphisms impact outcomes after a patient sustains a severe TBI. They used numerous measures including Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), and Neurobehavioral Rating Scale (NRS) to evaluate these outcomes over three, six, and twelve months post TBI. They identified nineteen mitochondrial single nucleotide polymorphisms with four of them (A10398G, A4917G, T195C, and T4216C) indicating significant associations ($p < 0.05$) [61]. Of particular relevance to mitochondrial haplotypes was the A10398G allele. The A10398 allele is associated with haplotype H whereas the 10398G allele is associated with haplotypes K and J with the former showing slower recovery time and the latter showing faster recovery time after a TBI [48,61].

In the same year, Bulstrode *et al*. [60] published a large study with over 800 patients and analyzed the frequency of the various mtDNA haplogroups in the United Kingdom. The researchers postulated that variability within mtDNA haplotypes could be a component of the various outcomes after a TBI. They specifically looked at individual haplotypes H, J, T, U, K, as these were commonly seen in the European population [60]. When they measured the GOS over a 6 month period after a TBI, they found that most patients exhibited haplogroup H and that their haplogroup distribution for their patient cohort was supported by other UK studies. Interestingly though, patients with haplotype K were significantly associated with a more favorable outcome after a TBI compared to patients without haplotype K ($p = 0.02$). In addition, haplogroups K and T were associated with a more protective effect as a result of advancing age ($p = 0.015$, $p = 0.017$, respectively) [60]. Since haplotypes T and K share a common maternal ancestor, this could explain their similar findings with regards to advanced aging.

The role of mtDNA haplotypes in TBI has not been thoroughly explored to date. Many literature articles published after 2014 reference Bulstrode's paper when discussing haplotypes and TBI recovery. Future efforts should be made to explore specifically haplotypes K, T, and J as these have been shown to be protective and lead to better outcomes after a TBI. In addition, studies to date have focused on European and American populations. Future research should include haplotypes from other populations to better understand and investigate potential protective effects not explored to date.

5. Role of Immune Cells

As mentioned previously, immune cells like microglia are thought to play a critical role in perpetuating inflammation during the subacute interval of TBI [22,23,25]. This has led researchers to investigate whether genetics influence microglial function, and by extension, patient outcomes post-TBI. DEGs represent one of the key findings arising from research in this area. By definition, DEGs refer to how all cells contain identical genomic DNA but variably express encoded genes depending on their function, environment, and host's disease state [62]. Section 2.1 highlighted how DEGs such as *Lgals3bp*, *Clec7a*, and *Lpl* were highly expressed by microglia in both subacute TBI patients and neurodegenerative patients; however, these constitute only a portion of the clinically important DEGs [20,23]. Other examples of microglial DEGs upregulated post-TBI include *Serpina3* and *Lcn2* which are associated with inflammation and neurodegeneration, respectively [63–65]. Contrastingly, Zhao *et al*. [63] also identified increased microglial expression of neuroprotective DEGs like *Timp1* which is known to help maintain patency of the blood-brain barrier [66]. Genetic components of microglia therefore serve as promising areas of future development, and other immune cells offer similarly exciting prospects.

Monocytes have an equally influential part in managing neurological inflammation after TBI. They are thought to infiltrate the blood-brain barrier from peripheral circulation through a variety of mechanisms following initial stress responses [67,68]. Like microglia, their prolonged activation has been shown to worsen inflammation, causing subsequent neurodegeneration and poor outcomes [69–71]. Much of the genetic research surrounding monocytes has subsequently revolved around qualities that predispose patients to high levels of central nervous system (CNS) monocyte invasion. The *Ccr2* gene has been of particular interest given its role in monocyte chemotaxis [72]. Multiple murine model studies have demonstrated improved neuroprotection (i.e., improved post-TBI cognition and mood) upon *Ccr2* gene knockout or silencing [73–76]. Conversely, Gyoneva *et al*. [77] showed that impairing *Ccr2* could also have deleterious effects. They found that although less *Ccr2* led to smaller TBI lesion volumes, it simultaneously built-up neurodegenerative phosphorylated tau proteins. Moving beyond *Ccr2*, additional genes of interest include *CXCR2* and *TLR4*. *CXCR2* is also involved in monocyte chemotaxis, so its increased expression has been correlated with increased monocyte invasion and poorer patient outcomes [78]. Inversely, the inhibition of *TLR4* facilitates monocyte infiltration. Baassiri *et al*. [79] interestingly showcased how blocking TLR4 actually improved TBI outcomes in mice, suggesting interplay from anti-inflammatory monocyte variants. These types of complex interactions are not limited to microglia and monocytes, instead extending to multiple other components of the innate immune system.

Regulatory factors serve as important signals that can dictate the role of immune cells during TBI. For example, macrophage colony-stimulating factor (mCSF) is a cytokine that is paramount for the production and function of both microglia and monocytes [80,81]. Modulation of mCSF has consequently become a target of interest in genetics research. Li *et al*. [82] reported that genes encoding mCSF were significantly upregulated in murine mod-

Table 2. Characteristics of gene therapy methods.

Gene therapy type	Current methods	Potential gene targets	Current limitations
Gene modification	Introduction of foreign genes via adenoviruses or liposomes to overexpress protein products from these genes	*Bcl-2* *APOE3* *IGF-1*	Current studies only completed in rats. Vectors exist to introduce foreign genes and are translatable.
Gene inactivation	Usage of siRNA or other gene knockout methods to decrease gene activity thereby decreasing protein products from these genes	*AQP4* *Sirt2* *RIPK1* *RIPK3* *CCR5*	Current studies only completed in mice or rats. Knockout methods that utilize siRNAs or pharmacological blockade appear most translatable in the near future.
Gene editing	Usage of CRISPR/Cas9 for gene removal or augmentation to overexpress or underexpress downstream protein products	*Keap1* *yCD-UPRT*	Studies only done at the cellular level or on mice.

Bcl-2, B-cell lymphoma 2; *APOE3*, apolipoprotein E3; *IGF-1*, insulin-like growth factor-1; *siRNA*, small inhibiting RNAs; *AQP4*, aquaporin 4; *Sirt2*, Sirtuin 2; *RIPK1/3*, receptor-interacting serine/threonine-protein kinase 1/3; *CCR5*, cysteine-cysteine chemokine receptor type 5; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9; *Keap1*, Kelch-like ECH-associated protein 1; *yCD-UPRT*, yeast cytosine deaminase-uracil phosphoribosyltransferase homolog.

els with favorable TBI outcomes, suggesting a neuroprotective effect. Importantly, however, mCSF is also known to induce inflammatory microglia variants in the presence of certain cytokines [83,84]. Further clinical studies are subsequently needed to elucidate the predictive role of mCSF genetics on TBI outcomes. Other relevant regulatory factors include IL-4 and TGF-β, which have both been historically associated with inducing anti-inflammatory variants of monocytes [85,86]. Studies have since demonstration extension of the property to TBIs, as impaired expression of *IL-4* and *TGF-β* have been correlated with worse neurological function and recovery [87,88].

6. Emerging Evidence on Gene Therapy for Brain Trauma

Gene therapy, a rapidly advancing field with significant potential, has recently gained considerable attention for TBI treatment. Gene therapy includes various methods like gene modification, repair, or inactivation [89]. In a recent study, Wang *et al*. [89] summarized potential gene therapy options for TBI treatment and all cited studies were within the past decade, except one. Here, we review the options summarized by Wang *et al*. [89], and discuss their potential (Table 2).

Gene modification involves modifying the expression of proteins from foreign genes. In TBI studies that utilized gene modification, common vectors such as adenoviruses and liposomes were used to introduce these foreign genes. Foreign genes introduced included B-cell lymphoma 2 (*Bcl-2*), *APOE3*, and *IGF-1* [90–92]. The overexpression of these genes all showed improved neurological outcomes such as improved behavior and working memory in rats with TBIs compared to controls. Bcl-2 and APOE3 reduced cell apoptosis and TBI-induced neuronal death respectively while IGF-1 reduced reactive gliosis [90–92]. One difference among these three studies was that in the study by Herrera *et al*. [92], the adenoviral vectors of *IGF-1* were injected intramuscularly into rats three weeks prior to subjecting them to the TBI whereas in the other two studies, the rats already sustained their TBI prior to receiving *Bcl-2* or *APOE3*. From a practical standpoint, *Bcl-2* and *APOE3* gene therapies appear to be more appropriate translational targets for gene modification since they are shown to be effective treatments after a TBI; whereas *IGF-1* gene therapy would need to be proven through trials where it is given after a TBI.

Gene inactivation involves utilizing gene knockout or small inhibiting RNAs (siRNA). Guan *et al*. [93] showed that siRNAs could inhibit *AQP4* expression and decrease brain edema at the early stages of a TBI in rats. Three other studies utilized gene knockout to demonstrate gene inactivation. Wang *et al*. [94] demonstrated that knockout of Sirtuin 2 (*Sirt2*) was neuroprotective against TBI in a mouse model by reducing brain edema, neuroinflammation, and neuronal pyroptosis while also improving neurological function when compared to controls. It was also found that mice who were receptor-interacting serine/threonine-protein kinase 1/3 (RIPK1/3) deficient had significantly less brain damage on imaging and improved memory function on behavioral tests compared to controls suggestive that *RIPK1/3* expression is correlated with necroptosis [95]. Joy *et al*. [96] discussed how cysteine-cysteine chemokine receptor type 5 (*CCR5*) knockdown in cornu Ammonis 1 and 3 (CA1 and CA3) hippocampal circuits can be beneficial for TBIs. In their discussion, they also found that Maraviroc, a *CCR5* antagonist commonly used treatment for HIV, shared similar results to *CCR5* knockout. They demonstrated that mice with CCR5 knock out or pharmacological blockade via Maraviroc made less errors in the Barnes maze post TBI when compared to controls [96–98]. While the *RIPK1/K3*

and the *Sirt2* studies have significant promise, these studies utilized rats that were specifically bred to have these gene knockouts so likely more time will be needed to translate these treatments. On the other hand, siRNA treatments do exist and the usage of siRNAs to inhibit *AQP4* expression may be readily translatable. Although *CCR5* knockout gene therapy sounds promising, it may make more short-term sense to continue exploring Maraviroc for TBI since CCR5 gene inactivation and Maraviroc have both shown efficacy. Exploring the potential treatment paths involving Maraviroc as a *CCR5* knockout substitute via pharmacological blockade and siRNAs for *AQP4* knockout seems to be within closest reach for the clinical treatment of TBIs.

Gene editing, frequently employing clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9), was another gene therapy method used by researchers to investigate treatments TBI. Hu *et al.* [99] discovered that knockout of Kelch-like ECH-associated protein 1 (*Keap1*) gene sequence led to enhanced anti-oxidation and anti-inflammation. Although conceptually this sounds promising for neurodegenerative conditions and TBI's, this study was done at the cellular level and more research would be needed to explore this in animals who have suffered TBIs. Imai *et al.* [100] took a different approach with CRISPR/Cas9 genome editing to create neural stem/progenitor cells (NS/PCs) that overexpressed yeast cytosine deaminase-uracil phosphoribosyltransferase homolog (*yCD-UPRT*) which showed that mice transplanted with NS/PCs during the acute phase of TBI had improved performances in both the beam walking and accelerating rotarod tests compared to the control group. Though results were promising, there were some limitations such as the use of immunocompromised mice. In general, gene editing shows promise but is likely farther away from becoming a treatment for TBI in humans relative to gene inactivation and modification methods.

7. Limitations and Future Directions

This review highlights the development of many promising novel gene therapies, but these therapies must overcome many challenges before they can become the standard of care for patients with TBI. Current limitations with gene therapy for TBI include the need to determine the optimal mechanisms for vector delivery into the CNS, dosing, and timing of administration. All known TBI gene therapy studies to date utilize murine models, so additional preclinical research refining specificity, safety and efficacy of gene therapy will be needed before human trials [101]. For instance, viral vectors are associated with broad tropism, high production costs and inflammation. Delivery systems are being designed and studied to combat such limitations, especially since inflammatory reactions are involved in the development of post-TBI neuropathology [102,103]. Additionally, while animal studies have evaluated the efficacy of gene therapy based on objective measures of TBI like imaging or biomarkers, not all studies have evaluated for neurological function such as improved memory, cognition, etc. The complex heterogeneity of TBI implies that improvements in objective measures may not directly translate to improvements in cognitive deficits. Therefore, functional outcomes will need to be assessed in preclinical TBI studies to better predict real-world clinical benefits for patients.

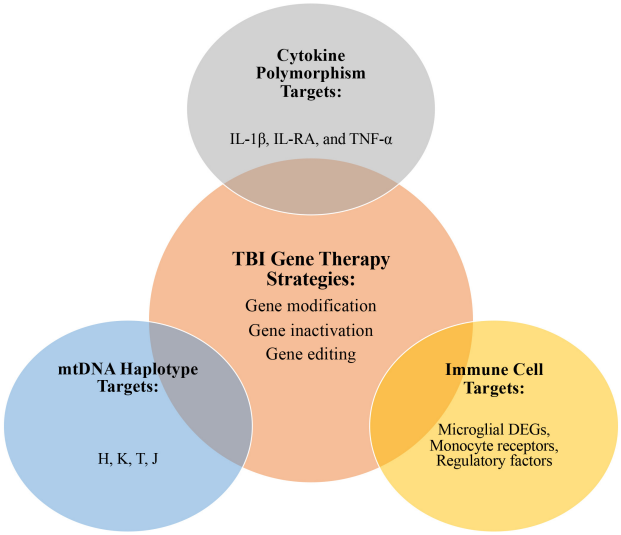

Fig. 3. TBI gene therapy strategies and possible genetic targets. Illustration of TBI gene therapy strategies and linked, possible genetic targets with examples. TBI, traumatic brain injury; IL-1β, interleukin-1 beta; IL-RA, interleukin-receptor antagonist; TNF-α, tumor necrosis factor-alpha; mtDNA, mitochondrial DNA; DEGs, differentially expressed genes.

Regarding future directions, gene therapy shows considerable promise for personalized neuroprotection for TBI. Specific targets for gene therapy are identifiable throughout the course of injury. Prior to injury itself, all patients could be prophylactically screened (i.e., at routine annual visits) for polymorphisms in genes encoding *IL-1*β, *IL-RA* and *TNF-*α in addition to mtDNA haplotype H. Apolipoprotein E screening would also be appropriate. Those with high-risk sequence variant could subsequently have a note made in their record, so patient-specific gene therapy could be immediately administered if they were to experience a TBI. Once primary injury has occurred, fast-acting gene therapy aimed at downregulating neurodegenerative-associated DEGs and monocyte receptors could limit initial inflammatory burden. After the subacute phase has been reached, secondary injuries like excitotoxicity could be mediated by enhancing expression of genes encoding glutamate transporters like glucose transporter protein type 1 (GLUT-1) [27]. Inverse gene therapies aimed at improving TBI recovery are also valid. Specifically, treatments aimed at upregulating neuroprotective DEGs, monocyte receptors, and regulatory factors could limit scarring and ensure maximum neurocognitive rehabilitation.

It is important to note that the gene therapy strategy described above is speculative at this time and requires extensive groundwork prior to becoming a reality. First, more guidance needs to be established regarding the ethics of personalized medicine. Rules surrounding agreeable use and privacy of patient-specific genomic data should be established well before widespread clinical testing. Second, significant additional research into the role of cytokine polymorphisms, mtDNA haplotypes, and immune cells in TBI is required (Fig. 3). Current data on all these topics is sparse with little to no testing on human subjects—a required precursor for any government-approved clinical treatment. And finally, third, exploration into new possible genetic targets and treatment modalities should remain a priority. Although advancement of research on known topics is critical, undiscovered genes may be more efficacious with less adverse effects. Similarly, combination gene therapy targeting multiple pathological mechanisms simultaneously may offer synergistic benefits. These steps may be rigorous but are invaluable in ensuring gene therapy to be both an available and reliable therapeutic avenue for TBI patients.

8. Conclusions

The pathophysiology of neurotrauma is complex and often requires a multidisciplinary approach to diagnose and manage patients with TBIs to minimize devastating complications. To date, there have been incredible efforts to research and understand the role of genetics in TBI and TBI recovery. This review aims to not only showcase these efforts, but also highlight research gaps that can lead to further exploration of genes and genetic mechanisms implicated in TBI recovery. The role of certain cytokine polymorphisms like *IL-1*β and *IL-RA* have been shown to be associated with higher rates of severe disability and persistent vegetative state after a TBI. In contrast, mtDNA haplotype K is associated with a more favorable outcome after a TBI. Immune cell genetics such as microglial DEGs, monocyte receptor genes, and regulatory factors can be both detrimental and beneficial to TBI recovery. Gene editing, modification, and inactivation in rat studies, have been shown to be neuroprotective, decrease brain edema post TBI, and lead to improved neurological outcomes. For example, overexpression of genes *Bcl-2*, *APOE3* and *IGF-1* are associated with improved working memory post TBI, inactivation of *Sirt2* was neuroprotective against TBI, and use of CRISPR/Cas9 editing to knockout *Keap1* showed anti-inflammation and anti-oxidation properties. While there is still more research to be done, current literature shows promising strides in these areas with a possible goal of developing targeted therapies to minimize complications or decrease recovery time from TBI. It is imperative to continue performing further studies related to the genes identified in this review and continue to explore the role that they can serve in treatment.

Author Contributions

DL conceptualized the idea and methodology. DL, SR, AB, JL, and GK conducted the investigation, formal analysis, and data visualization. DL and SR validated the reproducibility of the research methods. All authors contributed to the original draft and editorial changes in the manuscript. BLW designed the project and supervised the research team. DL oversaw project administration. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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