Review

Immunobiology of Facial Nerve Repair and Regeneration

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Abstract Immunobiological study is a key to revealing the important basis of facial nerve repair and regeneration for both research and development of clinic treatments. The microenvironmental changes around an injured facial motoneuron, i.e., the aggregation and expression of various types of immune cells and molecules in a dynamic equilibrium, impenetrable from the start to the end of the repair of an injured facial nerve. The concept of "immune microenvironment for facial nerve repair and regeneration", mainly concerns with the dynamic exchange between expression and regulation networks and a variety of immune cells and immune molecules in the process of facial nerve repair and regeneration for the maintenance of a immune microenvironment favorable for nerve repair. Investigation on microglial activation and recruitment, T cell behavior, cytokine networks, and immunological cellular and molecular signaling pathways in facial nerve repair and regeneration are the current hot spots in the research on immunobiology of facial nerve injury. The current paper provides a comprehensive review of the above mentioned issues. Research of these issues will eventually make immunological interventions practicable treatments for facial nerve injury in the clinic.

Key Words microglia; T cell; cytokine network; microenvironment; signaling pathway; repair and regeneration; facial nerve

Introduction

The neuronal response to injury, which includes immune involvement, has a dual nature. On the one hand, the inflammatory response exhibits features similar to those in other body tissues, namely, involvement of tissue remodeling. On the other hand, it behaves very differently because of the specialized nature of the neuronal tissue. The neuronal repair program and the immune surveillance response are two of the key modules regulating cellular changes in the injured brain. Both modules probably contain different subsets controlled by specific molecular mechanisms.

At present, neuritis and demyelization are generally acknowledged as common and pathophysiological bases of peripheral facial paralysis (Bell's paralysis, traumatic, infectious and others) by scholars worldwide. Cellular immune response and humoral immune response play a key role in the outbreak and development of peripheral facial paralysis. The time course and morphology of microglial activation suggest that preregenerative and neuroprotective functions are carried out by microglia. Cytokine network plays a vital role in the regulation of repair and regeneration of facial nerve by up- and down-regulating various parameters of immune function. Additionally, as central regulatory cells of the immune system, T cells mediate many of their functions via the secretion of cytokines. Moreover, a series of transcription factors, cell death signaling pathways, cell adhesion molecules signaling recognition, and other cellular and molecular events have been investigated extensively for their roles in the repair and regeneration of facial nerve.

In summary, multiple aspects of cross talks between the immune and the nervous systems are involved after neuronal injury. Immunobiological study is a key to discover the basis of facial nerve repair and regeneration. The focus in this review is on microglial activation and recruitment, T cell behavior,
the role of cytokine networks and immunological cellular and molecular signaling pathways in facial nerve repair and regeneration, in an attempt to provide essential information for transition of facial nerve research from the laboratory to the clinic.

**Microglial activation and recruitment**

**Microglia: more than the APC**

Studies have suggested that macrophages and/or dendritic cells may act as the antigen presenting cell (APC) in nerve injury. Another type of cells, e.g., microglia, are also capable of acting as an APC. It has been shown that, after facial nerve transection, microglia become activated and upregulate both major histocompatibility complex 2 (MHC II) and B7-2 (required for a cell to be classified as an APC). Additionally, it has been shown that T cells are present in the facial nucleus after facial nerve transection\(^3, 4\). Taken together, these data suggest that microglia, rather than a peripheral APC, may play a critical role in antigen presentation after nerve injury.

Microglial activation in the facial nucleus is triggered within hours after the injury, and increased numbers of activated microglia remain in the area for at least 2 weeks, at which time some axons have already reinnervated their targets. The time course and morphology of microglial activation suggest that proregenerative and neuroprotective functions are carried out by microglia. Perineuronal ensheathment of neurons by microglia accomplishes at least two neuroprotective actions: removal of excitatory input through displaced afferent synapses, and increase of physical proximity of axotomized neurons to microglial cells, which may facilitate targeted delivery of growth factors from activated microglia to injured neurons.

**Effects of immune surveillance with microglial activation and recruitment**

Microglial activation is among the first cellular changes in almost all forms of brain pathology. Kalla\(^5\) studied microglial activation and recruitment in repair and regeneration of facial nerve in a mouse model with macrophage colony-stimulating factor (MCSF) deficiency. This MCSF deficiency in the homozygous, osteopetrotic mice (op/op mice) interfered strongly with the early stages of microglial activation and proliferation and their spreading on the surface of injured but surviving facial motoneurons. These changes were accompanied by a clear reduction in the recruitment of T-cells during the first phase of lymphocyte infiltration into the axotomized facial motor nucleus within the first 24 hours after injury. In contrast, there were no apparent effects on the speed of axonal regeneration or neuronal survival. Astrocyte response and synaptic stripping were not affected. Delayed neuronal cell death also led to a normal microglial and lymphocyte response, with the formation of phagocytotic microglial nodules and a strong recruitment of T-cells to these breakdown sites of neuronal debris.

In the context of immune surveillance in the injured brain, this may lead to inactivation or disappearance of T-cells that recognize self-antigens on the surface of the bystander-activated microglial cells. In addition to the direct effects by MCSF on MCSF receptor-positive cells, MCSF deficiency in the op/op mice is also accompanied by a strong reduction in the recruitment of T-lymphocytes during the first phase of lymphocyte infiltration. The lack of MCSF receptors on T-cells themselves clearly points to a key role for the activated microglial cells in this early phase of immune surveillance\(^6\).

Activated microglial cells are a rich source of molecules that enhance or inhibit neuronal survival, regeneration, and other aspects of neural repair. The injury-mediated production of NO, interleukin-1 (IL1), reactive oxygen radicals, proteolytic enzymes, or excitotoxic substances may all contribute to the pathology in the injured brain and enhance secondary damage\(^6, 7\). Stimulated microglia also synthesize neurotrophic molecules such as nerve growth factor (NGF), transforming growth factor-β1 (TGF-β1), and thrombospondin (TSP). Some microglial molecules may also act as a double-edged sword, depending on the active concentration and the pathological condition.

**The two modules: neuronal repair program and immune surveillance**

Microglial cells are activated very rapidly, and they proliferate, adhere to damaged cellular structures, such as injured neurons, and spread on their surface. The up-regulation of the antigen-presenting molecules (MHC1) and co-stimulatory factors and the recruitment of T-cells all point to the microglia playing a pivotal role in the immune surveillance of the injured brain\(^8\). MCSF deficiency interferes with early microglial activation. These data suggest that the cellular reaction to neural injury is organized into several separate sets of effects, or response modules, and there may be little
cross-talk between the different sets. In this concept, the neuronal repair program and the immune surveillance response are two of the key modules regulating cellular changes in the injured brain. Both of these modules probably contain different subsets controlled by specific molecular mechanisms. At present, little is known about the neuronal triggers that initiate these different cellular responses. The induction of transcription factors such as c-jun, junD, and STAT3 and their subsequent phosphorylation and translocation to the nucleus are very early events in the neuronal response to injury.

Neural injury induces a highly elaborate response from a variety of cells both in the peripheral and in the central parts of the nervous system. Understanding the overall organization, the hierarchy, and the molecular mechanisms involved in this response is clearly critical in designing strategies to reduce secondary damage and to improve repair in the damaged brain. Moreover, selective defects in the activation of particular cell types, such as the defective early activation in the op/op microglia, provide a particularly instructive lesson about the contribution of this cell type to the overall response as well as its organization on the molecular level. The absence of MCSF severely impaires the early phases of microglial activation. It does not affect axonal regeneration, synaptic stripping, neuronal survival, or cellular response of the neighboring astrocytes. However, it reduces the early recruitment of lymphocytes into the axotomized facial motor nucleus, suggesting that this cytokine plays a key role in the initiation of inflammatory changes in the brain and in the interaction with the immune system.

**T cell behavior in facial nerve research**

**T cell activation in repair and regeneration of facial nerve**

T cell activation is a result of complicated action between multiple ligand-receptors, which is offered by T cells and antigen, including the formation of immunological synapse (IS). The interactivity integration triggers the biochemical events of inner T cells that lead to cell immune responses. Such effects as acceleration or inhibition on activation, proliferation, differentiation and domino effects are processed through cell factors secretion and cell-cell contact. T cell activation plays a key role in both normal and pathology immunity responses. The degree and direction of immunity responses are determined by the degree and direction of activated T cells.

In the mouse facial nerve axotomy model, T cells infiltrated the central nervous system (CNS) through an intact blood-brain barrier (BBB) and homed to affected motoneurons. T lymphocytes appear to confer neuroprotection upon a selective population of facial motoneurons, as severe combined immunodeficient (SCID) mice, which lack mature T and B cells, show decreased neuronal survival following nerve injury when compared to wild-types. Adoptive transfer of functional T cells into SCID mice restores the neuroregenerative capacity of these animals to the levels of wild-type mice. Interactions between T cells and microglia may be critical in mediating neuroimmunological processes associated with neuronal regeneration in mice. Evidence suggests that infiltrating T cells may, in part, modulate levels of microglial reactivity induced by facial nerve axotomy.

There are strain-dependent differences in T cell infiltration and microglial reactivity. Moreover, microglial responsiveness in the axotomized facial motoneuron (FMN) appears to be regulated independent of the peripheral immune response. These data suggest that (1) T cells do not appear to modify measures of microglial reactivity in the axotomized FMN; and (2) the impact of T cell processes on injured motoneurons in immunologically intact and in immunodeficient mice grafted with T cells by adoptive transfer may be different.

**T cell subsets and facial motoneurons**

Cells of the acquired immune system, specifically T lymphocytes have been considered detrimental during a neurological injury and/or disease state. For example, the demylinating disease multiple sclerosis is thought to be mediated by both CD4+ and CD8+ T lymphocytes. Serpe's findings suggest that cells of the acquired immune system play a beneficial role in both neuronal survival and nerve regeneration after peripheral nerve injury. The results establish that CD4+ T lymphocytes, but not CD8+ T lymphocytes or B cells, mediate FMN survival after peripheral nerve injury. Additionally, natural killer(NK) cells have been ruled out as playing a role in mediating FMN survival after injury. Additionally, recent data that supports a positive role for T lymphocytes after injury, have demonstrated that self-reactive T cells are beneficial following spinal cord injury and/or optic nerve injury.

Facial nerve injury triggers both a peripheral response at the site of injury and a central response in
the area that includes the cell body and surrounding glia. Thus, there are multiple sites and populations of APC that could potentially influence CD4⁺ T cell activation and subsequent effector function after a nerve injury, such as a peripheral bone marrow-derived APC vs. a central resident microglial APC. Two findings have developed from these studies. First, while peripheral APCs are able to initiate CD4⁺ T cell activation, they are unable to maintain activation to promote CD4⁺ T cell-mediated facial motoneuron survival. Second, while parenchymal microglia are unable to initiate CD4⁺ T cell activation, they are able to re-activate a peripherally activated CD4⁺ T cell to mediate facial motoneuron survival, given that the T cell is first activated peripherally[12, 15]. Taken together, these findings suggest that a multi-step mechanism exists for the development of CD4⁺ T cell-mediated facial motoneuron survival, and that this mechanism involves both an initial CD4⁺ T cell activation step mediated by a peripheral APC and a reactivation step mediated by a central parenchymal microglial APC. Thus, while perivascular microglial cells have been implicated in APC function resulting in neurodegeneration, data from the facial nerve injury paradigm in chimeric mice suggest, for the first time, that parenchymal microglial cells play a necessary role in regulating neuroprotective effects. These data have also documented, for the first time, the existence of a direct role for parenchymal microglia in antigen presentation to a CD4⁺ T cell in vivo[12,15].

All of the data generated thus far suggest the following model, following a facial nerve injury and the release of an as-yet-unknown antigen, a peripheral APC phagocytoses/endoctyeses the antigen and presents it to a naïve CD4⁺ T cell residing within the draining cervical lymph node. Meanwhile, an as-yet-unknown signal from the periphery communicates the injury to the central microglia, which may release chemoattractants to recruit the peripherally activated CD4⁺ T cells centrally to the site of the nerve cell body. Once in the central compartment, the CD4⁺ T cells previously activated in the periphery are re-activated by parenchymal microglia in the CNS. To perform the motoneuron survival function, either the re-activated CD4⁺ T cell, the parenchymal microglial cell, another unidentified cell, or all of these cells, provide a trophic contact- and/or soluble-mediated signal that maintains motoneuron survival[21].

Cytokine network in repair and regeneration of facial nerve

The imbalance of cytokine network in neuropathological microenvironment

Recent data have shown that cytokine network plays a vital role in the regulation of nervous repair and regeneration by up- and down-regulating various parameters of immune function[22-24]. As central regulatory cells of the immune system, T cells mediate many of their functions via the secretion of cytokines. The inhibition of T cell proliferation has been associated with a down-regulation of Th1 cytokine interferon-γ(IFN-γ) and inflammatory cytokine tumor necrosis factor-α(TNF-α) in supernatants of the lymph node cells, as well as a marked increase in the production of Th2 cytokine IL-4 in the sciatic nerves. Kunzendorf et al. suggest that generating a balance between expression of Th1 and the Th2 type of cytokines may be an optimal goal for inhibiting severe autoimmune disease[25]. However, the observations also indicate that the role of cytokines in immune regulation and autoimmune disease is more complex than a simple Th1-Th2 dichotomy would suggest[26]. This is a complex process that can be influenced by the microenvironment. The functional distinctions between Th1 and Th2 subsets have major implications in nerve injury and neurodegenerative diseases and may underlie the neural destructive-protective nature of the immune response to neural damage.

Facial nerve injury induces activation of microglia and astrocytes and an up-regulation of proinflammatory cytokine expression such as TNF-α and IFN-γ within the facial nucleus[27, 28]. The Th2 lymphocyte, known to down-regulate inflammation in the periphery[29], may promote FMN survival by modulating the activation of glia and the proinflammatory milieu within the facial nucleus following nerve injury. Th2 cells secrete IL-4, IL-10 and IL-13, which have been found to down-regulate adhesion molecules and to induce death of activated microglia, as well as to suppress Th1 lymphocyte proliferation[30, 31]. The putative regulatory role for Th2 lymphocytes in promoting FMN survival after facial nerve injury may involve mediating the inflammatory responses to maximize the beneficial components and to mitigate ensuing destruction.

Data presented in this review paper suggest that CD4⁺ T cells differentiate into both Th1 and Th2 subsets within the periphery. It is plausible to propose that, subsequent to differentiation, Th2 cells may migrate into the facial nucleus to mediate a
self-regulating Th2 response, propagated by neuropeptides, cytokines, and trophic factors; whereas Th1 cells, which preferentially migrate towards areas of inflammation\[^{12}\], may migrate instead to the peripheral nerve injury site.

**Neurotrophins in facial nerve repair and regeneration**

Studies concentrating on the speed of axonal regeneration in the distal part of the nerve have thus far focused on three groups of factors - the trophic factors insulin-like growth factor (IGF)-1, IGF2 and brain derived neurotrophic factor (BDNF), the TGF-\(\beta\) superfamily member glial-cell derived neurotrophic factor (GDNF), and the neurokines leukaemia inhibitory factor (LIF) and IL-6. All three groups are implicated in the endogenous regulation of the repair process. Application of the closely related exogenous growth factors IGF-1 and IGF-2 enhances and application of antibodies reduces the pinch test-determined speed of axonal regeneration\[^{33, 34}\]. The combined overexpression of the neurokine IL-6 and its receptor resulted in improved nerve regeneration\[^{35}\], whereas, genetic deletion of IL-6 has been shown to lead to a 15% reduction in the morphometrically determined speed of axonal regeneration in the crushed facial motor nerve\[^{36}\]. Similarly, a moderate effect has also been observed using a functional, walking test following sciatic nerve crush\[^{37}\]. In contrast to this consistent but mild IL-6-mediated action in the periphery, there is substantial controversy regarding its effects on the CNS. Thus, deletion of IL-6 has been shown to reduce glial scar formation and improve central axonal sprouting in the facial motor nucleus model\[^{38}\], enhance functional recovery after spinal cord injury\[^{39}\], but eliminate the conditional injury-induced spinal axon regeneration\[^{40}\]. It has been demonstrated that endogenous neurotrophins are key mediators of the myelination program in the peripheral nervous system (PNS). By elucidating the mechanism of neurotrophin action on the myelination process, and characterizing this previously uncharacterized neuronal-glial interaction, new therapeutic strategies into myelin repair and the functional recovery of demyelinating peripheral neuropathies may be possible\[^{40}\].

In normal intact nerves, trophic factors are produced in the target organs, and conveyed to the cell body retrogradely. If the communication of axons with the cell body is interrupted by injury, Schwann cells in Wallerian degeneration produce neurotrophic factors including neurotrophins such as NGF and BDNF. Neurotrophins are released from the Schwann cells and dispersed diffusely in gradient fashion around regenerating axons. Regenerating axons extend along the density gradient of neurotrophins to the distal segment. Although many other trophic factors including IGF and fibroblast growth factor (FGF) are shown to be involved in the promotion of the outgrowth of regenerating axons, It is thought that, because of absence of signal peptides in the molecules, FGF and ciliary neurotrophic factor (CNTF) are released from the cells not by secretion but by mechanical damage as in injury to the cells. Schwann cells in the intact mature nerve appear to be morphologically inert. However, following axotomy they begin to proliferate at the early phases of Wallerian degeneration. Such proliferative Schwann cells are considered to produce neurotrophic factors actively.

**IL1, TNF and IFN in facial nerve repair and regeneration**

Galiano and Bohatschek explored the molecular mechanisms associated with the induction of MHC1 in the mouse facial motor nucleus after facial nerve transection. Their findings implicated actions of IL6 in the early, and IL-1 and TNF in the late microglial responses\[^{36, 41}\]. Facial axotomy models are characterized by two distinct types of cellular response. In the early phase, 1-4 days after facial axotomy, the rapid molecular changes in the axotomized neurons are followed by activation and proliferation of microglial cells and their attachment to the cell bodies of the injured but living neurons\[^{31}\]. In the second, much later phase, transection of the facial nerve leads to a loss of approximately 20-40% of the affected motoneurons\[^{8, 21, 42}\], with a peak in cell death at day 14\[^{43}\]. The neuronal debris is taken up and phagocytosed by surrounding microglia, which transform into rounded macrophages that aggregate to form large glial nodules. Their interaction with the invading lymphocytes\[^{1, 18}\] places the microglia into a strategic position to present antigens. The initial phase is associated with a strong upregulation of IL-6, transforming growth factor 1 and the receptor for the macrophage colony stimulating factor. The second phase is associated with upregulation of IL-1, IFN-\(\gamma\) and TNF-\(\beta\)^\[^{31}\]. Both groups of cytokines play an important, phase-specific role during the cellular and molecular changes in the adult mouse axotomized facial motor nucleus: early cytokines in the first phase,
late cytokines in the second \cite{36, 42}.

In summary, the current review shows that neural injury in the facial nerve axotomy model leads to an increase in MHC2 cells, an expression pattern that is tightly controlled in the subpopulation of perivascular macrophages. This post-traumatic increase of MHC2 cells is associated with the induction of inflammation-associated cytokines. It is regulated by the receptors for IFN-\(\gamma\) and TNF-\(\beta\). The effects of TNFR2 and IFNR1 deletions point to a complex, counterregulatory role of these cytokines in the immune surveillance of the injured nervous system.

**Cellular and molecular signaling pathway**

**Transcription factor signaling pathway**

In injured neurons, the prompt arrival of signals of cellular injury and stress is followed by the induction of transcription factors, adhesion molecules, growth-associated proteins and structural components required for axonal elongation. Accompanying this is the activation of intracellular signaling molecules, particularly molecules that control cell cycle and differentiation, synthesis of axonal transport molecules and cytoskeleton components, secreted growth factors and cytokines. And there is a general increase in energy, amino acid and lipid metabolism\cite{44, 45}. Following activation of mitogen-associated protein (MAP) kinase pathways, phosphorylation and nuclear localization of a host of transcription factors including c-jun, junD, ATF3, P311, Sox11 and signal transducer and activator of transcription (STAT)3, as well as decreased expression and activity of islet-1, ATF2 and nuclear factor kappa B (NF-\(\kappa\)B) \cite{9, 46, 47}, contribute to the change in gene expression of the injured neuron. In many cases, complete deletions of these transcription factors are embryonically lethal, limiting studies in vivo, in the adult animal. Neuronal specific deletion of STAT3 increases neuronal cell death after injury\cite{48}, to a degree similar with that observed for CNTF and LIF\cite{49}, thus pointing to the role of STAT3 as an intracellular survival-promoting factor. The effects of transcription factors on nerve regeneration are well characterized in the case of c-jun. A recent study using the facial axotomy model has shown that neuronal deletion of c-jun hinders the expression of genes and proteins associated with axonal regeneration, reduces the speed of target reinnervation and functional recovery significantly, and completely blocks central axonal sprouting\cite{50}. This is in keeping with previously demonstrated data\cite{51, 52} where deletion of jun blocked post-traumatic neuronal cell death and leads to severe neuronal atrophy. It also inhibits the recruitment of lymphocytes, and the activation of neighboring microglia.

Some axonal regeneration continues in the absence of c-jun, highlighting the importance of alternative pathways and compensatory mechanisms, which may be shared during developmental axonal outgrowth. These compensatory molecules may incorporate additional transcription factors such as STAT3 and ATF3\cite{50, 53}. Clarification of their role is needed to understand the signals regulating gene expression switches occurring in the regenerating neuron. The contribution of various signaling cascades, which are activated in response to neurotrophic factors in order to support motoneuron survival, changes during development and STAT3 becomes increasingly important under pathological conditions.

STAT4 and STAT6 are key regulation proteins involved in the CD4\(^+\) T cell differentiation pathways leading to Th1 and Th2 cell development, respectively. To determine which CD4\(^+\) T cell subset mediates FMN survival, the facial nerve axotomy paradigm has been applied to STAT4-deficient (\(+/+\)) and STAT6-/− mice and study data suggest that STAT6-mediated CD4\(^+\) T cell differentiation into the Th2 subset is necessary for FMN survival\cite{53}.

**Cell death signals**

Activation of the Fas death receptor leads to the death of motoneurons in culture. Ugolini used several mutant mice deficient for Fas signaling and made a novel transgenic FADD-DN (FAS associated death domain-dominant-negative) strain to investigate the role of Fas in programmed cell death in pathological situations. He found a novel role for Fas as a trigger of axotomy-induced death and suggested that the Fas pathway might be activated in pathological degeneration of motoneurons\cite{54}. With the exception of TNFFR2, these cell surface receptors carry a cytoplasmic death domain that exerts a pro-apoptotic signal through FADD. Furthermore, expression of dominant negative form of FADD has been shown to block the axotomy induced cell death signal due to fas and TNFR\cite{54}. Associated, downstream cytoplasmic cell death signals play a key role in promoting neuronal cell death in neonatal and immature animals that are sensitive to axonal injury. Deletion of bax or inhibition of caspase 3 or the whole family of caspases has been shown to prevent cell death\cite{55, 56}, but with an enhanced and more persistent effect for broad caspase inhibitors.
than caspase 3 alone.\[58\] In both cases, bax and caspases appear to act downstream of jun phosphorylation (jun-P) and the decrease in neuronal metabolism, suggesting a sequence of events beginning with jun-P, leading to atrophy and activation of bax, and ending with the initiation of the caspase cascade.

3 Cell adhesion molecules signaling recognition

Functional studies in vivo have thus far centered on the role of laminin, its alpha7 beta1 integrin receptor and galectin. Deletion of the gene encoding alpha7 integrin subunit results in a severe, approximately 40% reduction in the speed of motor axon regeneration following facial nerve axotomy and a strong delay in the reinnervation of its peripheral target.\[59\] Neuronal jun-deficient mice do not show an up-regulation of alpha7 after injury, which appears to contribute to the very poor regenerative response seen in these animals.\[60\] The absence of laminin, the primary ligand for the alpha7 beta1 integrin, leads to similar but more marked and lasting effects. Alpha7-deficient mice show immense up-regulation of the beta1 integrin following injury, which corresponds with a significant increase in central axonal sprouting and may imply compensatory mechanisms involving other, closely related alpha subunits. In keeping with their trimeric and multimodal structure, various laminins can act as ligands for a plethora of different receptors, including the integrins, gicerin/CD146, the 67 kDa laminin-receptor, alphadystroglycan, and b-1, 4-galactosyltransferase.\[61, 62\]. Application of exogenous galectin-1 has been shown to promote the speed of neurite outgrowth, whereas removal of endogenous galectin with antibody neutralization or through gene deletion decreases it.\[63\]. Galectin-1, in its oxidized form, also stimulates the migration of Schwann cells from the proximal and distal stumps, assisting in the formation of cellular bridges permitting axonal growth into the distal part of the injured nerve.

Summary and future directions

In conclusion, investigations on microglial activation and recruitment, T cell behavior, cytokine networks and immunological cellular and molecular signaling pathways are the key research fields in understanding immunobiology of facial nerve repair and regeneration. Manipulation of these events may provide opportunities to make immune interventions practicable and facilitate their transition from the laboratory to the clinic. The key incidents of nerve repair and regeneration, including microenvironmental changes in the injured nerve cells and axon, aggregation of various kinds of immune cells and expressions of a variety of molecules in a dynamic equilibrium, impede the entire nerve injury repair process. The concept of "immune microenvironment for facial nerve repair and regeneration" mainly concerns with the dynamic interaction between expression/regulation networks and various immune cells/molecules after the nerve injury, which maintains a favorable immune microenvironment for nerve repair and regeneration. Activated T cells selectively recruit immune cells (e.g., monocytes) and cytokines (e.g., neurotrophic factors), through mechanisms involving T cell-axon and neuron-Schwann cell/glial cell interactions, and regulate proliferation of Schwann cells and their support for the axons. Many questions remain in facial nerve injury research, regarding activation and recruitment of monocytes and/or macrophages; mechanisms of communication and interactions between T cells, neuronal axons, Schwann cells and glial cells; growth factors and signal pathways important in activation and recruitment of T cells and the MC/MP system; and molecular mechanisms of the action of specific T cells on FMN survival, to name a few. Further research will help answer these questions and enable us to deepen our understanding of the complex processes involved in facial nerve repair and regeneration.

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References

5. Blakemore WF. Cross talk between the immune system and


39 Powell SK, Kleinman HK. Neuronal laminins and their...