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 injuried facial motoneuron, i.e., the aggregation and expression of various types of immune cells and molecules in a dynamic equilibrium, impenetrate 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 variaty 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; microenviroment; 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[1]. 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 proregenerative 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 [2]. 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,

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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 histocompability 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[5].

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), transfoming 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