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Case Report

Cellular Component Bands of Bungner

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Abstract

Peripheral nerve injuries are common clinical conditions; thus, understanding their pathophysiology and advances in the field of nerve regeneration are important for the optimal treatment of patients. Regenerative events after injury have become increasingly important. A unique phenotypic expression, derived from already present cells, largely affects this process as a key phenomenon for recovering injured nerve function. Here, the available literature is reviewed to better understand this regenerative event and determine the series of cellular and molecular processes occurring at the axonal level. This review is the product of an investigative exercise by a research group in Research Incubator.

ABBREVIATIONS

WD: Wallerian Degeneration; **SC:** Schwann Cell

INTRODUCTION

Peripheral nerve injuries are common and have many causes, including traumatic, congenital, and metabolic causes. Their detection, appropriate diagnosis and treatment are critical for patients' recovery [1]. Therefore, understanding their pathophysiology, especially the regenerative events that occur after the moment of injury, is critically important for seeking new treatment options, as this type of injury is catastrophic for the patient both personally and professionally [2]. Much remains to be investigated in this field, especially at the cellular and molecular levels, to understand the complex series of processes that occur during axonal regeneration and functional recovery. This knowledge also benefits improving and accelerating these processes for better and faster recovery. This report reviews the discoveries made to date regarding a key cellular phenomenon during the process of peripheral nerve injury and regeneration [3].

In response to peripheral nerve injury, inflammation begins in the nerve cell body, axons and neuromuscular junctions [4]. This is an exceptional regenerative process, evidenced by chromatolysis at the nuclear level, which indicates a metabolic increase, edema of the axonal stump to prepare for growth and Wallerian degeneration (WD) at the end distal to the lesion. This leads to axonal and myelin disintegration [5], as they prepare to receive the axons that begin growing from the proximal end [6].

Wallerian Degeneration is usually a transient, acute process in reaction to a lesion, which occurs to regenerate the peripheral nerves. The participation of Schwann cells (SC) (glial cells from the peripheral nervous system) is critical for WD (Figure 1). These cells have impressive regenerative properties with a high degree of phenotypic plasticity, triggering a large-scale transformation of the myelin and non-myelin cells from uninjured nerves to repair the Schwann cells of the injured nerves, which is a unique characteristic when promoting repair [7]. This functional recovery contrasts that of the glial cells of the central nervous system, which respond in a way that inhibits repair [8].

SC genesis, development and differentiation are promoted and depend on molecular signals from the axons (Figure 2).

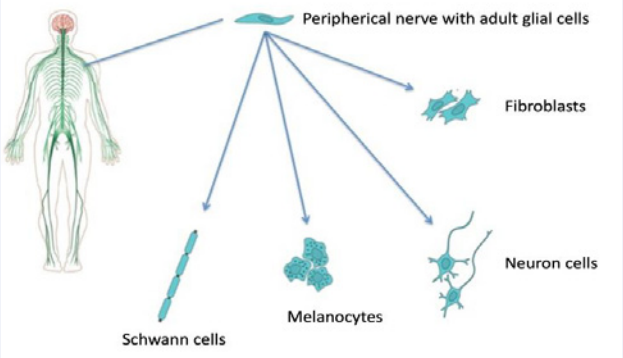

Figure 1 Peripheral glial cells are the sources of many neuroglial and mesenchymal cells.

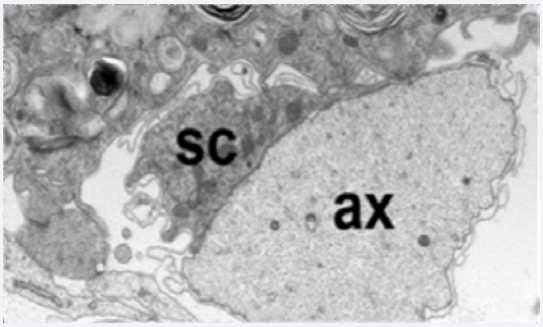

Figure 2 Electron micrograph of a healthy murine nerve showing an intact axon (ax) and its Schwann cell (SC).

During their life cycle, these cells can change naturally between a differentiated state and an immature or undifferentiated state known as the proliferative phenotype [9]. The differentiated state can be myelinating, which is a one-to-one association between axon and Schwann cell, or non-myelinating, in which multiple small-diameter axons align in the Schwann cell folds, forming Remak bundles [10] (Figure 3). Both states, and the process of changing between the states, are regulated by intrinsic cellular regulatory factors. Some factors are positive, such as Krox20, Sox10 and Oct6, which promote nerve myelination at the appropriate time during development and reestablish Schwann cell functions after a lesion, while others are negative, such as c-Jun, Sox2, Notch, Krox24 and Pax3, which lead to dedifferentiation and demyelination, thereby blocking the normal induction of myelination by cyclic AMP [11].

SC autophagy, or myelinophagia, during WD involves forming a double membrane for intracellular isolation that envelops a certain cytoplasmic load and transfers it to lysosomes known as autophagosomes for degradation. This autophagy is directed to destroy the myelin contained in the Schwann cells [12]. Thus, the myelin sheath is fragmented into oval segments, and its degeneration continues until it is reduced to intracellular detritus, a process that occurs during the first 5-7 days after injury [13]. The second phase of demyelination occurs by phagocytosis, an extrinsic process that attracts hematogenous macrophages to the injured nerve by Schwann cells, which, along with antibodies and the complement system, degenerate most of the lipids and myelin proteins. Schwann cells also participate in this phase to phagocytize the remaining myelin detritus [14].

Büngner cells

When injury occurs, Schwann cells passively return to a defective or immature cell state by inducing a blockade of factors that maintain their differentiation/myelination [15]. This process is described as double cell dedifferentiation, and along with this process, an alternative cellular repair pathway is activated those changes cellular functions [16]. In other systems, this process is known as transdifferentiation [17], and at the peripheral nervous system level, it results in new cells appearing that specialize in axonal repair (Figure 3), a process that continues to be studied [18].

This local axonal process consists of dedifferentiating mature Schwann cells into specialized repair cells called Büngner cells [19] (Figure 4). This involves an activation state and a new degree of cellular plasticity, representing a new cell type specialized in regenerating peripheral nerves by creating pathways that guide the axon to its target [20] by regeneration tracks called Büngner bands [21] (Figure 5). These bands carry the nerve fibers to the appropriate destination to restore function. In addition, they favor the survival of the affected peripheral neurons, preserving the axons that would otherwise die as well as opening the blood-brain barrier to recruit macrophages to the injury site for myelin debridement [22].

Transforming Schwann cells into Büngner cells requires extensive cell reprogramming that depends greatly on demyelination [23,24]. The mTOR pathway is activated in the

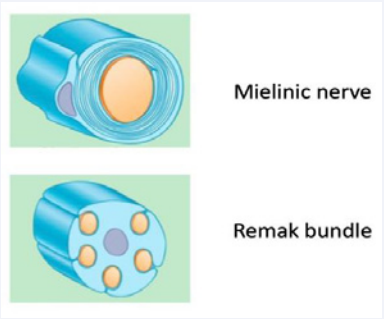

Figure 3 Transcription factors promote promyelination, in which Schwann cells acquire a one-to-one association with axons (myelinated axons). Other Schwann cells remain unmyelinated by adding multiple axons (Remak bundles).

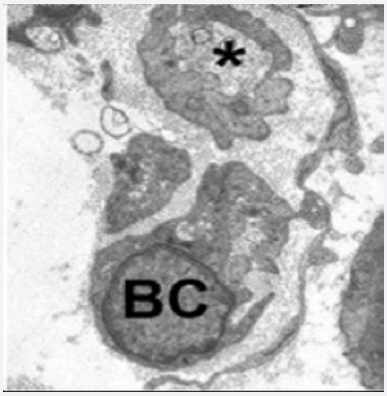

Figure 4 Small regenerative axonal buds (asterisk) and adjacent Büngner cells are typical tissue components of an injured peripheral nerve.

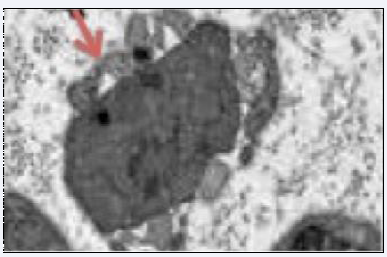

Figure 5 Regenerative pathway in the peripheral nerve distal to the lesion, composed of elongated Büngner cells (arrow) or Büngner bands.

injured nerve, which conducts important biosynthetic processes and accelerates catabolism and growth. These functions, along with demyelination, reorganize the morphological and molecular profiles of the myelin and non-myelin cells, converting them into Büngner cells [25].

This Schwann cell plasticity and Büngner cell appearance are regulated by a complex of signaling pathways and transcription factors that are activated at the distal end of the lesion as a response to injury [26].

Signaling pathways

Three signaling pathways, known as MAPK, have been described. First, the JNK pathway involves a serine-threonine kinase that phosphorylates the c-Jun factor, improving its activity and expression. Second, the Ras-MAPK pathway negatively regulates cell differentiation and myelination in Schwann cells [27,28]. Third, the p38 kinase pathway, with promyelinating action, is required to maintain the balance between promyelination and dedifferentiation [29,30] The primary transcription factors involved are c-Jun, Sox2 and the protein kinase Erk1/2, which induces generation of these cells and leads to a high expression of inflammatory cytokines, monocyte chemotactic protein 1 (MCP-1), macrophage inhibitor factor 1 and interleukin 1 (IL-1) [31,32]

c-Jun Factor

The transcription factor c-Jun is an antagonist of the promyelinating transcription factor, Krox-20 (also known as Egr2), and of promyelinic signals, such as elevation of cyclic AMP. c-Jun is upregulated during injury, leading to WD onset, demyelination or myelinophagia, and regulation of important neurotrophins, such as glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor, artemin and Sonic-hedgehog (Shh), and cell surface proteins, such as P75NTR, L1, NCAM and N-cadherin, molecules that may mediate Schwann cell and axonal interactions [33-35]

By promoting massive SC dedifferentiation into their multipotent precursors, phenotypic expression of Büngner repair cells and their neurotrophic and environmental support for effective axonal growth and neuronal repair at the proximal end of the lesion can also control the axonal regeneration rate [36,37]. In addition, c-Jun affects the genomic expression of Schwann cells, a function that is restricted during nerve injury and other pathological conditions, such as demyelinating diseases [38].

Sox2 Factor

The transcription factor Sox2 acts synergistically with the c-Jun factor to inhibit myelination and is critical for forming a “nerve bridge” through the lesional defect that will guide the proximal axon growth to the distal end [39]. This is mediated between the pre-formed Büngner cells and nerve fibroblasts, activating the N-cadherin to relocate and the injured nerve roots to collectively migrate [40,41]

DISCUSSION

Understanding the cellular and molecular mechanisms of SC interaction with axons components is essential by controlling axonal growth and regeneration and provides how to understand into the nerve repair and regeneration after different types of injuries [42]. Phenotypes changes during the process of nerve regeneration, are fundamental by optimize the different repair phases. One of those phenotypic modifications of the original SC, is necessary by formed the bands of Büngner, structure necessary by the axonal growth. For this process is relevant the expression of various molecular intracellular signals involved in SC motility and migration. The factor ERK 1/2 is important in mediating migration of SCs, and factor MAPK is a way of facilitating SC motility. It helpful in the expression of specific cytokine o pathways involved in these characteristics in the formation of bands de Bungner and promoting nerve regeneration [43]. Consequently, recued expression of these factors, mainly c-Jun and Sox-2 factors, reduce growth support and Büngner phenotype expression [44,45]. Therefore, the bands of Büngner they are formed by the phenotype change of SC, the Bungner cell, and for this to be fulfilled, it is necessary the expression of different types of factors, mediated by signals from distal stump of injured nerve and the process of wallerian degeneration.

CONCLUSION

SC are the key factors in regenerating peripheral nerves by returning to an undifferentiated state and giving rise to Büngner cells, which specialize in organizing and guiding axonal growth from one nerve stump to another as well as regulate transcription factors and molecular signals [42,45].

The characteristics exhibited by the c-Jun factor allow us to conclude that it acts as a “global regulator” of the repair program that leads to regenerating injured nerves. Understanding how c-Jun and other factors control this cellular repair, how these factors interact with other signals, and how their manipulation could increase the repair process and improve nerve repair has important clinical significance both for peripheral nerve lesions of various etiologies and for diseases that involve these tissues.

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