REVIEW ARTICLE

SCHWANN CELLS: LEADER OF NERVENKITT

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INTRODUCTION

Schwann cells (SC) are the major & only glial cell element of peripheral nervous system (PNS) which by virtue of their unique biological activities give the distinction of regeneration not only to the peripheral nervous system (PNS) but also induce regeneration in the central nervous system (CNS) by changing the hostile & inhospitable environments around its neurons to neurite promoting favourable conditions. These multifunctional cells synthesize, secrete & express many neurotrophic, neurotropic, neurite promoting & growth factors, major myelin glycoproteins, cell adhesive molecules (CAMs), basement membrane components as well as a cornucopia of receptors at various stages of life. Their important role in neural tissue development, organization & maintenance cannot overshadow their emerging vital contributions to the ongoing studies on demyelinating diseases (e.g. multiple sclerosis) & other debilitating and disfiguring neurological defects (e.g. neurofibromatosis). Underlying SC defects may be responsible for abnormalities in peripheral neuropathies. SC are the primary cells in the disfiguring disease of neurofibromatosis as well as shoulder the responsibility for Schwannoma & Neurilemoma tumours. Their versatility is evidenced by their phagocytic nature during Wallerian & traumatic degeneration. They are indispensable to the normal functioning of axons. Inhibiting their proliferation at the stage of regeneration not only retards axonal growth but profoundly impairs myelination. Their proliferation & physical presence is a prerequisite for the reparative process providing a proper terrain or scaffolding essential for the regeneration & survival of neurons.

HISTORICAL PERSPECTIVE

In the last more than one and a half century, since the recognition of SC in 1839 through the monumental work of the great German anatomist Theodor Schwann[1], tremendous work has been done to reveal the potential biological functions of the SC, but perhaps much more is left for the bicentennial celebrations of the cell. The story dates back to Theodor Schwann's attempts to study the cellular nature of living organisms & his claim that the fatty sheath of the peripheral nerve had a cellular nature & was not an amorphous entity. Although invention of the Electron Microscope settled the controversy in favour of SC but it opened a new era of conflicting findings, which will continue to keep the 21st century investigators sweating well into the near future.

Since the pioneering work of *in vitro* nervous tissue culture by Harrison (1906) and others, many investigators cultured a variety of tissues & cells[2]. It was in the middle of this century, among attempts by various laboratories to study the morphological & intracellular aspects, based on the ingenious work of Murray & Stout[3] who cultured the non-neuronal cells of adult & embryonic human peripheral nerves, that the miraculous nature of the Schwann cells came into the limelight.

Owing to the development of these cell culture techniques, SC have been isolated from many sources: human, rodent, reptile and avian; adult, young, neonate, fetus and embryo; fresh, cryopreserved and autopsy material. Despite distinct morphological features, SC have a long list of immunocytochemical markers to their credit as well.

REGENERATIVE ROLE

The great versatility of SC reaction to nerve injuries[4] is suggestive of the fact that these cells make significant, vital, decisive & multifaceted contributions to the recovery & restoration of functions of injured axons. Although the question whether the SC are the leaders or the followers during nerve regeneration is still un-resolved[5-7] but looking at the evidences provided by many excellent studies, the balance seems to be tilting in favour of the former role [8]. Viable SC are now proved to be a prerequisite for successful regeneration to occur in the nervous system by providing the trophic support for regrowing axons & establishing a regenerative milieu[9-11]. It has been reported that freeze dried acellular nerve grafts do not engender axon growth[10,12] & inhibiting SC co-migration with regenerating peripheral nerve axons into an acellular graft significantly impedes neurite out-growth[12]. Peripheral nerves & Retinal Ganglion Cells do extend neurites for some distance into peripheral nerve grafts devoid of SC but far less than in the presence of SC[10,12]. It has also been reported that preventing SC proliferation during regeneration retards the nerve regenerative capacity. The large number of SC (transplanted or proliferated by trauma) & their advantageous position, as well as their ability to present their own surfaces, basal lamina & multiple secretory activity count for their extraordinary ability to foster axonal resurgence in an effective manner[9].

In addition to its regenerative potential for PNS, SC when transplanted into CNS in the form of isolated cultured cells or as peripheral nerve grafts, induce the potentially capable CNS axons to regenerate by converting the unfriendly & iniquitous cellular milieu[13,14] of CNS (presence of oilgodendrocytes, astrocytes, CNS myelin, TN, lack

of basal lamina components & other neurotrophic & neurotropic factors) into a regenerative favouring microenvironment[4, 15-17].

MECHANISM OF REGENERATION

SC have the remarkable capacity to induce regeneration in the PNS as well as in the CNS when they are transplanted as isolated purified cells suspension, as a spreadsheet on collagen rolls, as a heterogenous cell population, in the form of a nerve segment, or even SC conditioned medium. SC influence the regenerating neurites in more than one way. They have been reported to function as the presidential motorcade for the resurging neurites to make the pathway by their proteolytic & susbstratum carpeting actions. Many of the neurotrophic substances have been reported to direct the axonal regrowth by targetting receptor sites on neurite growth cones[18,19].

Irrespective of the close relationship between functional status or type & their regenerative activities[20], the SC in whatever form they are presented, induce pronounced neurite outgrowth. The Wallerian degeneration within hours reprograms the traumatic site for axonal regeneration by stimulation of rapid proliferation of SC[21] (probably macrophage mediated); migration of SC from both stumps (predominantly proximal); preferential axonal growth along interfaces of basal lamina (BL) & SC surfaces; and reexpression of CAMs[8,22,23] (L1, N-CAM) & Extracellular Matrix Molecules [Laminin (LMN) & Tennacin (TN) accumulated at axon SC contact surfaces] by upregulating their mRNA. Antibodies against L1significantly inhibits this growth. Re-expression of CAMs has been indicated as the primary factor behind the significant post-transection regeneration. These events are further added to by increases in production of NGF & other NTFs[24]. BL tubes, in absence of SC, can support nerve regeneration[25] but not as effectively as in the presence of SC. SC also respond to trauma by changing their phenotype[26] thereby aiding to turn the degenerating nerve segment into an environment that would support regeneration of neurons; nonetheless the phagocytic role for SC has been reported long before in many animals.

SYNTHETIC FUNCTIONS

SC synthesize some of the most important Neurotrophic Factors (NTFs) & Growth Factors (GFs) like Nerve Growth Factor, Brain Derived Neurotrophic Factor, Ciliary Neurotrophic Factor, Fibroblast Growth Factor,

Interstitial Growth Factor, and Platelet Derived Growth Factor[27-30], reexpress a galaxy of receptors for many NTFs, Neurite Promoting Factors (NPFs) & GFs[30-32]; elaborate Cell Adhesive Molecules (CAMs)[4]; and synthesize, secrete & assemble basal membrane (BM) components[9,18] & apolipoproteins[33]. The neurotrophic requirements for cells (motor, sensory & sympathetic) contributing to the formation of peripheral nerves differ among them but SC & only the SC produce all these factors to effectively help regenerate the peripheral nerve axons[34]. The SC conditioned extracellular fluid has been reported to stimulate SC proliferation, adhesion & migration[5,35]. Recently a novel NPA has been reported[34], not particular for any class of neuron, in the SC from adult rat Sciatic Nerve & immortal SC clone which is not related to all of the previously known NTFs/NPFs, indicating a new cytokine or a novel NTF or combinatorial effect of the known NTFs. Leaving aside the NTFs, GFs, NPFs, CAMs, & BL components, they present perhaps the most abundant receptor sites on their surfaces. They synthesize Growth Associated Protein (GAP)[36], express c-met mRNA[37], Glia Fibrillary Associated Protein (GFAP) & myelin proteins[38], POU/SCIP[39], c-jun[40,41], enzymes[42] & SCF[43].

OTHER FUNCTIONS

In fact, SC neurite regenerating potentials have unjustifiably overshadowed their other so many unique & singular contributions to the development of the nervous system, its regeneration, reorganization & proper coordinated functioning. They have automitogenic activity[44,45] in long term cultures, while autoinhibitory action in short term cultures[46,47]. They are extensively involved in neurite directionality. The range of their fostering neurotrophic activities involves a wide range of cells including dopaminergic neurons, sensory, motor (both PNS & CNS) & sympathetic cells[34,48]. They are indispensable for the proper functions of rapid axonal conduction, axonal protection, maintenance & formation of myelin, remyelination of injured PNS as well as CNS axons[49], regulation of axoplasmic flow & metabolic activities. The myelin sheath, in addition to its insulating & conduction facilitating actions, is closely related to the molecular exchanges between axon & extracellular compartment.

CONCLUDING REMARKS

When one looks at the unbelievable synthesizing & expressing potentials of the SC, it leaves little doubt about their versatile functions. Also worth mentioning is their changing scenario of functional activities under different conditions. They promptly change their expressing activities & phenotypic characteristics at different stages of life as & when required.

Some other glial (astrocytes) & non-glial (macrophages) cells, reportedly play roles in the regenerative process but neither of them as well as none of the other glial cells can snatch the credit which for almost a century belongs to SC & would remain to give the distinction to them in the future[50]. None of the other glial cells have ever attempted to interfere in the domain of SC. These are the daring efforts of the SC which have effectively & successfully encroached

upon the CNS boundaries by challenging the hostile resident cues. SC deserve to be crowned as the true candidate for leading the team of glia.

Looking at the efforts on SC transplantation & their evaluation to determine the extent of SC as a therapeutic tool, for alleviating the impoverishing miseries caused by the nervous system injuries or certain incurable diseases with unknown aetiology, it does not seem too distant that the SC would one day assume the role of an established therapeutic agent for incapacitating & paralyzing disabilities. We should join our hands to bring that day "tomorrow".

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