Intrathecal autologous condensed PLT cytokine protocol for hyperinflammatory neurodegenerative disease

Anti-inflammatory sequence (A) for soluble mediators (blue) processed from autologous platelet (PLT) rich plasma, discharged after thrombin (T) activation. *Where:* Brain-derived neurotrophic factor (BDNF), supports neuron survival and induces differentiation of *de novo* neurons and synapses; Epidermal growth factor (EGF), a central element in cellular proliferation, differentiation, and survival; Fibroblast growth factor (bFGF), a mediator with broad mitogenic and survival actions; Hepatocyte growth factor (HGF), stimulates mitogenesis, cell motility, and matrix invasion with a key role in angiogenesis and tissue regeneration; Insulin like growth factors (IGFs) are required for cell stimulation and response to local microclimate; Interleukin-1β (IL-1β), a central inflammatory mediator involved in cell proliferation, differentiation, and apoptosis; Interleukin-2 (IL-2), an inducer of T-helper 1 (Th1) and Th2 cell differentiation and antagonist to inflammatory Th17 cells; Interleukin-6 (IL-6), a metabolic regulator and promoter of hypothalamic PGE_2; Interleukin-8 (IL-8, or 'neutrophil chemotactic factor') coordinates local angiogenesis; Interleukin-10 (IL-10) suppresses Th1 cytokines and MHC class II antigens and regulates the JAK-STAT signaling network; Ligand of CD40 (CD-40L), an inflammatory organizer of PLTs, leukocytes, and dendrites; Macrophage inflammatory protein 1-alpha (MIP-1α), a conditional trigger for cell migration, survival, and proliferation; Platelet derived growth factor (PDGF), modulates mitogenesis and mesenchymal proliferation; Platelet factor 4 (PF4), a chemotactic protein involved in PLT aggregation; Regulated after Activation of Normal T-cell Expressed and Secreted (RANTES), a monocyte attractant; Transforming growth factor beta (TGF-β), an activator of multiple downstream substrates involved in tissue repair; Tumor necrosis factor (TNF), highly diverse actions with multiple cross-talk nodes balancing cell proliferation and apoptosis; and Vascular endothelial growth factor (VEGF), a promoter of vascular development for improved perfusion. In addition to recorded changes in selected CSF markers, post-program reduction in serum C-reactive protein (CRP) is measured to document systemic anti-inflammatory response.

Tissue regenerative response (B) via gene ontology function after representative PLT cytokines (blue) shown with modulated intermediate and hub gene (green) targets associated with neuronal differentiation and downstream tissue effects. *Where:* CNTN2 = Contactin-2, CREB = cAMP responsive element binding protein-1, DLG4 = Discs large MAGUK scaffold protein-4, HOXA1 = Homeobox A1, MAPK8 = Mitogen-activated protein kinase-8, NRCAM = Neuronal cell adhesion molecule, NTRK2 = Neurotrophic receptor tyrosine kinase-2, PAX6 = Paired box protein-6 (aniridia type II protein), SEMA3A = Semaphorin-3A, SLIT1 = Slit guidance ligand-1, YAP = Yes-associated protein. Modified from [68]. Condensed plasma cytokines: BDNF = Brain derived neurotrophic factor, EGF = Epidermal growth factor, FGF = Fibroblast growth factor, IL-2 = Interleukin-2, IL-6 = Interleukin-6, NF-kB = Nuclear factor kappa-light-chain-enhancer of activated B cells, NRP-1 = Neuropilin-1, TGF-β = Transforming growth factor-β, TNF-α = Tumor necrosis factor-alpha, VEGF = Vascular endothelial growth factor. Both pathways converge synergistically (blue circle) to dampen inflammation and improve cellular function by promotion of tissue repair.