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Possible role of apolipoprotein A1 in healing and cell death after neuronal injury

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1. ABSTRACT

Limited axonal regeneration after traumatic injuries to the CNS presents a challenge in neuroscience. Investigation of CSF from subjects with spinal cord injury (SCI) has found that the lipid catabolism pathway is implicated in the post injury scenario. Sequestration of the CNS by the blood brain barrier ensures a mechanism of cholesterol metabolism and recycling distinct from that in the peripheral tissues. Apolipoprotein A1, the protein component of high density lipoprotein (HDL), is an abundant protein in the mammalian cerebrospinal fluid. Interaction of ApoA1 with its cellular receptor, ABCA1, gives rise to several signaling events, such as the activation of Cdc42 protein leading to actin polymerisation. Emerging evidences suggest that ApoA1 mediates anti-inflammatory effects and conversely, is negatively regulated by inflammatory cytokines. Collating these findings, added to the clinical evidences of using HDL as a therapeutic target for cardio vascular diseases, we hypothesize that ApoA1 could be useful in neurite outgrowth after mechanical injury by 1) mediating polymerisation of actin and 2) restricting inflammatory responses after injury which are deleterious to healing.

2. INTRODUCTION

Mechanical injuries to the central nervous system (CNS) cause irreversible tissue damage. Because the adult (CNS) is incapable of regenerating, partial or complete loss of sensory and/or motor functions prevails after brain and spinal cord trauma. Molecular events after brain injury may differ from that of the spinal cord but both injuries cause immediate and delayed cell death (1). A plethora of molecular perturbations follow neuronal injury, the most common of which are, immune response (2), glutamate excitotoxicity (3, 4), electrolyte imbalance (5), mitochondrial damage (6, 7), lipid peroxidation by reactive oxygen (8) and nitrogen species (9), demyelination (10), apoptosis (11), which is usually triggered by inflammatory responses, cytokine release, free radicals and excitotoxicity (12) and derangements of the vascular system (13).

Our understanding of the limited regeneration of functional neural connections after CNS injury is based on two specific and critical events after injury: inflammatory responses and exposure of neuritis to growth inhibitory molecules. Let us explore each of these briefly. After CNS injury, microglia, the macrophage of CNS produce inflammatory cytokines such as inteleukin-1β (IL-1β) and tumour necrosis factor α (TNF-α) (14-16). These cytokines are the major inflammatory mediators responsible for leucocyte recruitment at the site of injury. Because the brain and the spinal cord are different

anatomically and in cellular composition (17, 18), their responses to inflammatory stimuli vary. Neutrophil recruitment is greater in spinal cord, which has a larger population of microglia than the brain (19, 20). Activated microglia also produce inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS), both causing oxidative tissue damage and axon demyelination (21). An early study by Dusart and Schwab listed the chronological cellular events after dorsal hemisection injury of the rat spinal cord (22). Opening of the blood brain barrier (BBB) occurred at the lesion site within an hour of injury. From 3 to 6 hours after the initial trauma, necrotic cell death was initiated and was complete by twelve hours. The phase subsequent to the initial impact of the trauma is known as secondary phase of injury. It starts minutes after the injury and initiates a large number of physiological and molecular changes in and around the lesioned cord, an elaborate description of which may be found in the review by Oyinbo (23). The area of secondary cell death surrounded the primary lesion site and recruitment of neutrophils in this area followed the cell death phase. Two days after injury, recruitment and proliferation of microglia occurred (22).

This was, in a nutshell, the inflammatory events after injury resulting in tissue damage. Coming to why axons of the CNS don't regenerate, we will discuss the Nogo theory of axon growth inhibition. Myelin associated growth inhibitory factors are widely expressed in the myelin sheath and have their cognate receptors in the axonal membrane. Schnell and Schwab showed in 1989 for the first time, that some component on the myelin is responsible for axon growth inhibition (24) and that an antibody against myelin (referred to as IN-1) allowed axon regeneration in CNS (25). This inhibitory myelin component was a protein called Nogo-A discovered in 2000 by Chen *et al* (26) and subsequently the Nogo receptor was found by Fournier *et al* in 2001 (27). A family of Nogo receptors are known to us today (28). Myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMGp) act in conjunction with Nogo-A to restrict axon growth and their combined effects are synergistic (29). MAG (30, 31) and OMGp (32) also bind to Nogo receptors. Downstream of Nogo signaling, Ras homolog gene family member A (RhoA) and its effector Rho kinase (ROCK) are activated, causing actin depolymerisation (33, 34). Deletion of Nogo, MAG or OMGp causes increased axonal growth (35) and so does blocking Rho and ROCK (36).

Chondroitin sulphate proteoglycans (CSPGs) that form the extra cellular matrix of the CNS, also restrict axonal growth, in addition to myelin associated inhibitory factors (37, 38). Finally, astrocytes proliferate in the injured area (39) and secrete CSPGs and other growth inhibitory molecules like tenascin and cytotascin (40). The reactive astrocyte assemblage is commonly referred to as the glial scar. Discussing their mechanisms of action will take us away from the focus of the review and therefore, we shall limit our discussions here.

In previous studies from our lab, apolipoprotein A1 (ApoA1) was found to be more abundant in cerebrospinal fluid (CSF) from complete transection spinal cord injury (complete injury) (41) than from incomplete injury (where part of the spinal cord is intact). ApoA1 resolves into five distinct isoform spots in a 2-dimensional protein gel (2D gel). Jaleel *et al* have shown that acidic isoforms (with lower isoelectric point, IE) of ApoA1 constitute oxidatively damaged, older ApoA1, whereas, basic isoforms (higher IE) represent newly formed ApoA1 (42). We noticed in our 2-dimensional difference gel electrophoresis (2D-DIGE) experiments, a clear distinction of abundance pattern between newly formed and older ApoA1 (Figure 1). Older, oxidatively damaged isoforms predominated in complete injury CSF and newer isoforms were more abundant in incomplete injury CSF (43). This observation, though sidelined in the main story of perturbed pathways after spinal cord injury, caught our attention, and after probing into cellular functions of ApoA1, we hypothesized that it could facilitate healing after injury. To see how that might be, let us fist review the functions of ApoA1. ApoA1 is an apolipoprotein, the protein component of 'lipoproteins'.

Lipoproteins are molecular aggregates primarily involved in the transport of lipids in the aqueous plasma compartment (44). They are most studied in the context of atherosclerosis and are known to be involved in maintenance of cardiovascular function, disorders of lipid metabolism and neurological disorders (45-47). These dynamic molecular complexes are made of an outer monolayer of phospholipids (PL), free cholesterol (FC) and protein and an inner core of cholesteryl esters (CE) and triglycerides (TG) (48). They may have a range of densities and interestingly, since the heavier components (apolipoproteins) occupy the external domains of the lipoprotein particles, their diameters are inversely related to their densities (49). The lipoproteins are classified according to their sizes. While chylomicrons are the smallest lipoprotein particles in terms of size, very low density lipoprotein (VLDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL) and high density lipoprotein (HDL) are larger in ascending order (48). The apolipoproteins, which may comprise about 50% of protein content of the lipoproteins, constitute their external domains, stabilize the lipoprotein particles (50), are the main cofactors of lipid transfer proteins and are essentially the functional ligands to lipoprotein receptors on cells (51). On ligand binding, the cellular receptors of apolipoproteins initiate the activation of enzymes involved in lipid metabolism and several other cellular pathways (52).

The cholesterol metabolism of the CNS is distinct from that for the rest of the body, with no exchange of cholesterol across the BBB (53). CNS cholesterol is

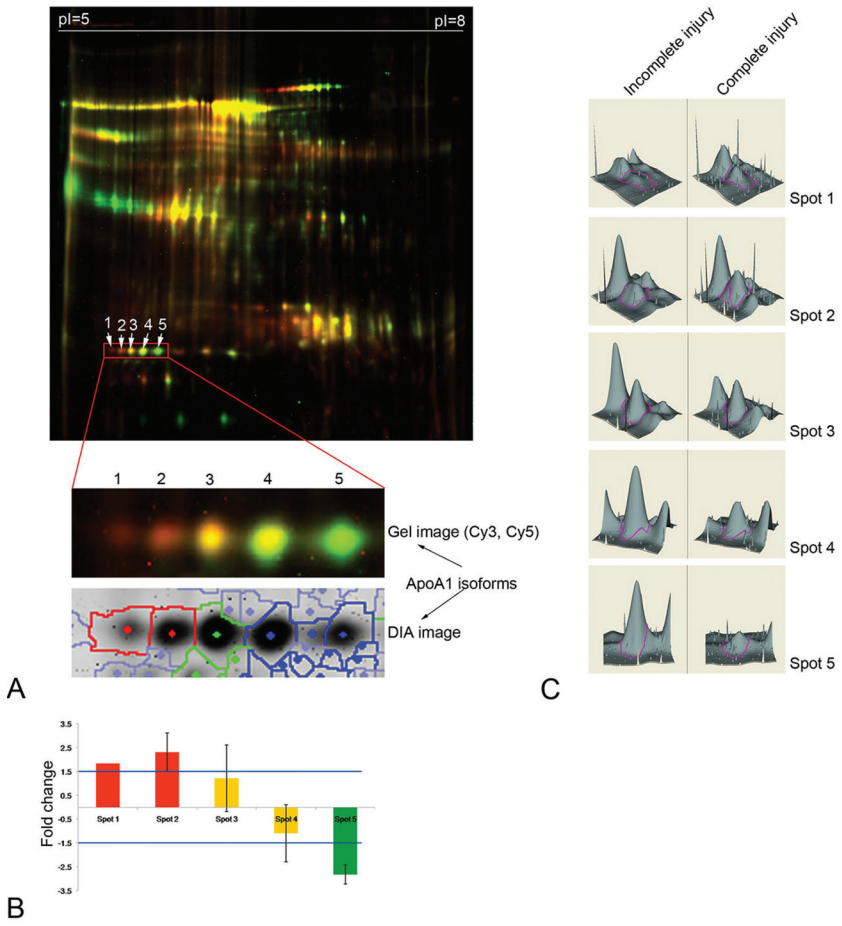

Figure 1. Differential abundance of ApoA[1] isoforms in complete and incomplete SCI. A. A 2-D gel of CSF from complete injury (labelled with Cy5; red) and incomplete injury (labelled with Cy3; green). Five isoforms of ApoA1 are marked and an enlarged window of the same is depicted below. Difference in-gel analysis (DIA) of the spots by DecyderTM software reveals increased abundance of lower IE isoforms (spots 1 and 2) in complete injury (red bordered spots) and increased abundance of higher IE isoforms (spots 4 and 5) in incomplete injury (blue bordered spots) CSF. The gel Figure is adapted from Sengupta *et al* (2014) (43). B. Fold change ratio (Cy5/Cy3 fluorescence signal) of the 5 isoforms (n=3). With a threshold fold change of ±1.5. (blue lines), spots 1 and 2 show greater abundance in complete injury (orange bars) and spot 5 (green bar) shows greater abundance in incomplete injury. Spots 3 and 4 show comparable abundance (yellow bars). C. 3-dimensional views of each spot in incomplete injury CSF (Cy3 channel) in the left column and complete injury CSF (Cy5 channel) in the right column for the gel Figure depicted in part A.

synthesized in the brain and is the major component of myelin sheath and plasma membrane of neurons and glia (54). In contrast to lipoproteins of various densities in the periphery, the main lipid carriers in the CNS are HDL like particles. ApoA1 (0.3.7±0.0.8 mg/dl) and ApoE (0.3.±0.2. mg/dl) are the most abundant apolipoproteins in the cerebrospinal fluid (CSF) although ApoJ, ApoD, Apo A-II and ApoA-IV are also present in CNS in lower abundance (43, 55, 56). The CSF lipoproteins are 7-15 nm in diameter, which is similar to that of the plasma HDL. They are spherical and contain the apolipoprotein ApoE (57).

ApoA1 is a 28 kDa exchangeable apolipoprotein which may be present in HDL and chylomicrons in plasma. Although it is one of the abundant apolipoproteins of the CSF (58), its mRNA has been undetected in CNS (59). The cellular receptors for ApoA1 are HDLR, which include ATP binding cassette transporter family of receptors like ABCA1 and ABCG1. Scavenger receptor class B type I (SR-B1), a multi ligand receptor expressed in macrophages, hepatocytes and setroidogenic tissues is the main acceptor of cholesterol from HDL in the liver (60). On binding to ABCA1, ApoA1 acquires cellular PL and FC to form nascent HDL. This process is not only the initiation of cholesterol efflux from cells (61) but also that for a number of signaling events in the cell (62, 63) of which, regulation of cell growth and inflammation are the foci of this review.

Recent evidence from our group suggests that the lipid catabolism pathway is perturbed in SCI of different severity grades (43). We also have evidences of differential abundance ApoA1 in the CSF between differently severe forms of SCI as discussed earlier (Figure 1). In this review, we propose that ApoA1 may

facilitate neurite outgrowth after mechanical injury. This proposition is based on two facts. First, there are evidences of ApoA1 being negatively regulated in an inflammatory situation (64). Inflammation accompanies CNS injury as we have discussed previously. Studies have shown that ApoA1/HDL mediated lipid efflux disrupts lipid rafts on antigen presenting cells (APC) and it is highlighted in the study by Murphy *et al* (65) and other studies, as discussed in section 4.2. This antagonises the antigen presenting functions of these cells. Consequently, ApoA1 may play a predominant role in diminishing inflammatory response and thereby ensure its own increased expression. Second, depolymerisation of actin by RhoA activation, downstream of signaling by myelin based inhibitory factors, is a prime molecular event responsible for axon growth cone collapse after CNS injury. Activation of 'Cell division cycle 42', (Cdc42) and further, polymerisation of actin is one of the several molecular pathways initiated by ApoA1/HDL mediated lipid efflux via ABCA1 (62, 66). ApoA1 could, therefore, mediate pro-growth situation in the injured CNS.

The physiology of lipid metabolism in the CNS with regard to HDL is reviewed first and subsequently the relationship of inflammation and ApoA1 metabolism is discussed. The various cellular signaling events that are triggered when ApoA1 binds to its cellular receptor ABCA1 are also explored, with emphasis to the activation of Cdc42 leading to actin polymerisation. The plausibility ApoA1 in mediating neurite outgrowth in an injury scenario is kept in the perspective.

3. APOA1 AND LIPID METABOLISM

3.1. Structure of ApoA1 in lipid free state and in association with HDL

Apolipoprotein A1 constitutes about 70% of the total plasma HDL and in the human plasma with normal lipid profile, it is present in approximately 130 mg/dl (50). It is primarily involved in the formation of nascent HDL by acceptance of PL from the cell surface via ABCA1. About 5-10% of ApoA1 in human plasma is present in lipid poor state known as pre-β1-HDL (67). Exchangeable apolipoproteins share a common gene ancestor, which encodes alpha helices that are often separated by a proline residue. Circular dichroism measurements of monomeric ApoA1 in dilute solutions (<0.1.mg/ml), have revealed 5 alpha helical segments at the N terminal two thirds of the molecule. While the C terminal, with residues 179-243 is unstructured (68) and forms alpha helix during interaction with PL-water interface (69), the N terminal alpha helices are in turn arranged in bundles that stabilise the individual component helices. This is achieved by arrangement of non polar residues at the interior of the bundle and ion pairs at the helix junctions (70). The helix bundle exists as a molten globule as the individual helices transiently open and close in the timescale of seconds (71). The flexibility of ApoA1 is the key contributing factor for the structural remodelling of HDL particles.

Studies suggest that initially the relatively hydrophobic C terminus of ApoA1 finds a lattice defect in the PL bilayer of a vesicle. The helix bundle of the N terminus subsequently opens to interact with PL (72). This is followed by incorporation of more helical domains of ApoA1 molecules in the PL bilayer. Finally, when the PL/ApoA1 ratio reduces, the PL vesicle disrupts into discoidal HDL particles with 2, 3 or 4 molecules of ApoA1 stabilising one discoidal HDL (73).

3.2. Basic path taken by HDL in a turnover cycle

The basic cycle of HDL in plasma starts with its biogenesis in the liver and intestine. Following its secretion, until it returns to the liver to be catabolised, it undergoes extensive remodelling. During this phase, it changes its shape, density and lipid and protein content (74). The HDL turnover in human plasma is 4-5 days. ABCA1 transporters interact with lipid poor/ free ApoA1 where the latter acquires cellular PL and FC to form nascent HDL, initiating the process of reverse cholesterol transport (RCT) (61). In discoidal HDL lecithin cholesterol acyl transferase (LCAT) catalyses the esterification of free cholesterol (75). Mature HDL interacts with VLDL LDL and IDL. The cholesteryl ester transfer protein (CETP) transfers CE from HDL to VLDL, LDL and IDL (76). Conversely, the phospholipid transfer protein (PLTP) transfers PL from VLDL and IDL to HDL (77). At every stage of remodelling, HDL can interact with the SR-BI receptor. Interaction with SR-BI mediates cholesterol efflux from the cells and selective uptake of CE by the cells (78). Finally the CE are converted to bile acids in the liver for excretion.

3.3. Lipid metabolism in the central nervous system

Brain is the most cholesterol rich organ of the body. While it is 2% of the body mass, it contains 25% of the total body cholesterol (79). Biosynthesis of cholesterol in brain is highest during embryogenesis. In CNS, as in the peripheral system, the main regulatory enzyme for cholesterol biosynthesis is hydroxyl-methyl-glutaryl CoA reductase (HMGCoAR) (80). The cholesterol requirement of the brain in the adult organism is mainly fulfilled by glial cells (45), which secrete cholesterol containing lipoproteins. There is no mixing of cholesterol from the periphery due to the relatively impermeable nature of BBB and blood CSF barrier (BCSFB) to cholesterol (53, 81), though one port of entry for cholesterol in the CNS is through SR-BI present the endothelial cells of the brain capillaries. SR-BI accepts cholesterol from plasma HDL and LDL.

The glial derived HDL are discoidal in shape, 8-12 nm in diameter and mainly contain ApoE and ApoJ,

whereas, CSF HDL is spherical, 13-20 nm in diameter and mainly contain ApoE and ApoA1 (82). ApoA1, which is not synthesized in the CNS, enters it in association with HDL by SR-BI mediated uptake (83). In the CNS, ABCA1 interacts with lipid poor/free ApoE and secretes discoidal ApoE containing HDL particles (84). It is involved in removal of excess cholesterol from neurons (85) by interaction with ApoE and ApoA1 containing spherical HDL. As the myelin membrane actively undergoes reconstitution, biosynthesis and removal of neuron cholesterol is almost a housekeeping occurrence in the CNS. The low density lipoprotein receptor (LDLR) in neurons and astrocytes interact with ApoE for the uptake of cholesterol (86).

The discoidal HDL particles originally secreted from astrocytes via ABCA1 undergo extensive remodelling in the CNS to form spherical HDL particles, which are commonly found in the CSF (82). In plasma, ApoA1 is the activator of LCAT, which acts on its substrate, discoidal HDL, to convert it into spherical HDL (87). Though the primary site for LCAT secretion is liver, small amounts of it is secreted by astrocytes and it is possible that ApoE is the activator of LCAT in CNS (88). CETP has also been detected in human CSF and in conditioned media of neuroblastoma and glioblastoma cells (89). The expression of PLTP in brain is limited to the endothelial cells of the brain capillaries (90).

4. RELATIONSHIP OF APOA1 WITH INFLAMMATION

ApoA1 expression and proteolysis is intimately linked with inflammation. A wide body of study exists to support the fact that ApoA1 is negatively regulated during inflammation and it in turn negatively modulates the initiation and progress of inflammatory events. It would be rather interesting to discuss the activities of ApoA1 in the backdrop of the chronic inflammatory scenario that prevails during the secondary phase of SCI (91). We will briefly discuss the link between ApoA1 and inflammation in this section.

4.1. HDL in innate and adaptive immunity

Of the total of up to 80 proteins identified in association with HDL, about one third are involved in cholesterol metabolism. The rest are acute phase proteins, antioxidants, antithrombins, proteases, or are involved in complement regulation (92). HDL is involved in innate immunity as it inhibits the pro inflammatory activities of lipopolysaccharide (LPS) and lipoteichoic acid (LTA) (93). Studies in human patients have shown HDL levels to be inversely related to severity of sepsis and contrarily, subjects with severe sepsis exhibit rapid lowering of HDL levels (94). LDLR and ApoA1 knockout mice develop autoimmune phenotype (95) and SR-BI deficient mice show increased proliferation of T and B lymphocytes (96). HDL and ApoA1 prevent activation and recruitment of monocytes and neutrophils to the site of inflammation (97). In macrophages, HDL plays a role in inhibition of Toll like receptor (TLR) induced expression of pro inflammatory cytokines by regulating their transcription (98). ApoA1 induces prostaglandin E2 and IL-10, both of which inhibit differentiation of dendritic cells (DCs). HDL reduces IL-12 expression and renders DCs incapable of stimulating T-cells (99).

4.2. ApoA1/HDL mediated disruption of lipid raft microdomains

Cellular cholesterol is not randomly arranged in the plasma membrane but are localised in lipid and protein rich microdomains called lipid rafts (100), which form the hub of extracellular ligand-receptor mediated signaling initiation point. Lipid composition and organisation of lipid rafts determine their functions and any modification to these may disrupt their functional activities. Depletion of cholesterol from lipid raft microdomains therefore alters their functions (101). Lipid rafts home the MHC molecules of APCs and receptors of B and T cells (102), and therefore, are indispensible for antigen presentation by APCs to B and T lymphocytes (103). Several studies have shown that the cholesterol content of lipid rafts is altered by ApoA1/HDL mediated cholesterol efflux via ABCA1 (65, 104). This phenomenon disrupts the lipid rafts and consequently abrogates raft localised initiation on inflammatory signals (105). Recent evidences have also shown that HDL/ApoA1 mediated cholesterol efflux alters the lipid raft structure, inhibits APC mediated T cell activation (106) and reduces neutrophil activation, adhesion, spreading and migration (107).

4.3. Modulation of HDL composition during acute phase

The half life of ApoA1 is reduced in acute phase plasma such as during sepsis and endotoxemia (108), occurrences that are associated with increased mortality (109). Inflammatory cytokines such as (TNF)-α and (IL)-6, increase the expression of serum amyloid A (SAA) (110), group IIA secretory phospholipase A_2 ($sPLA_2$-2A) (111) and endothelial lipase (112) and decrease that of LCAT and CETP (94, 113). SAA, which has a higher binding affinity to HDL relative to ApoA1, displaces the latter from HDL to become the sole protein component of acute phase HDL (Figure 2), accounting for 17-87% of HDL proteins (64). Lipid free ApoA1 undergoes rapid catabolism in the liver and kidneys (114). $sPLA_2$ hydrolyses phospholipids from HDL and reduces its size but it does not generate lipid free ApoA1 (115). A recent study has shown that $sPLA_2$ interacts directly with lipid free ApoA1 and causes its proteolysis (116). Collectively these events cause reduction in HDL and ApoA1 levels and modify the HDL composition compromising its functions (113).

4.4. ApoA1 and inflammatory cytokines: a vicious cycle

Inflammatory cytokines (IL)-1β and (TNF)-α expressed by activated macrophages repress the

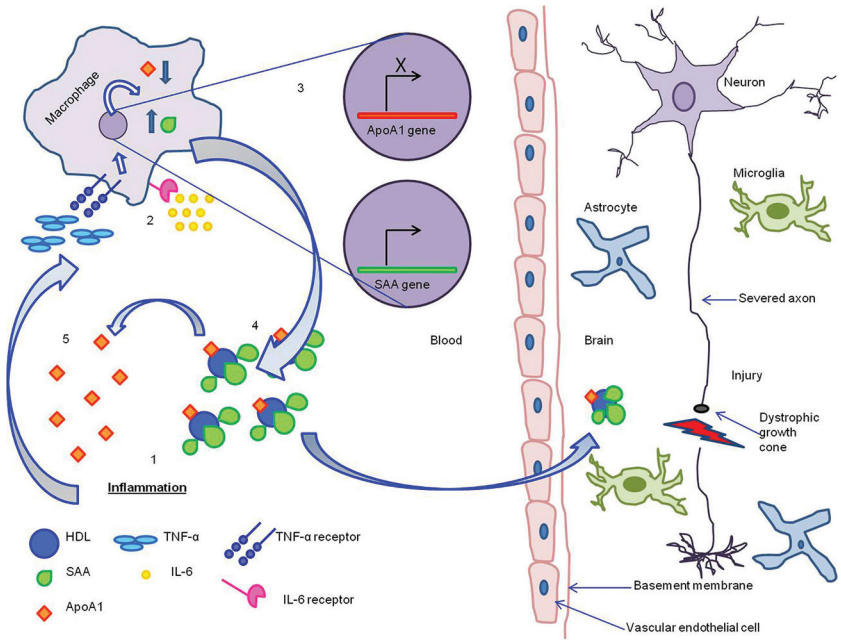

Figure 2. Diagrammatic representation of a model of ApoA1 involvement in inflammation. 1) Mechanical injury to the CNS gives rise to general inflammation. 2) Inflammatory cytokines TNF-α and IL-6 exert their effect on gene expression by 3) decreasing ApoA1 and increasing SAA gene expression. 4) SAA displaces ApoA1 from HDL. 5) Displaced, lipid free ApoA1 is rapidly catabolised lowering its availability in the CNS (64, 117, 118).

gene expression and rate of secretion of ApoA1 in hepatocytes (117, 118). (TNF)- α mediated repression of ApoA1 gene expression is dependent on JNK, p38 protein kinases and NFκB transcription factor (119).

These findings collectively place a picture of a feed-forward sequence of events in which ApoA1 is negatively regulated during inflammation and this results directly in the lack of ApoA1 mediated inhibition of inflammatory pathways, therefore paving a way for uncontrolled inflammatory response. In the secondary or sub-acute phase of spinal cord injury, which starts minutes after injury and persists for weeks to months (120), a number of molecular events are initiated, of which, immune system response and apoptosis are primary (23). Studies have shown that controlled inflammatory responses are pivotal for healing and repair (121, 122). Neutrophils accumulated at the site of injury remove microbes and cell debris. This phenomenon is crucial for regeneration of spared axons (23). Uncontrolled inflammation, however, contributes largely to the cell and tissue damage subsequent to traumatic neuronal injuries. Neutrophils and other immune cells secrete inflammatory cytokines such as (IL)-1β and (TNF)-α, free radicals and proteases. These activate an inflammation cascade which is ultimately detrimental for cells (91). ApoA1 could mediate healing by lowering the degree of inflammation. In this situation, we propose that ApoA1 might be able to control inflammatory activities after CNS injury and thereby ameliorate the tissue damages that accompany uncontrolled inflammation and also promote axonal repair.

5. SIGNALING EVENTS TRIGGERED BY APOA1-ABCA1 INTERACTION

ABCA1 mediated cholesterol efflux to lipid free ApoA1 initiates a number of signaling events downstream. These events are essential for the initiation of RCT pathway and regulation of ApoA1 and ABCA1 turnover (62) but are mainly necessary for regulation of cholesterol metabolism genes at the post transcriptional level (123). Transcriptional regulation of cholesterol metabolism genes has been reviewed by (124).

5.1. PKA, PKC, JAK-2, MAPK and Ca^{2+} pathways in cholesterol efflux

On binding to ApoA1, ABCA1 couples with $G\alpha_s$ leading to the activation of adenylate cyclase, cAMP production and PKA mediated ABCA1 phosphorylation, causing increased lipidation of ApoA1 (125). cAMP is involved in transcriptional regulation of ABCA1 gene, whereas, PKA in its post transcriptional regulation (126). Phosphorylation of ABCA1 by cAMP/PKA allows a more favourable orientation of ABCA1 for optimum binding to ApoA1 facilitating lipid transcolation (127).

PKC is activated on ApoA1-ABCA1 interaction, an event linked to efficient lipid efflux (128). Biochemical evidence shows that lipid efflux by ApoA1 activates phosphatidylcholine phospholipase (PC-PLC) causing hydrolysis of phosphatidylcholine to release diacyl glycerol (DAG). DAG further activates PKCα leading to phosphorylation of ABCA1 (129). PKC has been shown

to increase cholesterol efflux from mouse peritoneal macrophages and human THP-1 cells but PL efflux is not mediated (130). Interestingly, the α and δ isoforms of PKC have opposing effects on ABCA1 stabilisation. Whereas PKCα phosphorylation of ABCA1 protects the latter from calpain protease degradation (129), PKCδ mediated phosphorylation causes degradation of ABCA1 (131).

ApoA1-ABCA1 interaction stimulates autophosphorylation of JAK2 and the latter is obligatory for ApoA1 mediated cholesterol efflux but is not essential for ApoA1 mediated stabilisation of ABCA1 (132). JAK2 activation further leads to STAT3 activation (133) and the ApoA1 mediated activation of JAK-STAT pathway is linked to anti-inflammatory processes in the macrophage (134, 135).

The MAPK family members are implicated in cholesterol efflux. ERK1/2 increases ABCA1 expression and activity in mouse cells (136) whereas p38 and JNK do not affect cholesterol efflux or ABCA1 expression. In human fibroblasts, ApoA1 mediated cholesterol efflux activates the MKK4/JNK pathway with the upstream activation of the small GTPase Cdc42 (137) and inactivation of these pathways was shown to down-regulate cholesterol efflux.

ERK1/2 signaling is associated with development, survival, proliferation and differentiation of oligodendrocytes and is obligatory for myelin production by the oligodendroglial lineage of cells (138). Interestingly, it has been shown that mice with constitutively active MEK (MEK activates ERK1/2) are capable of more rapid and robust remyelination compared to WT mice in a situation of induced demyelination of dorsal spinal cord axons (139). These observations compounded to the finding that ApoA1 activates ERK1/2 (140) through ABCA1, places it as putative regeneration mediating molecule in the perspective of neuronal injury.

ApoA1 binding to ABCA1 induces Ca^{2+} ion influx with downstream activation of calmodulin (CaM) and calcineurin (141). CaM protects ABCA1 from calpain mediated proteolysis in a Ca^{2+} dependent manner (142). Conversely, extracellular Ca^{2+} is required for ApoA1 binding to ABCA1 and cellular cholesterol efflux (143). Interestingly, CaM activation involves JAK2 in lipid efflux and ABCA1 stabilisation (144). Inhibition of calcineurin by cyclosporine A abolishes lipid transfer to ApoA1 and JAK2 phosphorylation (141).

5.2. Cdc42 activation in lipid efflux

Cell division cycle 42 (Cdc42) is a small G protein involved in cytoskeletal organisation and intracellular vesicular transport (145). The C terminal of ABCA1 on interaction with ApoA1 interacts with Cdc42 and activates it. ApoA1 mediated activation of Cdc42 leads to downstream phosphorylations of PAK-1 and $p54^{JNK}$ finally leading to actin polymerisation (66). In fact Tangier disease fibroblasts (lacking ABCA1) show abnormal actin cytoskeleton and impaired activation of Cdc42 (146). Conversely, expression of dominant negative Cdc42 downregulates cholesterol efflux (137) and expression of constitutively active of Cdc42 enhances it in MDCK cells. The exact reason for the mutual functional enhancements of Cdc42 and ABCA1 is not yet known but it has been suggested that Cdc42 being a player in vesicular trafficking, makes intracellular cholesterol available to ABCA1 (147).

As we have discussed earlier, depolymerisation of the actin cytoskeleton by RhoA activation is the basis for growth cone collapse by myelin based growth inhibitors (148, 149). In contrast, as we have just discussed, ApoA1-ABCA1 interaction activates Cdc42 and causes actin polymerisation. This antagonist effect of ApoA1 to myelin based growth inhibitors might push the actin dynamics towards polymerisation in a growth inhibiting scenario of neuronal injury. Therefore, we propose that ApoA1 might be instrumental in mediating growth cone extension.

6. CAN APOA1 BE A MEDIATOR IN NEURONAL HEALING?

Functional recovery after traumatic injuries of the CNS has always been a challenge to physicians and researchers (150) and till date several investigations are aimed at functional recovery post neuronal injuries like SCI. In these cases, the main contributor to lack of regeneration is limited rebuilding of functional axonal connections owing to a number of molecular phenomena among which inflammation (2) and myelin growth inhibitory molecules (151) are some. Myelin based growth inhibitiors depolymerise actin in the axon growth cone (152). Our investigation of CSF from spinal injured patients with different severity grades of injury has shed light into some physiological systems that become imbalanced at the secondary phase of SCI (43). Lipid catabolism is one such pathway and it can be guessed that large scale destruction of myelin membranes post SCI demands rapid clearance of toxic myelin debris and availability of cholesterol for remyelination. ApoA1 is also found to be differentially abundant in more and less severe forms of SCI as discussed previously (Figure 1). That the newly formed ApoA1 (higher IE isoforms) are more abundant in incomplete injury CSF, and conversely, older and damaged ApoA1 isoforms (lower IE) are more abundant in complete injury CSF, it can be deduced that in a situation of complete SCI there is damage to existing ApoA1 which is not replenished by synthesis. Since the prognosis of complete injury is worse than that of incomplete injury (41), we may progress with the role of ApoA1 in the differential prognosis and compounded to the pro-healing functions of ApoA1 in inflammation and actin polymerisation, we put forth our present hypothesis

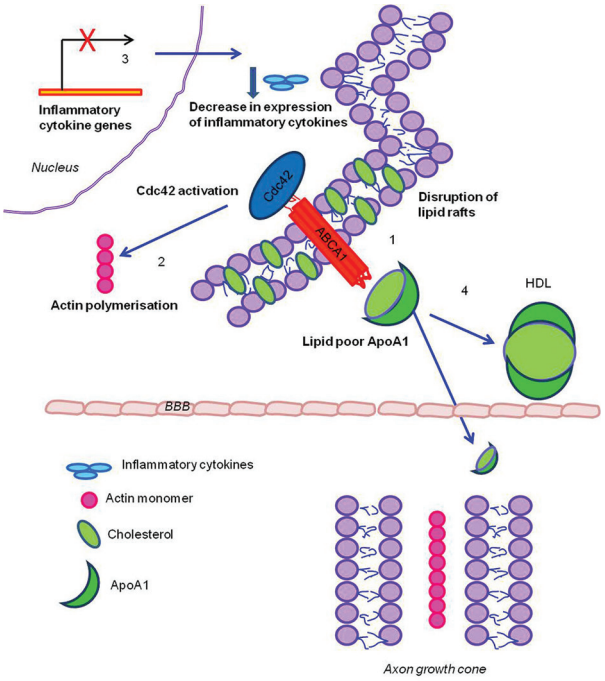

Figure 3. Involvement of ApoA1 in actin polymerisation and containing inflammation. 1). External ApoA1 can reduce the expression of inflammatory cytokines by lipid raft disruption in APCs. 2). In the damaged neuron, ApoA1 could also mediate actin polymerisation through Cdc42 activation leading to neurite outgrowth. 3). Lowered cytokine levels in general can restrict inflammatory responses after CNS injury. 4). Finally ApoA1 interacts with ABCA1 to acquire cellular cholesterol and PL to become spherical HDL (65, 66, 104, 105).

of ApoA1's role in healing. Although some investigations have shown that ApoE containing HDL promotes neurite growth in cell line and mouse model (153, 154), similar role for ApoA1 is only at the conjecture stage currently.

We have discussed earlier about neuronal and glial cholesterol turnover and its dependence on ApoA1 and HDL in the CNS. Regarding the intracellular pathways initiated by ApoA1 in the current context of neuronal injury, we emphasize on three points; 1) ApoA1 causes actin polymerisation via Cdc42 activation, 2) it activates ERK1/2, which is intimately linked to CNS myelination and possibly remyelination though the latter has not been extensively studied and 3) it mitigates inflammatory responses, a predominant occurrence after neuronal injury. Through its ensemble cellular roles, ApoA1 looks like a promising molecule in encouraging neurite outgrowth after mechanical injury.

At this juncture, we hypothesize that ApoA1 could ameliorate the inflammatory situation after mechanical neuronal injury. Secondly, it could potentiate growth and rebuilding of damaged axons by mediating actin polymerisation through Cdc42 pathway (Figure 3). Finally, it could favour myelination by driving cholesterol turnover and additionally activating the ERK pathway.

7. CONCLUDING REMARKS IN BRIEF

ApoA1, the key protein component of HDL, is the cholesterol and phospholipid acceptor from peripheral tissues. The progressive lipidation of ApoA1 on its journey from the tissues to the liver constantly changes the shape, size and density of HDL, making it a very dynamic molecular aggregate. Though not expressed in the CNS, several studies have confirmed that ApoA1 is an abundant protein in the CSF (155, 156) including ones from our group. Lipid transport aside, ApoA1 is a versatile protein taking part in diverse immune related functions like development of sepsis, infectious diseases (157), amyloidogenesis (158), myelopoiesis (159) etc. Interaction of ApoA1 with ABCA1 during cellular lipid efflux drives the activation of several signaling pathways essential to lipid efflux mechanism itself (62). It is most generally known and studied because of its relationship to the development and progression of atherosclerosis and a wide body of past and ongoing research have suggested that HDL is inhibitory to atherogenic progression (160-162). However, the feasibility of using HDL as a therapeutic agent in cardiovascular diseases (CVD) has been a matter of speculation (163). In the current review we have highlighted the plethora of ApoA1 initiated physiological processes in the context of injury to neurons. Probable involvement of ApoA1 in healing after injury has not been an active topic of investigation or discussion so far. Yet, the availability of ApoA1 in CNS via SR-B1 receptors of endothelial cells in the BBB implies that its potential healing mechanisms is not far-fetched. Being an abundant protein of the cerebrospinal fluid, it is deducible that ApoA1 is involved in CNS functions. Further study in this area, especially in the injury scenario could open doors to newer regenerative mechanisms since at present several different methods are constantly being researched for promotion of neurite growth but none have been completely fool proof.

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