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Mini Review Article

Neurologic disruption arising from Immunologic Aberration

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Abstract
Interactions between neurodegenerative states and immune system dysregulations may underlie several diseases that induce problems for neuropsychological and physical health. It seems increasingly evident that process of apoptosis, a central issue for health and well-being, is associated to greater or lesser extents with the balance and ongoing regulation of immune system proclivities. One key contributor to the regulation of structure and function of brain and behaviour has emerged to be the gastrointestinal microbiome, not least in the context of the neurodegenerative disorders. Certain genes identified in in these disorders encode for proteins with directly-acting immunoactive/immunoreactive roles, which when mutated lead to dysregulations in immune functions, thereby affecting the disease states; yet accumulating evidence implies direct malfunctions of immune ells in the brain and CNS as well as at the periphery of the nervous system. Remarkably, the therapeutic effects of anti-tumor, immune system-enhancing agents are emerging to awaken the necessity for consideration of immune system-nervous system interactions as reciprocal determinants of both neurodegenerative and inflammatory disorders.
Key-words: neurodegeneration; immune system; apoptosis; metabolism; therapeutic innovation; interaction.

Introduction

As registered in the US and Canada, cancer diseases remain the major cause of mortality in both Canada and the United States [2]. It has been well-established that cancer cells possess a heighten capacity for proliferating within suboptimal conditions through the accumulation of various and variety genetic mutations through several metabolic and immunogenic pathways that induce adaptations and operations sustained in the context difficult conditions [5]. Notwithstanding, the prevailing evidence for metabolic reprogramming in cancer cells has been forthcoming as a hallmark of cancer and a potential vulnerability that can be targeted to confront these disorders [11]. Apoptosis, the complex and physiological process of neuronal cell death, removes both unwanted cells and those with damaged DNA. In doing so, this process can act as a safeguard against the development of abnormal cells. The process of apoptosis may be initiated through incidence of DNA damage, oxidative stress, growth factor deprivation, and mitochondrial depolarization [19]. Nevertheless, a better understanding of the biochemical mechanisms of apoptosis has led to the development of novel therapies that target the involvement of cancer cells to induce cell death [19]. Various processes, including those mentioned above, may trigger distinctive pathways through which apoptosis may be launched and maintained. Through the intrinsic pathway of apoptosis, internal signals, such as DNA damage, may lead to a cascade of related events, that result in the activation of the Bcl-2 (B-cell lymphoma 2) family of proteins, which in their turn may activate Bax-like (Bcl-2-associated X protein and gene) proteins to permeabilize the membrane and release cytochrome c [19]. Cytochrome c release will lead to the activation of caspase proteins that induce apoptosis. In the extrinsic pathway, external signals, for example tumour necrosis factor (TNF) may lead to the activation of caspase and apoptosis [19]. The proceeding exploitation of vulnerabilities in cancerous cells, including oxidative stress susceptibility and mitochondrial membrane destabilization, may be associated with the development of novel therapeutic agents that initiate apoptosis and eradicate ongoing disease progression [27, 39, 42].

Programmed cell death, such as apoptosis, necroptosis and pyroptosis, exert essential influences upon neurodevelopment and the maintenance of homeostasis in brain tissues [9]. Apoptosis, a generally anti-inflammatory and necessary for the removal of non-functioning or malfunctioning to preserve homeostatic integrity, is a highly regulated process involving intrinsic factors, whereby cells 'self-destruct' due to 'cell-stress' and extrinsic, destruct due to signals from other cell, pathways [28,36] and consists of three phases: (i) The Initiation phase, which varies depending on the apoptosis-inducing agent and the biochemical pathway activated by it, (ii) The Commitment phase, which is common to different types of apoptosis, during which the cell "decides" to commit suicide, and, (iii) The Common degradation phase, which is characterized by activation of catabolic hydrolases. Mitochondrial dysfunctions induce various neurodegenerative disorders [38,12], such as Alzheimer's disease [45], Parkinson's disease [14] Huntington's disease [13] and Amyotrophic lateral sclerosis (), the so-called "mitochondrial diseases". Otherwise, necroptosis and pyroptosis present a 'coarser' type of programmed cell death [16,18, 43] These types of apoptosis imply that the plasma membrane undergoes a "bursting" action that bears with it the consequential release of intracellular content consisting of various molecular entities, including biomarkers for pro-inflammatory actions of the immune system [44, 46]. Neurodegenerative

disorders, including Alzheimer's disease and Parkinson's disease that are characterized by neuronal death, express excessive levels of neuroinflammation [26] HIV-associated neurocognitive syndromes despite combinations antiretroviral treatment present certain aspects of neurodegerative disorders. Although viral load may be suppressed with immune system intactness in HIV+ patients the CNS, functions as a viral reservoir and low-level expression of viral proteins interacting with mitochondria [9] Viral proteins and antiretroviral treatment cause alteres production of adenosine triphosine, mitochondrial dynamics, mitophagy, calcium signalling and apoptosis, oxidative stress, mitochondrial biogenesis and immunometabolism in the brain and CNS [35]

The apoptosis process presents evolutionarily-sustained morphological characteristics with several features including: membrane-blebbling, the development of protrusions/bulges (blebs) from the plasma membrane of a cell human bio-particulate or abscess with an internal environment similar to that of a simple cell, with a spherical, bulky morphology through decoupling of cytoskeleton from the plasma membrane, thereby degrading the internal structure of the cell, by granting the flexibility required to induce the cell to separate into individual bulges or capsules of the intercellular matrix, nuclear condensation, nuclear fragmentation, pyknosis, irreversible condensation of chromatin followed by karyorrhexisis (nucleus-fragmentation) and apoptotic body formation [18,38] The intrinsic pathway involves cytochrome c release after mitochondrial outer membrane permeabilization which in turn leads to the caspase-9 activation [33,34]. Extrinsic apoptosis occurs generally in the aftermath of the covalent linking of two ends of DNA or RNA molecules of death receptor, fas, subset of the tumor necrosis factor family located in the plasma membrane [17, 41]. The eventual activation of either the intrinsic or the extrinsic apoptosis pathways conducts caspase-3 and -7 activation in a downstream fashion to 'executioner' their actions implying apoptosis [20, 29]. In this connection, the recent strategy of targeting the gut microbiota in order to ameliorate Taken together, brain and CNS disorders through the understanding the underlying signalling pathways in which the microbiota impacts upon these disorders appear to be crucial for the development of future therapeutics for improving CNS functionality.

Mitochondrial actions and metabolic regulation are central to apoptosis, to the generation of ATP via oxidative phosphorylation, and as a source of ROS particularly in the event of mitochondrial dysfunction. The transformation of normal cells to the cancerous stage involves multiple genetic changes or mutations leading to hyperproliferation, resistance to apoptosis, and evasion of the host immune system. However, to accomplish hyperproliferation, cancer cells undergo profound metabolic reprogramming including oxidative glycolysis and acidification of the cytoplasm, leading to hyperpolarization of the mitochondrial membrane. Mitochondria are proving to be worthy targets for activating specific killing of cancer cells in tumors and a diverse range of mitochondrial targeted drugs are currently in clinical trial to determine their effectiveness as anti-cancer therapies. The mechanism of action of mitochondrial targeted anti-cancer drugs relies on their ability to disrupt the energy producing systems of cancer cell mitochondria, leading to increased reactive oxygen species and activation of the mitochondrial dependent cell death signaling pathways inside cancer cells. The majority of drug development research in the past has focused on targeting DNA replication, repair, and tubulin polymerization to induce apoptosis in cancer cells. Unfortunately, these are not cancer-selective targets. Recently, researchers have started focusing on metabolic, mitochondrial, and oxidative stress vulnerabilities of cancer cells that can be exploited as selective targets for inducing cancer cell death. Indeed, the hyperpolarization of mitochondrial membranes in cancer cells can lead to selective importing of mitocans that can induce apoptotic effects. Herein, we will discuss recent mitochondrial-selective anticancer compounds (i.e., mitocans) that have shown selective toxicity against cancer cells. Increased oxidative stress has also been shown to be very effective in selectively inducing cell death in cancer cells. This oxidative stress could lead to mitochondrial dysfunction, which in turn will produce more reactive oxygen species (ROS). This creates a vicious cycle of mitochondrial dysfunction and ROS production, irreversibly leading to cell suicide. We will also explore the possibility of combining these compounds to sensitize cancer cells to the conventional anticancer agents. Mitocans in combination with selective oxidative-stress producing agents could be very effective anticancer treatments with minimal effect on healthy cells.

D-Galactose (D-Gal) promotes accumulation of reactive oxygen species and formation of advanced glycation end-products, ultimately resulting in oxidative stress. D-Gal has been widely used to induce accelerated aging in anti-aging medical research. Although thymic epithelial cells are particularly sensitive to oxidative stress, there are few reports on the thymus changes accompanying D-Gal-induced aging in mice. In order to study the effects of D-Gal upon rodent thymus, we investigated the egree of thymus atrophy and changes in the atrophy relative index in C57BL/6J mice following subcutaneous injection of D-Gal at different doses (200, 500, 1000 mg/kg per day) for 60 days [6]. Compared with the vehicle-treated (0.9% saline) and young controls, D-Gal at doses of 500 and 1000 mg/kg per day led to a significant thymic atrophy; the latter dose caused atrophy similar to that observed in naturally aged (18-20-month-old) mice. Mice treated with high-dose D-Gal exhibited greater immunosenescence, defective central immune tolerance, increased levels of activated splenic immune cell, and chronic low-grade inflammation, i.e., outcomes similar to those observed in natural aging in mice. Albiet of a preliminary nature, these results serve to demonstrate that those mice treated with the high-dose D-Gal may offer a valid model for the study of laboratory-induced thymic atrophy and the effects of aging upon the immune system. Additionally, in the brain and CNS, the anti-inflammatory agent, retinoid acid signalling, presents a major consequence with substantial influences in neural patterning, differentiation, axon outgrowth in normal development, and other functional components impairments of which cause neuroinflammation, oxidative stress, mitochondrial malfunction, and neurodegeneration leading to progressive Alzheimer's disease [4].

The effects of anti-tumor, immune system-enhancing agents, e.g. marine brown algae, eckol, and melatonin, have received attention in their immune-regulatory role for endorsing resilience against neurodegenerative progression and immune system aberration [1,24]. Dieckol, isolated from Ecklonia stolonifera induced apoptosis in human hepatocellular carcinoma Hep3B cells [44]. In a sarcoma 180 xenograft-bearing animal model, eckol was administered, in low, middle and high dose levels, in order to assess the in vivo anti-tumor influences of the compound with TUNEL (terminal deoxynucleotidyl transferase mediated dUTP nick end labelling) used to detect the apoptotic tumor cells [49]. It was observed that there occurred a pro-apoptotic and anti-proliferative activity arising from eckol that was manifested by the elevated TUNEL-positive prescense of apoptotic cells, the up-regulated Caspase-3 and Caspase-9 expression, and the down-regulated expression of Bcl-2, Bax, EGFR (epidermal growth factor receptor) and p-EGFR in the eckol-treated transplanted S180 tumors. Notably, eckol stimulated the mononuclear phagocytic system by recruiting and activating DCs, and inducing the tumor-specific Th1 responses, as well as increasing the

CD4+/CD8+ T lymphocyte ratio, and enhancing the cytotoxic T lymphocyte responses among the eckol-treated animals, thereby implying its potent stimulatory property on innate and adaptive immune responses. Melatonin, an amphiphilic indole, synthesized from tryptophan exists in eukaryotes and prokaryotes and is secreted from various tissues including immune system and CNS [21,36] The reciprocal associations of melatonin, an immunological buffer acting both as antioxidant and anti-

inflammatory agent with pro-oxidant effects, and the immune system appear to underlie several neuroprotective-restorative propensities [11, 25]. It induces the differentiation of dental papilla cells among rats and regulate mitochondrial energy metabolism, ROS scavenging, and mitochondrial biogenesis [19]. The reciprocal associating between melatonin and the immune system is synchronized by the pineal hormone which induces apoptosis in tumor cells via the intrinsic and extrinsic pathways of apoptosis thereby protecting the immune cells [22]. Finally, the sirtuins present NAD+ (nikotinamidadenindinukleotid) dependent epigenetic and metabolic regulators at various sites, presenting critical roles in the physiology of central nervous system, immune system and metabolism and it the pathophysiology of disease states [8].

Conclusion

The balance and regular of the widely assorted immune system activities and involvement, modulating resistance to, for example, cancer development, seems to play a major role in determining the integrity of the brain and CNS, i.e. whether or not these are susceptible to neurodegenerative ravages. It has been argued that the sirtuins have emerged as key-regulators in the adjustment and conformance of neurodegeneration, autoimmunity and metabolism pathways. A number of chronic disorders, such as Alzheimer's, Parkinson's, and Multiple sclerosis are construed to arise from the interactions of genetic and environmental factors, embodying notions that have been assigned the "multiple hit hypothesis" whereby several bacterial/microbial infections were associated with increased risk of neurodegeneration, and in certain cases, the clearance of bacterial pathogens has been connected with ameliorations of brain and CNS deficits. Taken together, a plethora of evidence implies that agents presenting an inflammatory and/or immune system-enhancing action offer remarkable utility both for the development and maintenance of the brain and CNS, as well as other tissues, but also for restoring structure and function following tissus damage.

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