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A REVIEW ON ASSOCIATION OF CD14 WITH INCIDENT DEMENTIA AND MARKERS OF BRAIN AGEING AND INJURY

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ABSTRACT

The soluble cluster of differentiation 14 is a type of CD14 which is a glycoprotein expressed on monocytes and neutrophils. CD14 is involved in the innate immunity and facilitate pro-inflammatory and anti-inflammatory cytokines. Current researchers found that CD14 is a key component of incident dementia and also involved as a marker of brain aging and injury. Usually, the dementia forms such as Alzheimer's are diagnosed in later stages after sufficient damage to the brain had occurred. So, a marker like CD14can plays a vital role by the light of current researches that it could help in early detection and less costly. With this key component the detection of damage and injury can be including cognitive decline can be identified.

KEYWORDS: Soluble CD14, inflammation, dementia, brain injury and ageing.

INTRODUCTION

Currently dementia is diagnosed based on clinical signs and symptoms, but significant brain damage has already occurred by the time a clinical diagnosis of dementia is made and this may be too late for any effective intervention. It is therefore of great importance to define biomarkers such as CD14 that could permit early detection of apparently normal persons who are at high risk for developing dementia. A biomarker can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes or, pharmacological responses to a therapeutic intervention.[1,2]

CD14 A Key Component in Innate Immunity

A cluster of differentiation 14 (CD14) is a glycoprotein seen as both membrane-bound (mCD14) and soluble (sCD14) forms which are expressed on monocytes and neutrophils. sCD14 comprises mCD14 still in the microvesicles, mCD14 that has been cleaved off the cell via ectodomain shedding and an alternate splice from the liver, which is weak acute phase reactant. CD14 is a key component of innate immunity and is responsible for facilitating the generation of pro-inflammatory and anti-inflammatory cytokines in response to numerous potentially harmful molecular changes. CD14 is a receptor involved in the regulation of the inflammatory response of microglia in response to bacterial infection or lipopolysaccharide stimulation. A chronic inflammatory process with activation of microglial cells contributes to the neurodegeneration[3]

CD14 like biomarkers of neural inflammation can be a useful detector of incident dementia and is an associate with the biomarkers of brain aging and injury.CD14, TLR4 (toll like receptor- 4), and MD-2 (lymphocyte antigen 96) together form the multi-receptor complex that recognizes LPS (liposaccharide) on the cell membrane. LPS is the major component of the outer membrane of gram-negative bacteria and consists of lipid A, a core polysaccharide and an O- polysaccharide of different lengths.CD14 is a horseshoe-like the structure of leucine-rich-repeat-containing proteins with a hydrophobic pocket at the -NH2 terminal.The initial role of CD14 in LPS recognition is the enhancement of the sensitivity of innate immune cells to an inflammatory stimulus. By binding to LPS at picomolar concentration CD14 present and transfer it to TLR-MD2 for the initiation of the transduction pathway and followed by different activation pathways[4,5,6] Zanoni et al found that CD14 is capable of controlling the entire LPS receptor complex and the type I IFN (interferon) production.[7]

CD14 plays a crucial role in the cellular response regulation over LPS by:

- Facilitation of cellular response to low LPS doses by controlling LPS presentation to TLR4
- Irrespective of concentration control re-localization of the LPS complex to the endosome with subsequent activation of the TRAM-TRIF pathway and type I IFN production[8]

Thus, CD14 involved in the host defense mechanism in infections of both virus and bacteria but the contribution of CD14 to infection may be either positive or negative depending on microorganism and site of infection.[9]

CD14 AND HIV INFECTION

CD14 and fibrillar Aβ-42 interaction was 20-fold higher than that between CD14 and non-fibrillar Aβ1-42. Microbial translocation in HIV infection has been suggested to contribute to chronic inflammation and liposaccharides and soluble CD14 (sCD14) are markers of microbial translocation and the resulting monocyte activation. Several studies suggest that cognitive impairment may be caused by inflammation in the central nervous system (CNS). Thus, biomarkers of inflammation in the cerebrospinal fluid (CSF) have been associated with cognitive impairment. Systemic inflammation in HIV infected patients has been reported repeatedly and believed to be partly caused by microbial translocation. Microbial translocation and immune activation are predictors of disease progression and non-AIDS-related morbidity in HIV infection. During acute HIV infection, the gastrointestinal mucosa is depleted of T cells leading to translocation of the microbial products such as lipopolysaccharide (LPS) into systemic circulation. LPS activates cells of the innate immune system by binding to Toll-like receptors-4(TLR-4). CD14 needs to be present for LPS to activate the receptor. Cd14 is expressed on monocytes, macrophages, and neutrophils, and upon stimulation by LPS, as well as other microbial products, CD14 is secreted and cleaved from the cells as soluble CD14. Studies found a significant association between CSF sCD14 and markers of inflammation and axonal damage in the CSF.[10,11]

CD14 and Incident Dementia

Dementia is a term referring to several conditions that result from abnormal brain changes that affect the ability to think and it is a chronic neurodegenerative syndrome characterized by gradual loss of cognitive functioning and behavioural abilities. Dementia can be divided into several subtypes and most common types involve Alzheimer's disease, Lewy bodies, vascular, and frontotemporal. According to the patients and subtypes the symptoms may vary, the most prevalent include memory loss, inhibited communication and language, decreased focus and attention, altered reasoning and judgment, and loss of vision. Alzheimer's is the most common form of dementia, followed by vascular dementia, and it stems from microscopic bleeding and blood vessel blockage in the brain. The main characteristic of Alzheimer's disease is the deposition of beta amyloid containing plagues with a microglial-mediated inflammatory response. These inflammatory responses of innate immune signaling pathways involving the toll like receptors (TLRs). Microglia is the brain tissue macrophages that are representatives of the innate immune systems. In addition to biomarkers of Alzheimer's disease such as tau and amyloid, biomarkers of inflammation and neuronal injury may help to improve the prediction of clinical dementia. Inflammation has been identified as a contributor to many neurological conditions. Injury to the brain leading to dementia, whether due to vascular brain injury, Alzheimer's proteinopathy or head trauma, is accompanied by a neuroinflammatory response.[12,13,14]

Pase et al carried out research using prospective community-based Framingham Heart Study (FHS) and Cardiovascular Health Study (CHS) cohorts. The measurement of plasma sCD14was done at baseline and related to domains of cognitive function, the incidence of dementia and MRI- defined brain volumes. The study conducted with 1588 FHS and 3129 CHS participants.Meta-analysis reveals the SD unit increase in sCD14 was associated with a 12% increase in the risk of incident dementia(95% confidence interval 1.03-1.23; p=0.01) and pinpointed that high levels of sCD14 were associated with a higher risk of incident dementia across all threshold after adjustment for basic demographic variables. Persons with sCD14 in top decline displayed a 38% increase in the risk of incident dementia. Persons with top quintile displayed a non-significant 16% high risk of incident dementia, whereas each SD unit increase in sCD14 was associated with an 11% increase in the risk of incident dementia.[3]

CD14 and Biomarkers of Brain Aging and Injury

The researchers found that a high level of sCD14 was associated with brain injury and aging, as well as cognitive decline. Higher levels of sCD14 were associated with accelerated brain aging, a faster progression of age-related brain atrophy, and a more rapid decline in the executive functions.[15] Senatorov et al at Berkley found that anti-inflammatory drugs associated with brain inflammation may decelerate cognitive decline associated with aging.

In populations of microglia high or low expression of CD14 has been useful in determining the levels of microglial activation. Studies characterized the cellular localization of CD14 expression in microglia in human Alzheimer's affected brains. CD14 antibody stains blood monocytes in brain vessels can detect plague associated microglia.[16]

Glod et al give more information on the CD14 role that the homing of CD14 cells to an injury site, injury of vessels after the brain injury, implies that peripheral blood monocytes localized to injury sites initially and are then exposed to proangiogenic stimuli and develop endothelial-like characteristics. Thus help in determining the brain injury cd14 plays a crucial role ([17]. As studies show microglia plays a central role in the clearance of Aβ but the effectiveness of clearance decreases during aging and also causes the release of pro-inflammatory mediators which intern stimulate the immune response creating accumulation occurs. Pro inflammatory mediator overproduction leads to microglia sensitization or age related microglial priming, so that the aged

microglia produces an exaggerated but inefficient response to inflammatory stimuli.[18,19]

CONCLUSION

Soluble CD14 is a marker related to brain atrophy, cognitive decline, and incident dementia involved inflammation.CD14 is expressed in microglia and it can alter the neuroinflammatory environment and also affect Alzheimer's pathology.[3] Through exposure to infection higher levels of CD14 related to dementia. CD14 can be a useful marker involved in inflammation since the higher levels are associated with risk of dementia independent of vascular risk factors.[7]

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