PERSPECTIVE

Perspectives on mild cognitive impairment as a precursor of Alzheimer's disease

The aging population is growing rapidly all over the world due to the increase in average life. One of the major challenges associated with an aging population is dementia. Worldwide, it is estimated that by 2050 the number of people with dementia could triple, and dementia not only dramatically changes the lives of those who suffer from it, but it also results in a serious burden for health care systems and caregivers.

Recently, Vignini et al. (2019) studied plasma oxygen radical absorbance capacity and erythrocyte membrane fluidity in mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients to identify early events in the pathogenesis of the disease.

MCI (Albert et al., 2011; Knopman and Petersen, 2014) is defined as the symptomatic predementia stage on the continuum of cognitive decline, characterized by objective impairment in cognition, which is not sufficiently severe to require help with usual activities of daily living. MCI subtypes are defined based on the presence or absence of memory difficulties (amnestic *versus* non-amnestic MCI) and the number of impaired cognitive domains. The National Institute on Aging-Alzheimer's Association criteria define "MCI due to Alzheimer's disease," as "those symptomatic but non-demented individuals whose primary underlying pathophysiology is AD". MCI due to AD is characterized by memory impairment, progressive decline in cognitive function, and absence of vascular, traumatic, or other medical causes of cognitive decline (Albert et al., 2011).

Some evidence has shown that oxidative stress occurs in MCI (Baldeiras et al., 2008) with a decrease of plasma antioxidant levels (Baldeiras et al., 2008). Oxidative and nitrosative stresses are caused by an overproduction of chemical species containing oxygen or nitrogen, respectively, with reactive properties. Reactive oxygen species (ROS) include chemical species such as: hydroxyl radical (OH•), superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), hypochlorous acid (HOCl). Also reactive nitrogen species included nitric oxide (•NO) and peroxinitrite ($ONOO^-$) together with ROS can play a detrimental role in cellular damage (**Figure 1**).

In normal conditions, ROS are produced by macrophages to kill exogenous agents or by side reactions of the respiratory chain and they are readily neutralized by enzymatic and non-enzymatic antioxidant systems. A reduced capability of antioxidant system to counteract ROS formation will result in an imbalance of redox homeostasis with consequent damage to cell components.

Although oxidative stress plays an important role in aging, probably being involved in the development of age-related diseases, we recently found decreased oxygen radical absorbance capacity in plasma of MCI and AD subjects compared to healthy controls; in particular, plasma of MCI patients had a higher susceptibility to oxidative stress than in AD patients (Vignini et al., 2019). ROS, oxidizing membrane lipids and proteins, can impair normal cellular functions, altering either the physico-chemical properties (fluidity) of membranes or modifying the functions of enzymes and receptors.

Recently, Pluta and Ułamek-Kozioł (2019) found structural and functional membrane alterations in human erythrocytes during degenerative diseases. Erythrocytes are real unique cells able to recover their morphology, internal volume and membrane surface area repeatedly after passing through microvessels, and these characteristics are due to their specific structure, shape and cytoskeletal organization. Phospholipids of the erythrocyte plasma membrane are mostly composed of phosphatidylcholine, sphingomyelin, phosphatidylserine, phosphatidylethanolamine, and a composition of fatty acids which reflects that of the brain (Hedue et al., 2003). Therefore, we also measured erythrocyte membrane fluidity in MCI and AD patients and controls, observing a significative decrease of fluidity in MCI subjects and, interestingly, no differences in AD patients compared to controls (Vignini et al., 2019). As Cazzola et al. (2004) reported a negative correlation between membrane fluidity and plasma oxidative stress, we believe that the high oxidative stress in MCI patients might be responsible for lipid peroxidation with the consequent membrane rigidity.

Moreover, many studies have shown that cerebrovascular disease (CeVD) is related with these two conditions; in particular, recent findings provide the evidence that CeVD can affect the early structural neural network degeneration (Vipin et al., 2018). Tozzi et al. (1991) reported that erythrocyte membrane

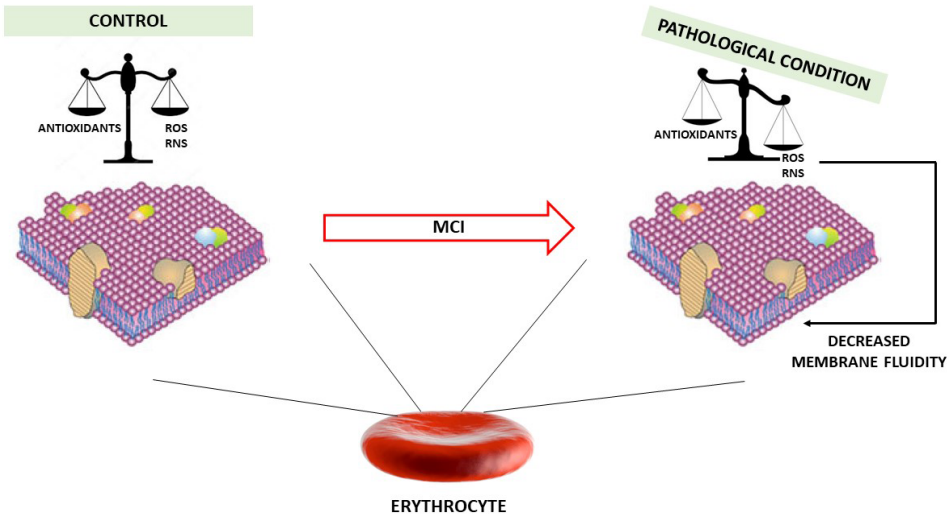

Figure 1 Modifications of erythrocyte plasma membranes as a result of the increase in ROS and RNS in MCI subjects.
MCI: Mild cognitive impairment; RNS: reactive nitrogen species; ROS: reactive oxygen species.

fluidity can influence hemoreological parameters in subjects with CeVD. They claimed that the decrease of erythrocyte membrane fluidity found in CeVD patients is decisive in reducing erythrocyte deformability in the microcirculation, thus increasing blood viscosity. A reduced blood flow implies a decreased delivery of nutrients and oxygen, compromising the energetic metabolism of the cell.

Since there is no effective pharmacological treatment for hindering the progression of these diseases so far, natural products have become a significant possibility in neurodegenerative research. Many ongoing studies in the field of nutrition are focused on slowing down the early negative events found in MCI in order to reduce the progression of neurodegeneration (Román et al., 2019).

There is accumulating scientific evidence on the possible efficacy of polyunsaturated fatty acid supplementation in neurodegenerative disorders and in particular in AD as they are essential for healthy development and functioning of the brain. Thus, dietary recommendations could be able to relieve some of the symptoms or slow down the cognitive and physical deterioration.

Dietary intake of oily fish and docosahexaenoic acid, and eicosapentaenoic acid has been shown to be associated with lower risk of AD. In particular, it seems that these long-chain omega-3 fatty acids seem to be more effective at the earliest stages of AD (i.e., preclinical, MCI) as they have been shown to improve neuronal transmission and regulate neuronal membrane excitability (Román et al., 2019).

Different randomized controlled trials point out that multi-ingredient supplementation and combined dietary interventions are a more efficient way of slowing down cognitive decline, than using a single nutrient (Oulhaj et al., 2016; Bianchi et al., 2019).

Polyphenols are natural products that are commonly found in many plants; they have been shown to be active in AD neurodegenerative changes, by providing protection through their role as antioxidants (Román et al., 2019).

Together, all these nutritional elements represent the basis of the Mediterranean diet which is one of the most widely studied dietary patterns, able to play a positive role in cognitive health. There is a general consensus that greater observance of the Mediterranean diet is associated with improved cognitive performance, a lower risk of developing MCI and AD, and a reduced risk of progression from MCI to AD (Román et al., 2019).

The concept of MCI is continuously in evolution and much effort is being put into making an early diagnosis. It is fundamental to detect early events, so as to make it possible to slow down the disease. Unfortunately, so far, no pharmacological therapy is able to reduce its progression but many data support the importance of diet, exercise and cognitive stimulation. Nevertheless, further research, in terms of longitudinal follow up or interventional studies, should be encouraged, addressing other various aspects of clinical–cognitive effectiveness by a tailored diet.

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