The role of haemoglobin proteins in molecular pathology of multiple system atrophy

Research

Multiple system atrophy (MSA) is a rare neurodegenerative disease, with onset in adult lifeand characterised by progressive deterioration. The cause of MSA is unknown, but a distinguishing feature is the overproduction of a protein in the brain called alpha-synuclein which causes degeneration of nerve cells in several areas of the brain.
MSA is clinically characterised by varying degrees of the features of Parkinson's disease (PD) such as shaking, rigidity, slowness of movement, and difficulty with walking, and autonomic disorders of the genito-urinary system and cortex. MSA equally affects both men and women, primarily in their 50s; however, disease onset as early as age 30 has been diagnosed. The progression of disease is rapid, and patients are confined to bed within five years of symptom onset with death resulting within an average of nine years. With three cases per 100,000 individuals, MSA is considered rare; however, its prevalence is similar to multiple sclerosis (2.5 per 100,000) and motor neuron disease (1.5-2 per 100,000).

We recently discovered that haemoglobin genes are highly expressed in the MSA brain. Haemoglobin protein transports oxygen throughout our tissues. It is the largest source of peripheral iron in the human body and it may play a role in regulation of iron level in the brain. We hypothesised that the increased levels of haemoglobin cause oxidative stress, which leads to impaired function of brain cells. Moreover, oxidative stress, together with increased levels of haemoglobin proteins, might have a direct impact on alpha-synuclein aggregation and overproduction.

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Outcome

The Brain Foundation Research Gift enabled us to discover that haemoglobin overexpression and alpha-synuclein aggregation is accompanied by a cellular response. In this project we analysed how a type of non-neuronal brain cell (oligodendrocytes) responds to two types of the alpha-synuclein protein (soluble and fibrillar). Using mass spectrometry (MS) we evaluated changes upon haemoglobin overexpression and alpha-synuclein exposure as well as assessed post-translational modifications as a result of alpha-synuclein aggregation. Analysis of certain proteins revealed that the differences between untreated control cells and cells exposed to soluble oligomeric alpha-synuclein are not significant. In contrast, analysis of the protein spots from cells exposed to fibrillar alpha-synuclein showed significant differences compared to control cells.
We identified proteins involved in regulation of transcription, DNA replication, cell signalling and regulation of translation.

Taken together, the results of this project suggest that haemoglobin overexpression has a significant impact on alpha-synuclein aggregation and maturation of oligodendrocytes which is a primary target of MSA molecular pathology.

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