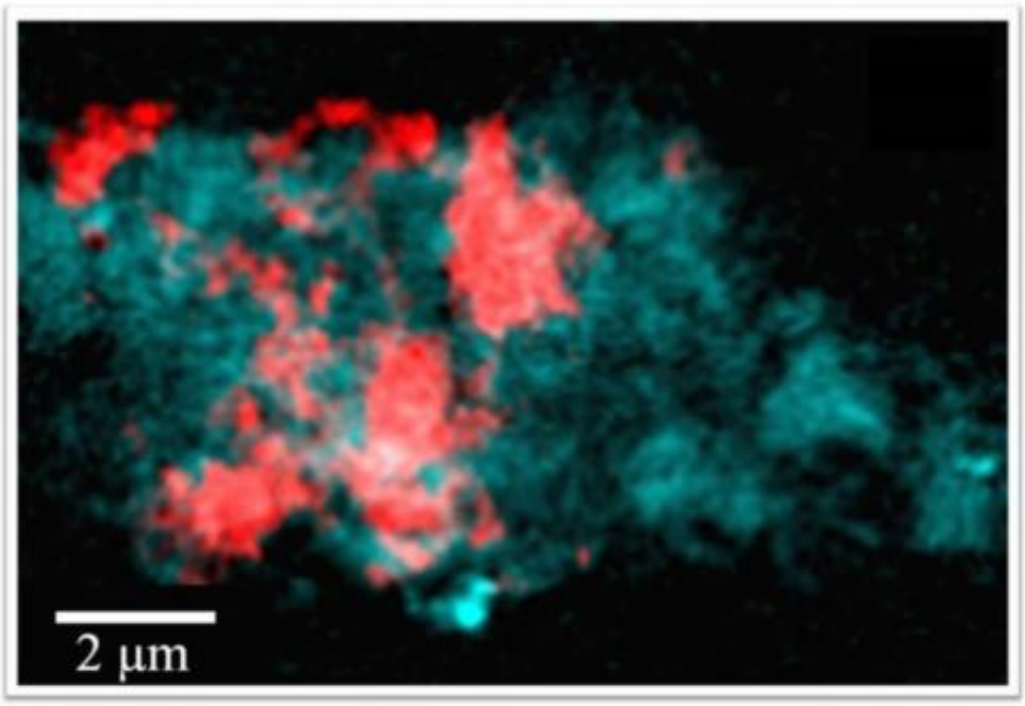
'Big Science' uncovers another piece in the Alzheimer's puzzle

March 26 2014



Credit: Diamond Light Source

In a paper published today, British scientists have found evidence that biological material contributing to lesions in the brain, characteristic in Alzheimer's patients, may also cause the build-up of brain-cell-damaging toxic iron. Scientists have made the discovery using advanced imaging techniques at giant X-ray facilities - the Diamond Light Source

synchrotron in Oxfordshire and other synchrotrons in Switzerland and the US.

Iron occurs naturally in the human body, including the brain. The conversion of this iron between two chemical forms is essential for normal function. However, one of these forms of iron, known as ferrous iron, can be highly toxic if it is overproduced or builds up in tissues where it can't be processed and removed properly. Scientists have known for some time that this toxic iron builds up in the same location as the brain lesions caused by Alzheimer's disease.

Researchers have been studying the protein fragment that makes up the Alzheimer's lesions, a peptide known as beta-amyloid, to try to understand how and why the build-up of toxic iron is occurring; and whether it's a cause or a symptom of the brain cell damage in Alzheimer's patients.

At the UK's national synchrotron, Diamond Light Source, beams of light 10 billion times brighter than the sun, were used to shine a light on the problem, to study the chemical and magnetic makeup of the iron after it had interacted with the beta-amyloid peptide. By using these techniques along with electron microscopy they witnessed predominant biological form of iron changing into the more toxic ferrous form. As well as Diamond Light Source, studies were also carried out at the Swiss Light Source and the Advanced Light Source in the USA, using applied advanced x-ray techniques, more commonly used to study the latest hi-tech materials.

The experiments revealed that the peptide that makes up Alzheimer's lesions is capable of converting iron into the form which could be causing damage to brain cells. This means that the lesions caused by Alzheimer's could be causing a subtle disruption in how the brain manages iron, confronting brain cells with a level of toxicity that they

simply cannot manage.

This discovery paves the way for future medical research into treatments that could halt or manage the conversion of iron into this toxic form, potentially slowing or limiting the damage to the brain. It could also lead to developments in using magnetic resonance imaging (MRI) to detect early stages of the disease by mapping altered patterns of iron in the brain.

Dr Neil Telling from the University of Keele, who lead the research in collaboration with colleagues at the University of Warwick and the University of Florida, commented: "Alzheimer's is a sensitive and emotive area of research. The disease involves progressive brain cell failure, the reasons for which are still not fully understood. When findings showed increased levels of toxic iron within Alzheimer's disease tissues, we realised that techniques we had used to study other iron based materials could be applied to understand where this toxic iron came from. Our observations suggest an origin for the toxic iron; that it may well be made toxic by the lesions themselves. This could open up new avenues of research into treatments to stop the build-up of this neurotoxic substance, potentially limiting the damage done by Alzheimer's. Understanding how this toxic iron forms could also tell us where to look for early stages of the disease in MRI scans, perhaps even before irreversible brain damage occurs. It's at an early stage but these promising results seem to be another piece of the jigsaw to fully understand Alzheimer's."

Dr Doug Brown, Director of Research and Development at Alzheimer's Society, commented: "Clumps of amyloid beta are a hallmark of Alzheimer's disease although why they accumulate in this way or cause brain cells to die is still being understood. This study suggests that the protein may cause iron to turn into its toxic form, leading to damage to brain cells. Why this might happen and how it can be stopped are

important future avenues for research.

"There will be a million people with dementia in the UK by 2021 yet we still don't know what causes the condition and there are only limited treatments available. We desperately need more research aimed at unravelling the underlying causes of dementia to help us in our quest to find better treatments and ultimately a cure."

Andrew Harrison, CEO of Diamond Light Source, commented: "It is always wonderful to see a piece of research come out of Diamond Light Source which has the potential to have a positive impact on people's lives. Research done at Diamond is leading step changes in our understanding of diseases like this, and supporting technological innovation and new drug designs for a range of different diseases. We put an enormous amount of work into maintaining Diamond as a centre of cutting edge research and making our light source available to 3,000 scientists every year; these groups rely on our advanced facilities to further their research and make crucial steps forward."

More information: The full research paper "Ferrous iron formation following the co-aggregation of ferric iron and the Alzheimer's disease peptide β-amyloid (1-42)" was published in *Journal of the Royal Society Interface* on Wednesday, 26th March 2014 DOI: 10.1098/rsif.2014.0165 .

A related paper was published recently online by the same research team in the journal ACS *Inorganic Chemistry* entitled "Evidence of Redox-Active Iron Formation Following Aggregation of Ferrihydrite and the Alzheimer's Disease Peptide β-Amyloid" DOI: 10.1021/ic402406g.

Diamond Light Source