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Coming Events

2016

EPMA 2016: Electron Probe Microanalysis Topical Conference
May 16–19, 2016
Madison, WI
www.microbeamanalysis.org/topicalconferences/epma-2016-1/epma-2016

APMC11 – 11th Asia-Pacific Microscopy Conference
May 23–27, 2016
Phuket, Thailand
www.apmc11.org

EBSD 2016: Electron Backscatter Diffraction Topical Conference
May 24–26, 2016
Tuscaloosa, AL
www.microbeamanalysis.org/topical-conferences/ebsd-2016/welcome

Inter/Micro: 68th Annual Applied Microscopy Conference
June 6–10, 2016
Chicago, IL
www.mcri.org

43rd MSC Annual Meeting
June 7–10, 2016
Edmonton, Alberta
http://conference2016.msc-smc.org

Microscopy & Microanalysis 2016
July 24–28, 2016
Columbus, OH
www.microscopy.org

65th X-ray Analysis Conference
August, 1–5, 2016
Rosemont, IL
www.dxcicdd.com

European Microscopy Congress
August 28–September 2, 2016
Lyon, France
http://emc2016.fr

2017

Microscopy & Microanalysis 2017
July 23–27, 2017
St. Louis, MO
www.microscopy.org

2018

Microscopy & Microanalysis 2018
August 5–9, 2018
Baltimore, MD
www.microscopy.org

2019

Microscopy & Microanalysis 2019
August 4–8, 2019
Portland, OR
www.microscopy.org

2020

Microscopy & Microanalysis 2020
August 2–6, 2020
Milwaukee, WI
www.microscopy.org

More Meetings and Courses
Check the complete calendar near the back of this magazine.

Carmichael's Concise Review

Visualizing Changes in Mitochondria in Alzheimer's Disease

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Alzheimer's disease (AD) presently affects more than 5 million Americans with numbers expected to grow. The specific molecular mechanisms of AD are still under investigation thereby hindering the development of effective therapies. Progressive memory decline is associated with synaptic loss and neuronal cell death. Significant hypometabolic changes can be detected early in AD patients, which suggests that abnormal energy metabolism underlies disease etiology. Mitochondria are dynamic organelles that constantly move within the cell and undergo fission and fusion (collectively termed "mitochondrial dynamics"). Such changes are important for proper responses to cellular energy demands. Fidelity of mitochondrial dynamics is especially important for the proper functioning of neurons where mitochondria need to travel over long distances to provide energy for distant parts of axons. Excessive mitochondrial fragmentation was observed in brain tissue of transgenic animal models of AD and postmortem brain from AD patients. These data suggested modulation of mitochondrial dynamics could represent novel therapeutic strategies for AD treatment. However, the understanding of the molecular mechanisms and details involved in the changes in mitochondrial morphology are incomplete and are hindered by the lack of tools that could study these dynamic changes in intact brain tissue. In an elegant study, Zhang, Salisbury, Trushina et al. used three-dimensional electron microscopy (3D EM) to look for changes in mitochondria in the brain of patients and animal models of AD.

Using well-accepted transgenic mouse models of AD (and non-transgenic littermates as controls) Zhang et al. noticed differences in mitochondrial morphology in the CA1 hippocampus using standard transmission electron microscopy and super-resolution immunofluorescence. In order to better visualize these morphological changes they used 3D EM that provided a "virtual" specimen thickness of 0.9 µm to 3.6 µm in 10 to 40 consecutive serial sections that were stacked, aligned, and reconstructed using 3D reconstruction software (Figure 1). They identified a previously unknown mitochondrial fission arrest phenotype that results in elongated interconnected organelles that they dubbed "mitochondria-on-a-string" (MOAS). Their data suggested that MOAS formation may occur at the final stages of the fission process and was not associated

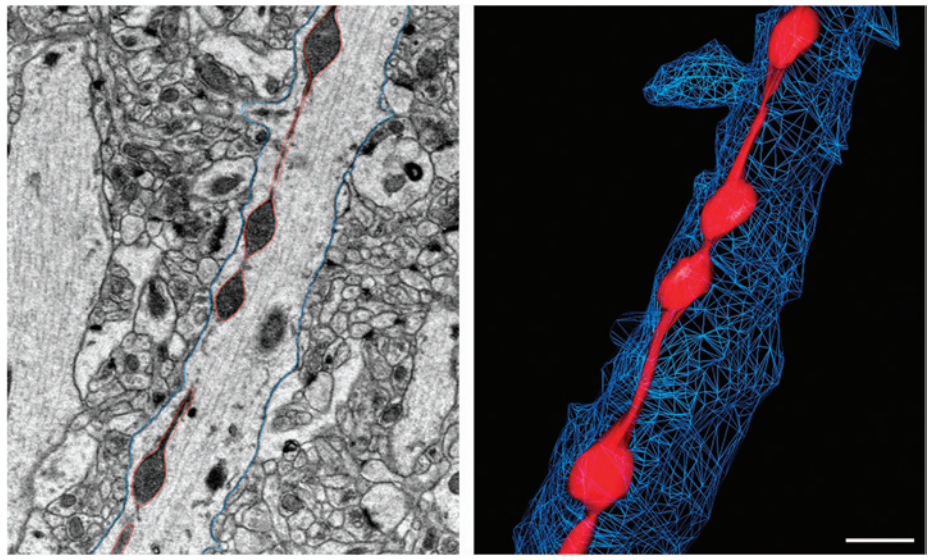

Figure 1: 3D EM reconstruction of the CA1 hippocampal brain region from an APP/PS1 (Alzheimer's Disease model) transgenic mouse. Left: Standard TEM images like the one presented were collected from serial thin sections, stacked, aligned, and visualized using reconstruction software. Right: The resulting 3D image of an individual neuropil (blue) allows for a detailed observation of mitochondria morphology (red) within the neuropil indicating presence of MOAS. Scale bar = 1.0 µm.

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with altered translocation of activated dynamin-related protein 1 to mitochondria. Fission and fusion machinery depends on the fidelity of this and other proteins. Instead, MOAS formation was associated with reduced guanosine triphosphatase activity, possibly associated with an energetic crisis that results in fission arrest or delay, leading to the formation of MOASs. Most important, MOAS could be easily mistaken for multiple individual organelles if the thin membrane connections are missed because of the limitations of 2D EM or low spatial resolution of fluorescence microscopy.

Zhang et al. also examined samples of the human CA1 hippocampus taken at postmortem from normal and AD patients. A MOAS phenotype in AD samples was found. Their data suggested that MOAS formation has relevance to the human disease condition. Taken together with the findings in mice, the discovery of a novel mitochondrial phenotype that occurs in brain tissue in response to energetic–stress—an early contributing factor to the development of AD associated with mitochondrial dysfunction resulting in altered energy production and utilization—can be accurately detected by 3D EM reconstruction. This argues for a major role of mitochondrial dynamics in regulating neuronal survival. This work also emphasizes the importance of using advanced tools to study the morphology of a 3D organelle in the context of 3D tissue architecture, in this case to accurately determine mitochondrial morphology. Another "piece of the puzzle" regarding an underlying mechanism that leads to the progression of Alzheimer's disease may have been found!

References

[1] L Zhang et al., *Scientific Reports* 6, article number 18725 (2016) doi:10:1038/srep18725.

[2] The author gratefully acknowledges Drs. Eugenia Trushina and Jeffrey Salisbury for reviewing this article.

MT

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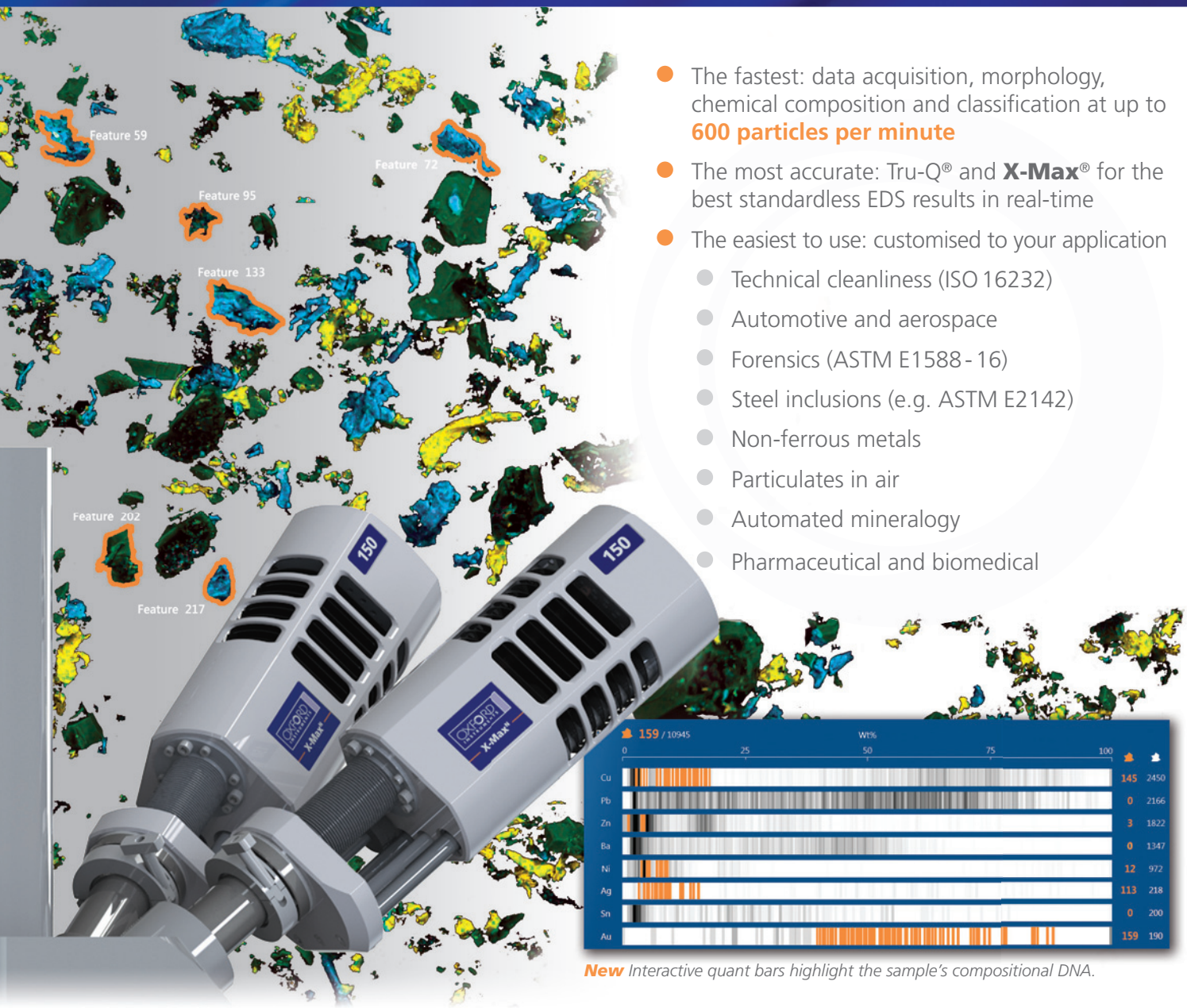

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