The role of DNA damage in the formation of Langhans-type multinucleated giant cells in Giant Cell Arteritis

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Background:

Giant cell arteritis (GCA) is distinguished histologically by the presence of Langhans-type multinucleated giant cells (LMGCs). Characterisation of these cells is primarily morphological and their origin and role in disease remains unclear. Investigating how they develop may help us understand the pathogenesis of GCA and distinguish patients with GCA from those with other forms of inflammation.

Methods:

Human CD14+ monocytes were isolated from healthy donor peripheral blood and cultured in GM-CSF and IFNγ. Morphology was assessed by confocal microscopy. LMGCs were identified using DRAQ5 or DAPI. Time-lapse confocal microscopy was performed with SiR-DNA. Sequencing libraries were generated using SmartSeq2.

Results:

Time-lapse microscopy revealed multinucleation occurred in this in vitro model through failed cytokinesis. Immunofluorescence and electron microscopy confirmed this by demonstrating chromatin bridges linking nuclei in large LMGCs but absent in osteoclasts. Electron microscopy identified multiple chromatin bridges in GCA-affected tissue LMGCs. Single cell RNA sequencing of both in vitro LMGCs and GCA-affected temporal artery macrophages revealed enrichment of gene modules associated with autophagy, inhibition of cell cycle progression and DNA damage response.

Conclusion:

These data suggest LMGCs form in conditions of cellular stress with DNA damage inhibiting proliferation. The effect of DNA damage occurring in-situ in GCA affected arteries is unclear and needs further her investigation.

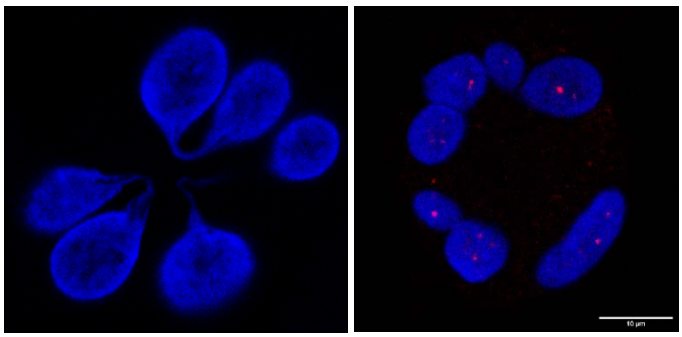

Figure: Microscopy of in vitro-derived multinucleated giant cells reveals evidence of DNA damage. Left: In vitro derived-multinucleated giant cells stained with DAPI (blue) to highlight nuclei and chromatin bridges. Right: The same cells stained with anti-p21 antibody (red).