Institute of Molecular Biology and Biotechnology
Foundation for Research and Technology-Hellas

PRESS RELEASE

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IMBB researchers reveal that DNA damage triggers a chronic auto-inflammatory response leading to fat depletion

Research carried out at the Institute of Molecular Biology and Biotechnology-FORTH and published today in Cell Metabolism (http://www.cell.com/cell-metabolism/) reveals that intrinsic DNA damage triggers a chronic auto-inflammatory response leading to fat depletion.

Lipodystrophy syndromes represent a large group of heterogeneous disorders characterized by the selective loss of fat tissue. Lipodystrophy has attracted keen scientific interest for two major reasons: i) the metabolic consequences of fat depletion bear remarkable similarities to those of obesity and ii) recent progress in understanding the genetic basis for several inherited forms of lipodystrophy has provided novel insights into adipocyte biology. Despite much research in the field, their etiology remains currently unknown. Using animals carrying a DNA repair defect systemically or in adipose tissue, the IMBB researchers Ismene Karakasilioti, working together with the head of the research team Prof. George Garinis, revealed that that persistent DNA damage signaling triggers a chronic auto-inflammatory response that leads to severe fat depletion in mice.

Integrity of the genome is critical for normal cellular function but the DNA is continually challenged by intrinsic and extrinsic genotoxic factors. To counteract DNA damage, cells have evolved DNA repair mechanisms ensuring that the genome remains functionally intact and is faithfully transmitted to progeny. Nucleotide excision repair (NER) is a major DNA repair mechanism that cells employ to remove a wide class of bulky, DNA-distorting lesions from the genome. The importance of NER defects in man is illustrated by rare syndromes that either show increased cancer predisposition or dramatic features of accelerated aging, including depletion of fat depots. However, with the exception of cancer, the links between defects in NER and the rapid onset of progeroid features are not well understood.

Using genetically modified mice that carry the NER defect systemically or only in the fat tissue, the IMBB researchers provide evidence for a causal link between persistent DNA damage and the gradual manifestation of progressive lipodystrophy in NER progerias; we find that the accumulation of irreparable DNA inter-strand crosslinks (ICLs) triggers the transcriptional derepression of pro-inflammatory cytokines in adipocytes, the recruitment of leukocytes to sites of tissue damage and the destruction of white adipose tissue depots in NER-defective animals.

Taken together, the findings provide a novel mechanism by which stochastic, endogenous DNA damage instigates tissue-specific pathology in accelerated aging syndromes and by analogy likely with aging.

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