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TET altered functionality determines accretion of iterative methyl-cytosine modifications in human cardiac fibroblasts from diabetes patients: Correction by pharmacogenomic interventions

Background: The hyperglycemic/metabolic memory is clinically evident in patients in which glycaemic control is not beneficial on the progression of complications including cardiovascular accidents. This condition has been recently associated with altered epigenetic mechanisms and the presence of dysmetabolic pathways. The molecular mechanism underlying this process is still uncharacterized.

Methods & Results: Total genomic DNA was extracted from non-diabetic-cardiac fibroblast (ND-CF) and diabetic-CF (D-CF) and analysed for the global content of modified cytosines including 5 methyl-cytosine (5mC), 5 hydroxy-methyl-cytosine (5hmC), 5 formyl-cytosine (5fC) and 5 carboxy-cytosine (5caC) by colorimetric ELISAs. Remarkably, D-CFs, cultured between passage 4 and 8 since isolation, accumulated all types of modified cytosines compared to cells obtained from normoglycemic controls. Similar findings were observed in DNA samples obtained from the heart of streptozotocin-induced diabetic mice as well as in the Ins2 Akita mouse model of genetic insulin defect. RNA-seq experiments showed that human D-CFs have a reduced content of transcripts encoding for proteins involved in proliferation, DNA synthesis and packaging, chromosome organization and metabolic processes. Moreover, D-CFs showed a significant reduction in the number of mitochondria, in Isocitrate Deidrogenase 1-2 (IDH1, 2) activity and in α-Ketoglutarate (αKG) levels. The latter is an important cofactor for the regulation for ten-eleven-translocation (TET) demethylases. Treatment with exogenous αKG or a TET activator, such as vitamin C, rescued proliferation in D-CFs as consequence of an active demethylation process.

Conclusion: DNA demethylation machinery may be important during the onset of the hyperglycemic/metabolic memory. TET activators may represent a novel tool to treat diabetic complications and reduce cardiovascular risk.

Biography

Carlo Gaetano is a 2012-present: Professor, Faculty of Medicine, Johannes Wolfgang Goethe Unicersity, Frankfurt am Main, Germany. 2006-12: Consultant, Laboratorio di Biologia Vascolare e Medicina Rigenerativa, Istituto Cardiologico Monzino, via, Pareo 4, 20138, Milano, Italy. 1996-12: Senior Investigator, Laboratorio di Patologia Vascolare, Istituto Dermopatico dell\'Immacolata, via dei Monti di Creta 104, 00167, Roma 1999-00: Associate Professor, McMaster University, Hamilton (ON), Canada 1995-96: Visiting Scientist, National Cancer Institute, NIH, Bethesda (MD), USA 1992-95: Postdoctoral fellow, Istituto Regina Elena, Roma, Italy 1989-91: Postdoctoral fellow, National Cancer Institute, NIH, Bethesda (MD), USA. 1984-88: Intern, Dipartimento di Immunologia, Univ. La Sapienza, Roma, Italy 1981-83: Intern, Dipartimento di Virologia, Univ. La Sapienza, Roma, Italy.

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