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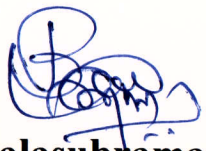
Details of the research work duly signed by the applicant, for which the Sun Pharma Science Foundation Research Award is claimed, including references and illustrations (not to exceed 6000 words).



Dr.M.Balasubramanyam

ICMR Emeritus Scientist

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The important research contributions of **Dr.M.Balasubramanyam** is that he has meticulously utilized and transformed the Diabetes-based epidemiological studies in to successful molecular medicine investigations and demonstrated ***'the clinical significance and subclinical relevance of cellular stress signals (oxidative stress, inflammation, glycation, ER stress, miRNA dysregulation, accelerated senescence and telomere shortening) in patients with Type 2 diabetes'.***

Adaikalakoteswari A, Balasubramanyam M and Mohan V. Telomere shortening occurs in patients with Type 2 diabetes. Diabetic Medicine, 22, 1151–1156, 2005.

This landmark work is the first study in the world literature to demonstrate shortened telomeres in patients with type 2 diabetes. Seeking a dynamic and long-term biomarker of molecular stress signaling in the genesis of diabetes and its complications, Balasubramanyam and colleagues reported shortened telomeres in Asian Indian patients with type 2 diabetes. Several of the continuing works on this direction demonstrated **accelerated aging** as an underlying cause for insulin resistance and type 2 diabetes which could be reversible and hence amenable for therapeutic and/or lifestyle intervention.

The following are the research contributions of Dr.M.Balasubramanyam and colleagues central to the role of telomere shortening and accelerated senescence markers.

1. Prabu P, Poongothai S, Shanthirani CS, Anjana RM, Mohan V, **Balasubramanyam M**. Altered circulatory levels of miR-128, BDNF, cortisol and shortened telomeres in patients with type 2 diabetes and depression. Acta Diabetol. 2020, 57(7):799-807

2. Chandru S, Prabhu P, **Balasubramanyam M**, Subhashini R, Mangesh Tiwaskar M, Pramodkumar TA, Pradeepa R, Anjana RM, & Mohan V. Beneficial Primary Outcomes of Metabolic Surgery with Changes in Telomere Length and Mitochondrial DNA in Obese Asian Indians with Dysglycemia. Journal of The Association of Physicians of India, 2021, 69 :43-47.

3. Raghavan S, Malayaperumal S, Mohan V and **Balasubramanyam M**. A Comparative study on the Cellular Stressors in Mesenchymal Stem Cells (MSCs) and Pancreatic β-cells under Hyperglycemic Milieu. Mol Cell Biochem. 2021 Jan;476(1):457-469. doi: 10.1007/s11010-020-03922-4
4. Soundararajan A, Prabu P, Mohan V, Gibert Y, **Balasubramanyam M**. Novel insights of elevated systemic levels of bisphenol-A (BPA) linked to poor glycemic control, accelerated cellular senescence and insulin resistance in patients with type 2 diabetes. Mol Cell Biochem. 2019; 458(1-2):171-183

5. Soundararajan A, Yogananthara jah P, Raghavan S, Mohan V, **Balasubramanyam M**, Gibert Y. Bisphenol A exposure under metabolic stress induces accelerated cellular senescence in vivo in a p53 independent manner. Sci Total Environ. 2019;689:1201-1211

6. Sathishkumar C, Prabu P, Mohan V**, Balasubramanyam M**. Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. Hum Genomics. 2018 Aug 23;12(1):41. doi: 10.1186/s40246-018-0173-3.

7. Monickaraj, F., Gokulakrishnan, K., Prabu, P., Sathishkumar, C., Anjana, R.M., Rajkumar, J.S., Mohan, V & **Balasubramanyam, M**. Convergence of adipocyte hypertrophy, telomere shortening and hypoadiponectinemia in obese subjects and in patients with Type 2 diabetes. Clinical Biochemistry 2012, 45(16-17):1432-8

8. Monickaraj, F., Aravind, S., Gokulakrishnan, K., Satishkumar, C., Prabu, P., Prabu, D., Viswanathan Mohan, V. & **M. Balasubramanyam**. Accelerated ageing as evidenced by increased telomere shortening and mitochondrial DNA depletion in patients with Type 2 diabetes. Molecular and Cellular Biochemistry 2012, 365(1-2):343-50

9. Adaikalakoteswari A**, M. Balasubramanyam**, M, Ravikumar, R, Deepa. R. and Mohan, V. Association of telomere shortening with impaired glucose tolerance and diabetic macroangiopathy. Atherosclerosis, 195:83-9, 2007.

10. Finny Monickaraj F, Aravind S, Nandhini P, Prabu P, Sathishkumar C, Viswanathan M, **Balasubramanyam, M**. Accelerated fat cell aging links oxidative stress and insulin resistance in adipocytes. Journal of Biosciences 2013, 8(1):113-22

11. Balasubramanyam M, Adaikalakoteswari A, Sameermahmood Z, Mohan V. Biomarkers of oxidative stress: methods and measures of oxidative DNA damage (COMET assay) and telomere shortening. Methods Mol Biol. 2010; 610:245-61.

12. **Balasubramanyam M**, Adaikalakoteswari, A, Finnymonickaraj, S. Mohan, V. Telomere shortening and metabolic/vascular diseases. Indian Journal of Medical Res. 125: 441-450, 2007.

13. **Balasubramanyam M,** Adaikalakoteswari A & Mohan V. Telomere shortening: A marker of atherosclerosis? Current Science, 87, 422-24, 2004.

14. Gielen M, Hageman GJ, Antoniou EE, Nordfjall K, Mangino M, **Balasubramanyam M** et al (TELOMAAS Group) Body mass index is negatively associated with telomere length: a collaborative cross-sectional meta-analysis of 87 observational studies. Am J Clin Nutr. 2018;108(3):453-475. doi: 10.1093/ajcn/nqy107.

Adaikalakoteswari A**, M. Balasubramanyam**, M, Ravikumar, R, Deepa. R. and Mohan, V. Association of telomere shortening with impaired glucose tolerance and diabetic macroangiopathy. Atherosclerosis, 195:83-9, 2007.

It is well known that increased risk for coronary artery disease (CAD) is seen not only in subjects with Type 2 diabetes but also at the stage of pre-diabetes or impaired glucose tolerance (IGT). This has also been shown for sub-clinical atherosclerosis as measured by carotid intima-medial thickness (IMT). We recently demonstrated the occurrence of telomere shortening in leukocytes from Asian Indian Type 2 diabetic patients thus raising the possibility that telomere shortening might be a long-term risk marker of diabetes and macro-vascular complications. There are no studies to our knowledge that have looked at telomere shortening in prediabetes, i.e., at the stage of IGT. This study presents three important observations. First, in Asian Indians who are considered more insulin resistant and have a higher risk of developing Type 2 diabetes, there is an association of telomere shortening with impaired glucose tolerance. To the best of our knowledge this is the first study to show telomere shortening in subjects with IGT. Secondly, Type 2 diabetic subjects with atherosclerotic plaques had significantly shorter telomeres compared to diabetic subjects without atherosclerotic plaques. Thirdly, shortening of telomeres was associated with increased markers of systemic inflammation and oxidative stress.

Sathishkumar C, Prabu P, Mohan V**, Balasubramanyam M**. Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. Hum Genomics. 2018 Aug 23;12(1):41. doi: 10.1186/s40246-018-0173-3.

Linking a role of lncRNAs (long non-coding RNAs) in the etiology of Type 2 diabetes: This work unraveled a new-biology link in the etiology of type 2 diabetes as we demonstrated an association of altered long non-coding RNAs (LncRNAs) with accelerated senescence, inflammation and insulin resistance in patients with type diabetes. This got wide science media attention as appeared in European Medical Journal site as: **'Altered LncRNAs signify an upstream link in the etiology of type 2 diabetes'.** Highlights of this study include the following: At the transcriptional level, senescence markers (p53, p21, p16, and β-galactosidase), proinflammatory markers (TNF-α, IL6, MCP1, and IL1-β), and epigenetic signature of histone deacetylase-3 (HDAC3) were significantly ($p < 0.05$) elevated in patients with type 2 diabetes compared to control subjects. Interestingly, mRNA expression of Sirt1 and telomere length were significantly ($p < 0.05$) decreased in patients with type 2 diabetes compared to control subjects. Majority of the altered lncRNAs were positively correlated with poor glycemic control, insulin resistance, transcriptional markers of senescence, inflammation, and HDAC3 and negatively correlated with telomere length. Logistic regression analysis revealed a significant association of altered lncRNA signatures with T2DM, but this association was lost after adjusting for insulin resistance (HOMA-IR) and senescence markers.

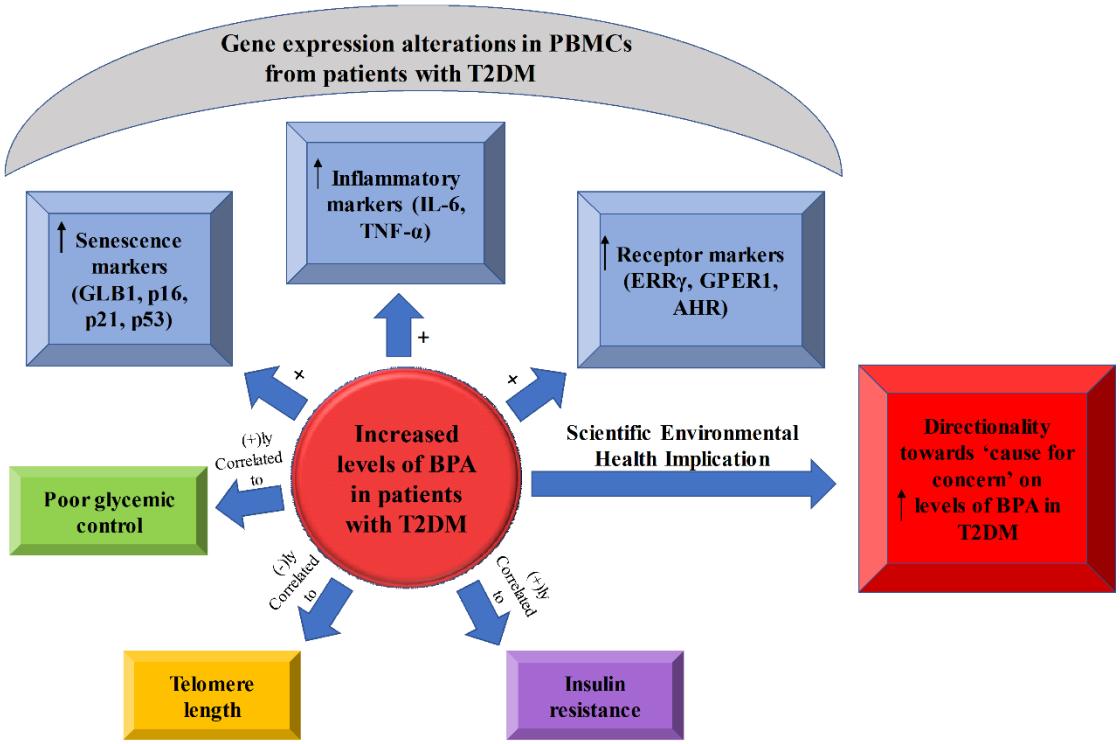
Monickaraj, F., Aravind, S., Gokulakrishnan, K., Satishkumar, C., Prabu, P., Prabu, D., Viswanathan Mohan, V. & **M. Balasubramanyam**. Accelerated ageing as evidenced by increased telomere shortening and mitochondrial DNA depletion in patients with Type 2 diabetes. Molecular and Cellular Biochemistry 2012, 365(1-2):343-50

This study by Balasubramanyam and colleagues unraveled clustering of biomarkers of accelerated aging in patients with type 2 diabetes as evidenced by an association of shortened telomeres with

decreased mtDNA, hypoadiponectinemia and increased oxidative stress. The finding assumes greater significance because, it is in a clinical setting, we showed the existence of a molecular connection between the nuclear and mitochondrial ageing processes which occur in a 'fast-forward' way in patients with type 2 diabetes. Unlike the chronological aging, accelerated aging could be reversed and hence amenable for intervention. It is emphasized that maintenance of appropriate mitochondrial function and telomere length either by pharmacological means or lifestyle modification will have promising therapeutic potential for Type 2 diabetes and associated vascular disorders. This study has been quoted in Nature India as **'Fast forward aging link in diabetes'**

Soundararajan A, Prabu P, Mohan V, Gibert Y, **Balasubramanyam M**. Novel insights of elevated systemic levels of bisphenol-A (BPA) linked to poor glycemic control, accelerated cellular senescence and insulin resistance in patients with type 2 diabetes. Mol Cell Biochem. 2019; 458(1-2):171-183

While there is cause of concern on endocrine disruptors (like BPA) as environmental risk for type 2 diabetes and other metabolic disorders, there is lack of data on this in India. Our work not only demonstrated elevated systemic levels of BPA in patients with type 2 diabetes but also delineated its association with cellular alterations of several signatures including accelerated senescence.

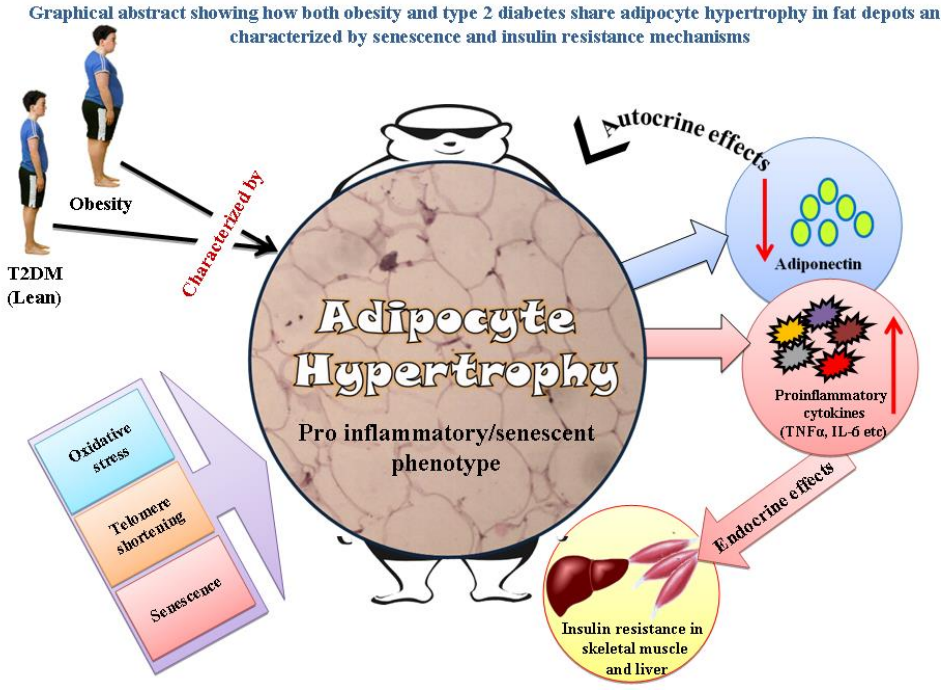


Prabu P, Poongothai S, Shanthirani CS, Anjana RM, Mohan V, **Balasubramanyam M**. Altered circulatory levels of miR-128, BDNF, cortisol and shortened telomeres in patients with type 2 diabetes and depression. Acta Diabetol. 2020, 57(7):799-807

In this study, patients with type 2 diabetes and depression were shown to exhibit increased circulatory levels of miR-128 and serum cortisol and decreased levels of BDNF and shortened telomeres. These neuroendocrine signatures were more markedly altered in those with combined diabetes and depression.

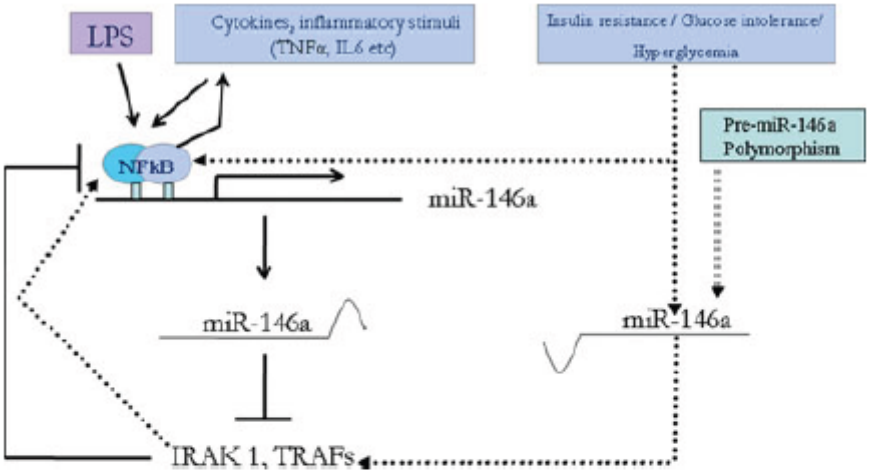
Monickaraj, F., Gokulakrishnan, K., Prabu, P., Sathishkumar, C., Anjana, R.M., Rajkumar, J.S., Mohan, V & **Balasubramanyam, M**. Convergence of adipocyte hypertrophy, telomere shortening and hypoadiponectinemia in obese subjects and in patients with Type 2 diabetes. Clinical Biochemistry 2012, 45(16-17):1432-8

One of the factors that contribute to accelerated diabetes epidemic in Asians is referred to as "normal-weight metabolically obese" phenotype. However, the biochemical or molecular basis for **'metabolic obesity'** is poorly understood. In this study, the measurements of adipocyte cell size from human visceral and subcutaneous fat tissue demonstrated that non-obese diabetics are characterized by increased adipocyte cell size (adipocyte hypertrophy). In addition, adipose tissue from these lean diabetics showed increased senescence as evident from shortened telomeres and compromised secretory profile as evident from low levels of circulatory adiponectin. This is again for the first-time in India, the telomere length has been reported utilizing adipose tissue. The finding by Balasubramanyam and co-workers assumed greater significance because it is in a clinical setting, they unraveled the molecular basis for 'metabolic obesity' in diabetic patients. This study exposed adipocyte hypertrophy and senescence pathway as targets for new drug discoveries. This study has been quoted in Nature India as **'Why lean diabetics could be metabolically obese'.**



Balasubramanyam M, Aravind S, Gokulakrishnan K, Prabu P, Sathishkumar C, Ranjani H and Mohan, V. Impaired miR-146a expression links subclinical inflammation and insulin resistance in type 2 diabetes. Mol Cell Biochem. 2011 351(1-2):197-205

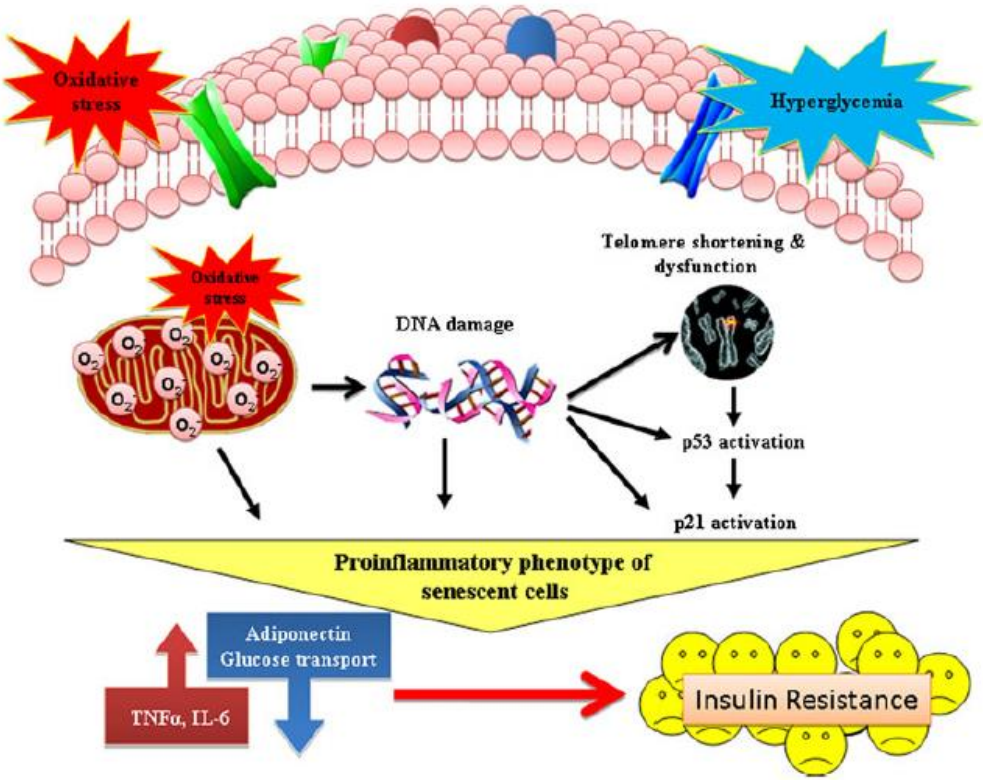
Over the past 5 years, it has become increasingly clear that miRNAs are not only important for normal organismal development and physiology, but also in the pathologies related to many metabolic diseases. While Indians are considered highly insulin-resistant, prone to develop diabetes and vascular diseases and subclinical inflammation is a part of the pathogenic mechanisms, the regulatory mechanisms of pro-inflammation are poorly understood. Utilizing peripheral blood mononuclear cells (PBMCs) as a surrogate cell model, Balasubramanyam and collegues demonstrated impaired miR-146a expression linking subclinical inflammation and insulin resistance in type 2 diabetes. In this study, miR-146a exhibited a negative association with several proinflammatory target genes such as TRAF-6 and NFkB and circulatory levels of TNFα and IL-6. Interestingly, miR-146a levels also showed a negative association with insulin resistance and glycated hemoglobin. While the work demonstrated an association of impaired miR-146a with subclinical inflammation in patients with type 2 diabetes, it also provided an avenue to look for specific and appropriate miRNA mimics including small molecule modulators as novel anti-inflammatory therapeutic measures.



Schematic diagram for the role of miR-146a in immune regulation: during LPS exposure or cytokines augmentation (*solid line*), NFκB gets activated and thereby increase miR-146a levels in order to perform negative feedback regulation and control of immune responses. During hyperglycemia (*dotted line*), miR-146a levels might be decreased despite NFκB activation and augment cytokine signalling and proinflammatory responses. Decreased miR-146a levels might also originate from pre-miR-146a polymorphisms

Finny Monickaraj F, Aravind S, Nandhini P, Prabu P, Sathishkumar C, Viswanathan M, **Balasubramanyam, M**. Accelerated fat cell aging links oxidative stress and insulin resistance in adipocytes. Journal of Biosciences 2013, 8(1):113-22

Senescent cells lurk in our tissues. They escape elimination due to impaired programmed cell death or altered immune surveillance. It is inferred from the recent studies that senescent cells behave badly, secrete chemicals that degrade surrounding tissue and harm neighboring cells and their increasing omnipresence contributes to accelerated aging and age-related pathologies. In our study, fat cells subjected to oxidative stress become *senescent associated secretory phenotype* (SASP), started *'SMSing'* proinflammation, exhibited shortened telomeres and become insulin-resistant – a hallmark characteristic of diabetic state. This study warrants that we need to find a robust way of identifying senescent cells and selectively removing them and this should pave way for either prevention or delaying of age-related pathologies including diabetes. There is exciting news at least in animal models that it is possible to selectively target senescent cells, eliminate them and delay or prevent age-related pathologies. This calls for further research on *'clearing away old cells'* either pharmacologically or by lifestyle modifications to achieve *healthy aging* if not anti-aging.



Prabu P, Rome S, Sathishkumar C, Aravind S, Mahalingam B, Shanthirani CS, Gastebois C, Villard A, Mohan V, **Balasubramanyam M.** Circulating MiRNAs of 'Asian Indian Phenotype' Identified in Subjects with Impaired Glucose Tolerance and Patients with Type 2 Diabetes. PLoS One. 2015 May 28;10(5):e0128372. doi: 10.1371/journal.pone.0128372. eCollection 2015.

Circulatory microRNAs characteristic of 'Asian Indian phenotype": This is the first study in India to expose the biomarker role of circulatory microRNAs characteristic of 'Asian Indian phenotype' in type 2 diabetes patients. As the technologies related to miRNA measurement are evolving, our study implied that specific miRNA profile either singly or as a panel would qualify as potential tool for personalized medicine. This study has been highly appreciated in the media and quoted in ResearchSEA as **'MicroRNA markers for Madhumeha'.**
When we showed alteration of miR-128 in prediabetes and type 2 diabetes is of Asian Indian phenotype characteristic, one of our recently studies also showed a positive correlation of miR-128 with shortened telomeres.

Prabu P, Rome S, Sathishkumar C, Gastebois C, Meugnier E, Mohan V, **Balasubramanyam M**. MicroRNAs from urinary extracellular vesicles are non-invasive early biomarkers of diabetic nephropathy in type 2 diabetes patients with the 'Asian Indian phenotype'. Diabetes Metab. 2019; 45(3):276-285

As microRNAs from extracellular vesicles (EVs) have been proposed as promising biomarkers for a number of diseases, one of our studies explored their potential as urine-based biomarkers of diabetic nephropathy (DN) in a discovery and validation cohort. A panel of four urinary EV miRNA signatures was found to identify patients with microalbuminuria (MIC). With the limitations of MIC test (a gold-standard for predicting DN), this study endorses the clinical utility of urinary miRNAs from EVs as non-invasive 'liquid biopsies' to stratify patients at risk of developing macroalbuminuria (MAC) and diabetic kidney disease. This study has been quoted in the Asia Research News as '**Liquid-biopsy microRNA markers to predict risk for diabetic kidney disease'.**

Chandru S, Prabhu P, **Balasubramanyam M**, Subhashini R, Mangesh Tiwaskar M, Pramodkumar TA, Pradeepa R, Anjana RM, & Mohan V. Beneficial Primary Outcomes of Metabolic Surgery with Changes in Telomere Length and Mitochondrial DNA in Obese Asian Indians with Dysglycemia. Journal of The Association of Physicians of India, 2021, 69 :43-47.

Although metabolic surgery has been shown to offer beneficial primary outcome results in obese individuals / obese Type 2 diabetes mellitus (T2DM) patients, there is paucity of information on the underlying mechanisms. In the recent years, estimations of non-invasive molecular parameters viz., telomere length and mtDNA copy number (mtDNAcn) assume significance as robust biomarkers. However, there is lack of evidence about this especially, in the Indian context. Our study is unique in that it reported an increase in telomere length and decrease in circulatory mtDNA copy number levels at 6 and 12 months post metabolic surgery in obese individuals with T2DM.

Raghavan S, Malayaperumal S, Mohan V and **Balasubramanyam M**. A Comparative study on the Cellular Stressors in Mesenchymal Stem Cells (MSCs) and Pancreatic β-cells under Hyperglycemic Milieu. Mol Cell Biochem. 2021 Jan;476(1):457-469. doi: 10.1007/s11010-020-03922-4

β-cell dysfunction is a critical determinant for both type 1 diabetes and type 2 diabetes and β-cells are shown to be highly susceptible to cellular stressors. Mesenchymal stem cells (MSCs) on the other hand are known to have immunomodulatory potential and preferred in clinical applications. However, there is paucity of a comparative study on these cells in relation to several cellular stressors in response to hyperglycemia and this forms the rationale for the present study. INS1 β-cells and MSCs were subjected to high-glucose treatment without and with Metformin, Lactoferrin, or TUDCA and assessed for stress signaling alterations using gene expression, protein expression, as well as functional read-outs. Compared to the untreated control cells, INS1 β-cells or MSCs treated with high glucose showed significant increase in mRNA expressions of ER stress, senescence, and proinflammation. This was accompanied by increased miR146a target genes and decreased levels of SIRT1, NRF2, and miR146a in both the cell types. Consistent with the mRNA results, protein expression levels do reflect the same alterations. Notably, the alterations are relatively less extent in MSCs compared to INS1 β-cells. Interestingly, three different agents, viz., Metformin, Lactoferrin, or TUDCA, were found to overcome the high glucose-induced cellular stresses in a concerted and inter-linked way and restored the proliferation and migration capacity in MSCs as well as normalized the glucose-stimulated insulin secretion in INS1 β-cells.

Gielen M, Hageman GJ, Antoniou EE, Nordfjall K, Mangino M, **Balasubramanyam M** et al (TELOMAAS Group) Body mass index is negatively associated with telomere length: a collaborative cross-sectional meta-analysis of 87 observational studies. Am J Clin Nutr. 2018;108(3):453-475. doi: 10.1093/ajcn/nqy107.

Even before the onset of age-related diseases, obesity might be a contributing factor to the cumulative burden of oxidative stress and chronic inflammation throughout the life course. Obesity may therefore contribute to accelerated shortening of telomeres. This collaborative cross-sectional meta-analysis of observational studies conducted to investigate the associations between BMI and TL across the life span, reports that a higher BMI is associated with shorter telomeres, especially in younger individuals.

In nut-shell, with the state-of-the-art clinical research, our studies resulted in outstanding research contributions demonstrating the accelerated cellular senescence (biological ageing) in type 2 diabetes linked to alterations in a panel of miRNAs, LncRNAs, HADCs as well as increased mitochondrial and ER stress. Most of our studies have clinical foresight and warrant 'targeting aging' so as to pave way for the development of novel therapeutic regimen of anti-ageing / senolytic agents as well as mitochondrially targeted antioxidants and ER stress inhibitors/Chemical Chaperones.

nature INDIA

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doi:10.1038/nindia.2012.53; Published online 17 April 2012

Research highlight

Fast forward aging link in diabetes

Researchers have shown a molecular connection between the nuclear and mitochondrial aging processes that occur in patients with type 2 diabetes[1].

The human body has a chronological age as also a biological age. The biological age is represented by the length of telomere — the DNA sequence at the end of each chromosome, like the plastic tips on shoelaces. The telomeres get shorter each time a cell divides. Short telomeres reflect accelerated ageing.

Many recently discovered genes that can be manipulated to slow the aging process also belong to pathways involved in the control of metabolism. Metabolic syndrome, in addition to being a precursor of metabolic disorders such as type 2 diabetes mellitus (T2DM) and cardiovascular disease, has been shown to be a sign of premature aging. Diabetes is a state of accelerated aging.

While telomere shortening is associated with T2DM, there is a lack of studies that explore the relationship among all the biomarkers — telomere length, oxidative stress, mitochondrial DNA (mtDNA) content, and the levels of adiponectin (a protein produced by fat cells that may play an important role in the development of obesity).

The researchers reasoned that the susceptibility to develop T2DM and cardiovascular diseases in Asian Indians could be explained by studying all these emerging biomarkers. "In a clinical setting, we have shown the existence of a molecular connection between the nuclear and mitochondrial ageing processes which occur in patients with type 2 diabetes," says lead author Muthuswamy Balasubramanyam.

Unlike chronological aging, accelerated aging can be reversed. "In other words, maintenance of appropriate mitochondrial function and telomere length either by pharmacological means or lifestyle modification will have promising therapeutic potential for Type 2 diabetes and associated vascular disorders", he adds.
The authors of this work are from: Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, Chennai, India.

References

Monickaraj, F. et al. Accelerated aging as evidenced by increased telomere shortening and mitochondrial DNA depletion in patients with type 2 diabetes. Mol. Cell Biochem. doi: 10.1007/s11010-012-1276-0 (2012)

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doi:10.1038/nindia.2013.36; Published online 20 March 2013

Research highlight

Aging fat cells signal diabetes

Researchers have found that aging fat cells could signal diabetes. In a new research, they show that aging fat cells provide a molecular link to a person's insulin resistance, a precursor for many metabolic diseases including diabetes[1].

The researchers have shown in animal models that it is possible to selectively target aging cells, eliminate them and delay or prevent age-related pathologies. This calls for further research on 'clearing away old cells' either pharmacologically or by lifestyle modifications to achieve healthy aging.

In response to a variety of stress signals, including nutrient deprivation, oxidative stress, dysfunctional telomeres and DNA damage, normally dividing cells can permanently withdraw from the typical cell cycle. These cells are then said to be in a state of 'cellular senescence', where their capacity to replicate is destroyed. Growing evidence suggests that these senescent cells contribute to aging in a variety of organisms, including mice and humans.

Senescent cells lurk in our tissues. They escape elimination due to impaired programmed cell death or altered immune surveillance. Senescent cells have been reported to behave badly, secrete chemicals that degrade surrounding tissue and harm neighboring cells. Their increasing omnipresence contributes to accelerated aging and age-related pathologies.

"In our study, fat cells subjected to oxidative stress became senescent associated secretory phenotype (SASP), started signalling proinflammation, exhibited shortened telomeres and became insulin-resistant. This is a hallmark characteristic of diabetes" says lead author Muthuswamy Balasubramanyam.

Promising Epigenetic Drug Target for Diabetes - Newswise

www.newswise.com/articles/view/669131?print-article ▾

Feb 8, 2017 - **Promising Epigenetic** Drug **Target for Diabetes** ... be the way for future anti-**diabetic** drugs with novel mode of actions and newer therapeutic options", said Muthuswamy **Balasubramanyam**, Dean of Research Studies & Senior Scientist from the Madras **Diabetes** Research Foundation in Chennai, India.

Sathishkumar et al. Human Genomics (2018) 12:41
https://doi.org/10.1186/s40246-018-0173-3

Human Genomics

PRIMARY RESEARCH Open Access

Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes

Chandrakumar Sathishkumar, Paramasivam Prabu, Viswanathan Mohan and Muthuswamy Balasubramanyam*

ALTERED LNCRNAS SIGNIFY AN UPSTREAM LINK IN THE ETIOLOGY OF TYPE 2 DIABETES

15 OCTOBER 2018 | DIABETES

Researchers from the Madras Diabetes Research Foundation (MDRF), Chennai, India have unraveled a new-biology link in the etiology of type 2 diabetes as their work[1] demonstrated an association of altered long non-coding RNAs (LncRNAs) with accelerated senescence, inflammation and insulin resistance in patients with type diabetes.

nature INDIA

doi:10.1038/nindia.2015.86 Published online 29 June 2015

Tiny RNA molecules as diabetes marker

Researchers have identified a specific microRNA (miRNA) that has higher serum levels in people with prediabetes and type 2 diabetes than healthy individuals[1]. Thus, the serum levels of this miRNA could be monitored to predict the risk and onset of type 2 diabetes.

nature INDIA

doi:10.1038/nindia.2011.70; Published online 16 May 2011

Research highlight

RNA clue to inflammation

Short RNA molecules called miRNA (or microRNA) play a critical role in inflammatory response and in diseases related to chronic inflammation[1].

Researchers have demonstrated this with studies on patients with Type 2 diabetes, who were found to have reduced levels of miR-146a in peripheral blood mononuclear cells (PBMCs). These reduced levels were associated with proinflammatory markers (increased gene expression of TRAF-6 and NFκB & increased plasma levels of TNF-α and IL-6).

The reduced levels of miR-146a were also associated with insulin resistance and poor glycemic control. This makes the research clinically significant.

When these proinflammatory lymphocytes or monocyte phenotypes infiltrate other organs, they are known to trigger a 'catchy inflammatory fire' in target sites and mediate atherogenesis, apoptosis, insulin resistance, Type 2 diabetes, and obesity. This provides an insight into disease progression and would help in management of diseases related to chronic inflammation.

References

Balasubramanyam, M. *et al*. Impaired miR-146a expression links subclinical inflammation and insulin resistance in type 2 diabetes. *Mol. Cell Biochem.* **351**, 197-205 (2011) | Article | PubMed | ISI | ChemPort |

http://www.nature.com/nindia/2011/110516/full/nindia.2011.70.html

Medicine News

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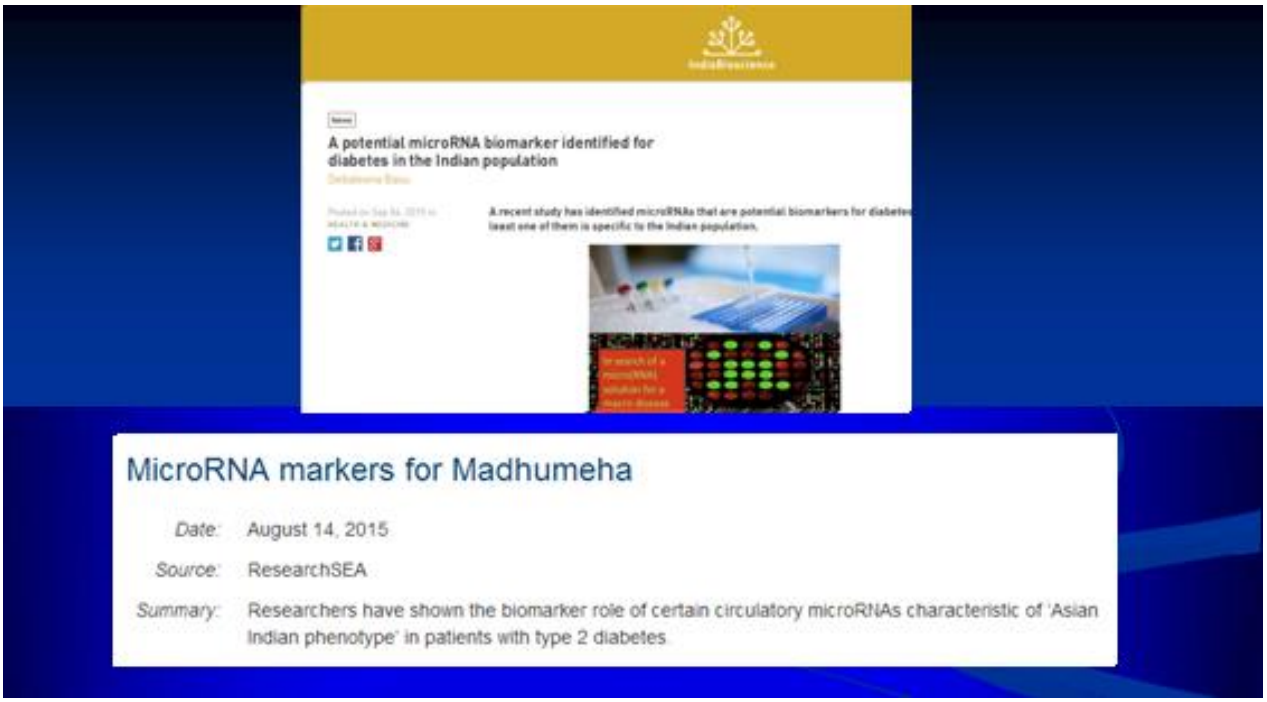
"Liquid-Biopsy" microRNA biomarkers to predict risk for diabetic kidney disease

A recent study from the Madras Diabetes Research Foundation, Chennai, India & University of Lyon, France – brings a new hope for using 'liquid-biopsy' exosomal microRNA biomarkers (miRNAs) from urine to predict risk for kidney disease in diabetes patients.



Medical News Article on *Diabetes*

Studies from M. Balasubramanyam and Co-Researchers Update Current Data on Diabetes

2011 MAY 24 -- "Type 2 diabetes patients exhibit subclinical inflammation but the regulatory mechanisms are poorly understood. We sought to evaluate the role of miR-146a expression along with its downstream proinflammatory signals in relation to glycemic control and insulin resistance," scientists writing in the journal *Molecular and Cellular Biochemistry* report.

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predominant AGEs, constituting up to 80% of total AGEs" he adds. "The association of CML modified peptides of albumin with prediabetes, diabetes, and microalbuminuria is a clinically relevant and therapeutically important finding" says Balasubramanyam. Heterogenous AGEs, particularly CML has been shown to predict the development of microvascular complications of diabetes independent of HbA1c in the DCCT (Diabetes Control and Complications Trial) study. Very recently increased CML-AGEs have been shown to predict incident diabetes also.

Glycated albumin - a promising marker for diabetes and glucose control

doi:10.1038/nindia.2012.119; Published online 14 August 2012

Research highlight

Why lean diabetics could be metabolically obese

Researchers have found molecular evidence to answer why some type 2 diabetics who appear lean are actually 'metabolically obese'[1].

Overweight and obesity are known to be important risk factors for diabetes and cardiovascular diseases. In Asia, obesity rates do not directly correspond with diabetes rates. India has a low prevalence of obesity but notably high rates of type 2 diabetes.

In Asian populations, a higher risk of diabetes starts at a lower body mass index than in Europeans. Thus, one of the factors that contributes to the diabetes epidemic in Asians is the 'normal-weight metabolically obese' phenotype. Till now, the biochemical or molecular basis for 'metabolic obesity' was poorly understood.

To probe this, the researchers measured the size of fat cells (adipocytes) from human visceral and subcutaneous fats and found that lean diabetics had higher adipocyte cell size (adipocyte hypertrophy) than control subjects. Also, adipose tissue from these lean diabetics showed faster aging (senescence) as evident from their shortened telomeres. They also had a secretory profile going by the low levels of adiponectin, the protein involved in regulating glucose levels as well as fatty acid breakdown.

"When such fat cells switch to a senescent and proinflammatory phenotype, they also change their job from 'fat storage' to 'fat spillage'. This fat accumulation complicates functioning of several other organs including the heart and triggers cardiovascular disease in diabetes patients" says lead researcher Muthuswamy Balasubramanyam. The study exposes adipocyte hypertrophy and senescence as targets for new drug discoveries, he adds.

The research urges timely prevention and management to reduce adverse outcomes in all patients with type 2 diabetes, particularly in metabolically obese normal-weight patients, who may have a false sense of protection because they are not overweight or obese.

The authors of this work are from: *Madras Diabetes Research Foundation, Chennai, Dr. Mohan's Diabetes Specialities Centre, Chennai & LifeLine Multi-Speciality Hospitals, Chennai, India.*

References

1. **Monickaraj, F. *et al*. Convergence of adipocyte hypertrophy, telomere shortening and hypoadiponectinemia in obese subjects and in patients with type 2 diabetes. *Clin. Biochem.* doi: 10.1016/j.clinbiochem.2012.07.097 (2012)**