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The role of sirtuins in Alzheimer's disease

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Sirtuins are highly conserved NAD$^+$-dependent enzymes that were shown to have beneficial effects against age-related diseases. Alzheimer's Disease (AD) is the most common neurodegenerative disorder associated with aging and the effects of sirtuins on AD have been investigated using different mouse and cell culture models. In most of these studies, it has been found that the overexpression of SIRT1 has protective effects against the AD phenotype. Therefore, designing therapeutics based on SIRT1 activity might be important to investigate treatment methods for this disease. In this review, we summarize the recent research regarding the functions of sirtuins and their potential roles in designing therapeutics for AD.

Keywords: sirtuins, aging, Alzheimer's disease, neurodegeneration, genetic models

INTRODUCTION

Sirtuins are conserved NAD$^+$-dependent enzymes that display beneficial effects in age-related disorders. They are also stress-response proteins that help mammals adapt to dietary manipulations (Donmez and Guarente, 2010). Various substrates have been discovered for sirtuins, especially for SIRT1, the most widely studied sirtuin in the brain (Haigis and Sinclair, 2010). SIRT1 has been analysed in many common neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's Diseases, among others (Donmez, 2012). In this review, we will focus on the findings regarding the functions of sirtuins and their implications in Alzheimer's Disease (AD).

SIRTUIN BIOLOGY

Sirtuins were first identified in yeast, named as silent information regulators (SIRs) and grouped as class III histone deacetylases (HDACs). They function by removing acetyl groups from lysines via consuming NAD (Sinclair and Guarente, 1997). There are seven human homologs of sirtuins (SIRT1-7), each of which displays different enzymatic activities and functions (Table 1). SIRT1, 2, and 3 have strong deacetylase activities, while SIRT4, 5, and 6 have display weak deacetylase activities. SIRT4 and SIRT6 also display ADP-ribosylase activities, and SIRT5 was shown to have demalonylase and desuccinylase activities (Shih and Donmez, 2013). In addition to having unique functions, sirtuins are also located in different areas of the cell, including the nucleus (SIRT1, 6 and 7), cytoplasm (SIRT2), and mitochondria (SIRT3-5) (Table 1). SIRT1, however, was also reported to shuttle between cytoplasm and nucleus (Imai and Guarente, 2010).

Numerous target proteins and enzymes have been identified for sirtuins located in the nucleus, cytoplasm, or mitochondria (Haigis and Sinclair, 2010). It is established that NAD-dependent post-translational modification of these targets by sirtuins leads to the regulation of important biological processes in different subcellular compartments and also the effects on age-related disorders (Donmez and Guarente, 2010).

ALZHEIMER'S DISEASE

AD is the most common neurodegenerative condition and the most common form of dementia in the elderly. Unfortunately, there is no cure for this disease. In 2006, there were 26.6 million people who suffered from AD worldwide, and the disease is predicted to affect 1 in 85 people globally by 2050 (Brookmeyer et al., 2007). Patients with AD suffer from neurological dysfunction resulting in memory loss, as well as cognitive and functional decline. AD is identified neuropathologically in mouse models and postmortem patient brains by the presence of amyloid plaques and neurofibrillary tangles. In addition, dominant mutations were found in the Amyloid Precursor Protein (APP) gene and in the presenilin 1 and 2 genes (PSEN1 and PSEN2), which encode for components of gamma-secretase (Hardy and Selkoe, 2002). APP is cleaved by beta-secretase and gamma-secretase sequentially to generate Abeta 1-40 and Abeta 1-42 amyloid peptides, which accumulate to form the amyloid plaques that are characteristic of AD (Tanzi and Bertram, 2005).

Neurofibrillary tangles are aggregates made up of hyperphosphorylated microtubule-associated protein tau. The tau proteins are the product of alternative splicing from a single gene that is designated as MAPT (microtubule-associated protein tau) in humans (Weingarten et al., 1975). All of the six tau isoforms are present in a hyperphosphorylated state as filaments in the AD brain. These tau aggregates were also reported to be present in other neurodegenerative disorders (Alonso et al., 2001).

Table 1 | Activity and localization of mammalian sirtuins and their effects on AD.

	Enzymatic activity	Sub-cellular localization	Effects on AD	Targets related to AD
SIRT1	Deacetylase	Nuclear, cytoplasmic	Neuroprotective (Chen et al., 2005; Qin et al., 2006b; Kim et al., 2007; Julien et al., 2009; Donmez et al., 2010; Min et al., 2010)	RARb, Tau, PGC1a, LXR, NFkB
SIRT2	Deacetylase	Cytoplasmic, nuclear	Genetic association (Polito et al., 2012)	Unknown
SIRT3	Deacetylase	Mitochondrial	Genetic association (Weir et al., 2012)	Unknown
SIRT4	Deacetylase ADP-ribosyltransferase	Mitochondrial	Unknown	Unknown
SIRT5	Deacetylase Demalonylase Desuccinylase	Mitochondrial	Unknown	Unknown
SIRT6	ADP-ribosyltransferase Deacetylase	Nuclear	Unknown	Unknown
SIRT7	Deacetylase	Nucleolar	Unknown	Unknown

ROLE OF SIRT1 IN AD

INITIAL STUDIES

SIRT1 is the only sirtuin that has been extensively studied in AD. Previous studies showed that the adaptive responses to calorie restriction (CR) are mediated by SIRT1 (Imai and Guarente, 2010). SIRT1-deficient mice were reported not to be able to adapt to CR normally (Boily et al., 2008). On the other hand, the phenotypes of SIRT1-overexpressing transgenic mice mimic the physiological changes observed in CR (Bordone et al., 2007). These studies established the connection between CR and SIRT1. The effect of CR on AD was first observed in studies where the Abeta plaques were reduced in the brains of AD mice that are calorie-restricted (Patel et al., 2005). Additionally, the cortex of calorie-restricted squirrel monkeys displayed a reduction in Abeta plaques, which was inversely correlated with SIRT1 levels (Qin et al., 2006a).

In a following study, activation of SIRT1 was also shown to be the mechanism underlying prevention of amyloid neuropathology by CR in mouse (Qin et al., 2006b). The authors showed that exogenous human SIRT1 resulted in reduced serine/threonine Rho kinase ROCK1 expression and elevated alpha-secretase activity in vivo. ROCK1 inhibits non-amyloidogenic alpha-secretase processing of APP (Qin et al., 2006b). These results demonstrated SIRT1 as an underlying mechanism through which CR rescues the AD phenotype in vivo.

STUDIES WITH CELL CULTURE MODELS

SIRT1 was found to be protective against stress in a study conducted with cultured neuronal cells (Qin et al., 2006b). In this study, SIRT1 expression was found to promote alpha-secretase activity and attenuates Abeta peptides in primary Tg2576 neuron cultures and CHO-APPswe cells. In another study, SIRT1 was also shown to protect against microglia-dependent amyloid-beta toxicity in cells through inhibiting inflammatory NF-kappaB signaling (Chen et al., 2005). In addition to these, N2A cells stably overexpressing APPswe/PSEN1dE9 transgenes transfected with SIRT1 displayed reduced Abeta peptides and increased ADAM10 protein levels (Donmez et al., 2010).

Cell culture studies have also helped to discover the effect of SIRT1 in the tau model and inducible p25 models of AD. In a recent study, SIRT1 was found to deacetylate tau in HEK293T cells and primary cortical neurons during maturation in culture (Min et al., 2010). An earlier study showed that treatment of primary cortical neurons with low concentrations of ionomycin and H_2O_2 induces rapid upregulation of SIRT1 associated with generation of p25 (Kim et al., 2007). The authors showed that, in cell-based models for AD/tauopathies and amyotrophic lateral sclerosis (ALS), SIRT1 and resveratrol, a SIRT1-activating molecule (STAC), promote neuronal survival (Kim et al., 2007).

STUDIES WITH GENETIC MOUSE MODELS

One of the first studies that showed SIRT1 protects against AD and ALS used mouse models and primary neurons challenged with neurotoxic insults (Kim et al., 2007). The authors showed that resveratrol reduced neurodegeneration in the hippocampus, prevented learning impairment, and decreased the acetylation of the known SIRT1 substrates PGC-1alpha and p53 in an inducible p25 transgenic mouse, a model of AD and tauopathies (Kim et al., 2007). In addition, increased levels of SIRT1 in primary neurons were shown to confer protection against neurotoxicity induced by a mutant form of superoxide dismutase 1 (SOD1G37R), which has been linked to human ALS (Kim et al., 2007).

Other studies showed that SIRT1 targets both Abeta and tau in vivo. By crossing a SIRT1-overexpressing mouse or a SIRT1 brain-specific knockout mouse with the APPswe, PSEN1dE9 mouse model, SIRT1 expression could be elevated or deleted in the mouse brain, respectively (Donmez et al.,

2010). The authors observed that overexpression of SIRT1 reduces Abeta plaques in the mouse brain, while deletion of SIRT1 exacerbates it. As an underlying mechanism, SIRT1 was shown to deacetylate retinoic acid receptor (RAR)-beta and activates ADAM10 (alpha-secretase) transcription, which increases ADAM10 levels in neurons and leads to upregulated APP processing by alpha-secretase (Donmez et al., 2010).

In addition to reducing Abeta formation, SIRT1 also inhibits the tau-related AD phenotype. In one study, SIRT1 reduction was found to parallel tau accumulation (Min et al., 2010). SIRT1 decreases tau accumulation by deacetylating the acetylated tau and consequently reducing its level. Conversely, SIRT1 inhibition leads to the opposite effect, increasing levels of tau, and exacerbating the accumulation of pathogenic forms of phosphorylated tau (Min et al., 2010).

One study used triple-transgenic mouse model of AD, which is known to accumulate amyloid beta and tau (Julien et al., 2009). Cortical SIRT1 RNA and protein levels were analyzed in this mouse model and found to remain unchanged (Julien et al., 2009).

PATIENT-RELATED STUDIES

Having identified the potential protective role of SIRT1 in cell culture and genetic mouse models, it is also crucial to investigate the association of SIRT1 with the disease in AD patients. A recent study compared the mRNA and protein expression levels of SIRT1 in the brains of AD patients and controls using Western immunoblots and in situ hybridization (Julien et al., 2009). A significant reduction in RNA and protein expression levels of SIRT1 was reported in the parietal cortex of AD patients. This reduction was not observed in the cerebellum. The authors conducted further analyses with a second cohort of 36 subjects demonstrating that cortical SIRT1 was decreased in individuals with AD but not with mild cognitive impairment. SIRT1 mRNA and protein levels were negatively correlated with the duration of symptoms and the accumulation of tau, but were weakly correlated with the amyloid-beta 42. The authors concluded that the results of the study indicate that the loss of SIRT1 is closely associated with the accumulation of amyloid-beta and tau in the cerebral cortex of AD patients (Julien et al., 2009).

ROLE OF OTHER SIRTUINS IN AD

Not much is known about the role of SIRT3 in AD. One recent study showed that pharmacological augmentation of mitochondrial ROS increases Sirt3 expression in primary hippocampal culture (Weir et al., 2012). Furthermore, SIRT3 mRNA is upregulated in a specific spatio-temporal manner in a PDAPP mouse model of AD, which overexpresses human APP carrying the V717F mutation and forms Abeta plaques in mouse brain. In this study, Sirt3 mRNA expression is significantly increased in samples of the AD temporal cortex compared to matched controls (Weir et al., 2012).

SIRT2 has also been found to be associated with AD, as demonstrated by a genetic case-control study (Polito et al., 2012). In this study, three single nucleotide polymorphisms (SNPs) were analysed in a number of AD patients and non-demented control subjects. An association between SIRT2 rs10410544 T allele and AD was found in the APOE ε4-negative Caucasian population, necessitating further investigation (Polito et al., 2012). In the same study, authors also identified three SNPs for the SIRT3 gene.

CONCLUSIONS

Although, SIRT2 and SIRT3 seem to play a role in AD based on recent research, SIRT1 is the most extensively studied sirtuin in AD. Interestingly, overexpression of SIRT1 was found to be protective in most of the studies conducted. This might lead to the design of SIRT1 activators that are able to cross the blood brain barrier to treat AD. Obviously, SIRT1 has numerous targets, which is a concern since activating various targets might not be beneficial for a specific disease. Overall, studies that use animal and cell culture models show that SIRT1 plays a neuroprotective role in the brain, a finding that encourages the design of therapeutics for AD based on SIRT1 activation.

Resveratrol is a natural polypenolic compound that is known as an activator of SIRT1. However, the association between SIRT1 and the mechanisms and the biological effects of resveratrol is currently debated. Three STACs, SRT1460, SRT1720, and SRT2183, which are structurally unrelated to, and 1000-fold more potent than resveratrol, have also been identified as a result of high throughput screens. When these activators were implemented in rodent animal studies, including high-fat-diet-induced obese mice, ob/ob mice, and Zucker fa/fa rats, they were able to normalize glucose homeostasis (Milne et al., 2007). A very recent study showed that specific hydrophobic motifs found in SIRT1 substrates such as PGC-1α and FOXO3a facilitate SIRT1 activation by STACs (Hubbard et al., 2013). The authors also demonstrated that a single amino acid in SIRT1, Glu(230), located in a structured N-terminal domain, is critical for activation by all previously reported STAC scaffolds and a new class of chemically distinct activators. It was concluded therefore, that SIRT1 can be directly activated through an allosteric mechanism common to chemically diverse STACs (Hubbard et al., 2013).

Nicotinamide (NAM) inhibits the catalytic activity of sirtuins by binding to a conserved region in the catalytic site (Avalos et al., 2005). The first sirtuin inhibitor, sirtinol was identified by phenotypic screening in yeast (Grozinger et al., 2001) and was shown to act as an anticancer molecule in various models, inhibiting Ras-MAPK pathway (Ota et al., 2006).

In future studies, it would be interesting to see whether or not other sirtuins have an effect on the AD phenotype or disease pathology. Except for SIRT1, none of the sirtuins have been analysed extensively in AD. Studying the other sirtuins will also unravel their novel functions in the mammalian brain. Identifying these functions of sirtuins and their relations to AD will give rise to therapeutic avenues where new drugs can be developed in an effort to find a cure for the disease.

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Sirtuin 1, a Diagnostic Protein Marker and its Relevance to Chronic Disease and Therapeutic Drug Interventions

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Mini Review

Sirtuin 1, a Diagnostic Protein Marker and its Relevance to Chronic Disease and Therapeutic Drug Interventions

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Abstract

Critical interpretations and analysis in diagnostic proteomics have accelerated with relevance to various biomarker tests that involve proteomics, lipidomics and genomics that assist with drug therapy to prevent programmed cell death with relevance to severity of global chronic disease progression. Reversal of global non-alcoholic fatty liver disease (NAFLD) is essential with analysis of various plasma components that may override diagnostic proteomics with relevance to defective nuclear-mitochondria interactions and therapeutic drug efficacy. Therapeutic drug effectiveness and the measurement of multiple proteins/peptides for patient care requirements now require anti-aging gene Sirtuin 1 (Sirt 1) analysis that is related to toxic amyloid beta:protein interactions and relevant to therapeutic drug metabolism in diabetes and neurodegenerative diseases.

Keywords: *Sirtuin 1; Diagnosis; Global; Disease; Drug; Proteomics; Amyloid Beta; Non-Alcoholic Fatty Liver Disease; Diabetes; Neurodegeneration*

Proteomics has been the systematic study of many proteins to provide structure, function and control of biological systems in health and disease. Advances in methods and technologies designed for peptide/protein complex analysis has advanced rapidly with mass accuracy and sensitivity [1-3]. Proteomics with proteomic pattern diagnostics is now an expanding field of research. The plasma proteome is now in an important position to interpret the intersection between prevent programmed cell death with relevance to severity of global chronic disease progression. Proteomic-based approaches for biomarker investigation may allow elucidation of pathways and identification of individuals who are most likely to respond to specific drug therapeutic interventions [4,5] with possible prediction of patients side effects to various drugs [6]. The majority of current drug targets are proteins, such as G protein-coupled receptors, ion channels, enzymes and components of hormone signaling pathways [7]. The progress and challenges in the translational application of proteomic technologies are to interpret post-translational modifications and protein-protein interactions in disease.

Prevalent global chronic diseases such as cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), diabetes and neurodegenerative diseases have raised major concern. Factors that regulate chronic disease progression have been explored with major changes in proteomic profiles involved in the acceleration of chronic diseases. The proteomic profiles [1-3] may not be relevant to drug therapy/metabolism or stabilize insulin resistance relevant to disease progression [8,9]. The need to assess proteomic profiles with relevance to biomarker tests [10-14] in chronic disease may not be relevant and may not optimize drug therapy or improve therapeutic outcomes with possible drug-drug interactions [15] or drug-protein interactions [16-18] relevant to mitophagy in the global chronic disease epidemic. Interest in applying proteomics to gain a better understanding of disease progression requires identification of novel proteins and their interactions for early detection of disease associated with acceleration of drug therapeutics [4-6]. The importance of diagnostic proteomics is now connected to nutrition, neurodegeneration with its important role in the primary regulation of the amyloid clearance pathway [19-22] connected to drug/xenobiotic metabolism [23].

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Diagnostic proteomics and its relevance to early diagnosis of neuron apoptosis has accelerated with the plasma proteome analysis that may be relevant to neuron mitochondrial apoptosis [24]. Proteins such as apelin, angiotensin II, adiponectin, transforming growth factor beta, Tumour necrosis factor alpha, GDF11, heat shock proteins (HSP 70,HSP 60), gelsolin, insulin like growth factor 1, fibroblast growth factor 21, hepatocyte growth factor, nerve growth factor and thrombospondin 1 are now relevant to the transcription factor p53 [23] and its post-transcriptional regulation of the nuclear receptor Sirtuin 1 (Sirt 1). Sirt 1 is a nicotinamide adenine dinucleotide (NAD+) dependent class III histone deacetylase (HDAC) that targets transcription factors such as p53 to adapt gene expression to metabolic activity and the deacetylation of nuclear receptors indicate their critical involvement in insulin resistance [23]. Sirt 1 is now important to mitochondrial biogenesis and its regulation of protein/amyloid beta [21,22] and drug metabolism is connected to mitochondrial apoptosis and neurodegenerative disease [24].

Dietary regulation of nuclear receptors involves the calorie sensitive gene Sirt 1 involved in the metabolism of glucose, fatty acids, cholesterol and xenobiotics [25,26]. Sirt 1 activation of pregnane X receptor (PXR) is responsible for cytochrome p450 expression and the hepatic metabolism of drugs [25]. Therapeutic drug interventions involve activation of Sirt 1 by healthy diets that contain Sirt 1 activators connected to the reversal of NAFLD [9,27,28]. Sirt 1 is critical to pharmacological management with relevance to antibiotic resistance, epilepsy induced stroke, insulin therapy and antimicrobial activation [29-33].

To avoid inadvertent errors in proteomics and the systematic study of many proteins, Sirt 1 (plasma, cytoplasmic and nuclear analysis) should be conducted to interpret proteomic pattern diagnostics in biological systems in health and disease [34-40]. Sirt 1's analysis in the nucleus and cytoplasm may assist with defects in nuclear-mitochondria interactions and may override misinterpretations in proteomic pattern diagnostics (Figure 1). Sirt 1 plasma analysis is important to the regulation of toxic amyloid beta oligomers with its direct interaction with specific acute phase proteins (serum amyloid protein P, serum amyloid protein A, adiponectin/alpha 2 macroglobulin, adiponectin/TSP-1, gelsolin, complement components, transthyretin and clusterin) [19,21,41-44] that may override important proteomic technologies [1-3,45,46]. Sirt 1 regulation of toxic amyloid beta-protein interactions (Figure 1) are critical to drug metabolism [4,5,22] with decreased plasma Sirt 1 levels [34-40] associated with increased drug-protein interactions [16-18] or drug-xenobiotic interactions [47-49].

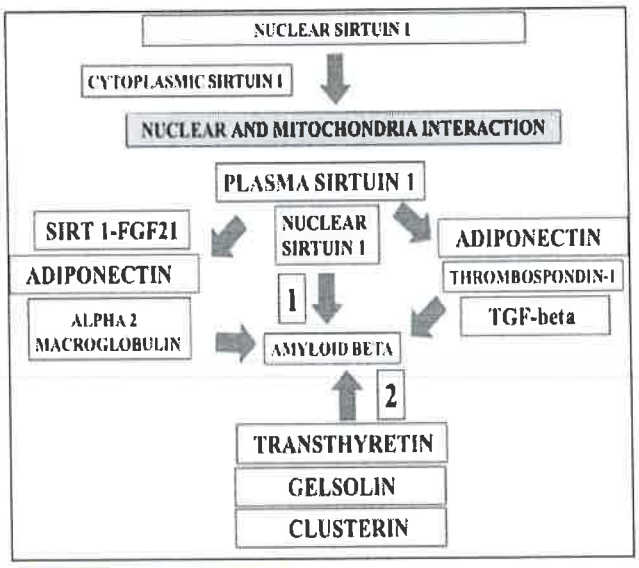

Figure 1: *Plasma proteome profiles require Sirt 1 analysis important to toxic amyloid beta: protein interactions and drug:protein interactions with relevance to drug metabolism and connected to mitochondrial apoptosis and global chronic disease. Sirt 1 regulation of adiponectin levels is related to adiponectin interactions with alpha 2 macroglobulin and thrombospondin 1 with relevance to toxic amyloid beta metabolism. Acute phase proteins such as Sirt 1 that regulate hepatic toxic amyloid beta metabolism determine amyloid beta interactions with other plasma proteins such as transthyretin, clusterin and gelsolin. Sirt 1 (plasma, cytoplasmic and nuclear analysis) should be conducted to interpret defects in nuclear-mitochondria interactions in health and disease to avoid inadvertent errors with proteomic pattern diagnostics in advanced proteomic technologies with relevance to accelerated neuron death.*

Plasma Sirt 1 and its regulation of heat shock protein 70 (HSP 70) and antimicrobial proteins metabolism are connected to the immune system [31,51] with repression of Sirt 1 related to HSP 70 induced programmed cell death with relevance to inactivation of drug therapy [52]. Dietary regulation of Sirt 1 is important to chronic disease with bacterial lipopolysaccharides (LPS) and patulin relevant to defective posttranslational/post transcriptional alterations [53-56]. The progress and challenges in the translational application of proteomic technologies are to interpret post-translational modifications and protein-protein interactions [57] in disease but LPS and mycotoxin have now become important and may override proteomic interpretations in health and disease. Interest in plasma Sirt 1 analysis has become important to amyloid beta-acute phase proteins interactions with LPS critical to hepatic Sirt 1 repression and membrane transformation with relevance to drug metabolism [9,54-56]. LPS regulates Sirt 1 levels [58-60] and Sirt 1 is now referred to as an inflammatory target protein in vivo [61]. LPS inactivates toxic amyloid beta metabolism by interference with apolipoprotein E-phospholipid transfer protein, apolipoprotein A1, albumin, transferrin, and lactoferrin [62-64].

Nutritional proteomics [65,66] has become important to prevent programmed cell death with relevance to severity of global chronic disease progression. The links between diet and genomics [23] are now important to Sirt 1 regulation with connections to nutritional proteomics and nutritional lipidomics [67,68]. Sirt 1 is now an important nutritional biomarker [69,70] that is connected to the nuclear-mitochondria interaction and plasma Sirt 1 levels are important to proteomics and drug metabolism. Sirt 1 activators and their consumption determine Sirt 1 levels important to proteomic technologies (protein profiles) to gain a better understanding of drug therapy in chronic disease progression.

Conclusion

Proteomic-based approaches for biomarker investigation is now important to interpret the intersection between proteomic pattern diagnostics and programmed cell death with relevance to severity of global chronic disease progression. Proteomic profiles that include plasma Sirt 1 and protein analysis are critical to determine defects in the nuclear-mitochondria interaction relevant to the severity of cardiovascular disease, NAFLD, diabetes and neurodegenerative diseases. Sirt 1's control of biological systems in health and disease involve toxic amyloid beta and protein interactions with Sirt 1 repression associated with inactivation of drug/xenobiotic metabolism with acceleration of chronic disease progression. Interest in applying proteomics to disease progression requires early plasma Sirt 1 analysis for detection of disease protein biomarkers associated with inactivation rapid toxic amyloid beta and therapeutic drug metabolism.

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Evaluation of diagnostic tests in human health and disease.

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Abstract

Evaluation of diagnostic tests and biomedical data that have promised detection of early disease progression have raised concerns with under-diagnosis of various chronic diseases associated with the prevalence of various global chronic diseases. Diagnostic tests and plasma analyte analysis do not determine nuclear-mitochondria defects with discoveries in clinical eipgenetics that identify the gene Sirtuin 1 to be defective and to be involved in toxic immune reactions relevant to mitophagy. Proteome blood analysis is now an important diagnostic procedure in medicine with existing proteomic biomarkers correlated with early disease progression in health and disease. Sirtuin 1 analysis in plasma and body fluids is essential to determine the importance of diagnostic clinical biochemisty tests and will allow early diagnosis of disease progression that involves cardiovascular disease, non alcoholic fatty liver disease, metabolic disease and neurodegenerative diseases.

Keywords: Clinical chemistry, Tests, Public health, Diagnosis, Analytes, Plasma, Diabetes, Mitophagy, NAFLD, Sirtuin 1, Epigenetic.

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Introduction

Clinical chemistry in public health care has become of considerable importance to the global community and is now a multibillion dollar industry. Substantial progress has been made over the past 40 years in clinical chemistry with relevance to various plasma/serum diagnostic tests and plasma/serum analytes (Figure 1) in the diagnosis and evaluation of various chronic diseases such as non alcoholic fatty liver disease (NAFLD), cardiovascular disease, obesity, diabetes and neurodegenerative diseases. Several advances in machine learning [1] has led to analysis of high-dimensional and multimodal biomedical data that have promised improvement in the detection, diagnosis, and therapeutic monitoring of early disease progression [2]. Physicians have raised concerns for the prevalence of under-diagnosis [3] of various chronic diseases associated with the acceleration of programmed cell death in global diabetes and organ disease [4].

Discussion

Mitophagy exists as a major concern (Figure 1) with relevance to chronic diseases in spite of various plasma/serum clinical chemistry tests that may provide early diagnosis for the nature of disease. In health and disease mitochondrial apoptosis [5,6] is now responsible for apoptotic and necrotic death in various tissues. Analysis of plasma lipids, hormones, electrolytes (kidney function), enzymes (liver function) and immune tests have failed to prevent mitochondrial apoptosis relevant to various chronic diseases. Mitophagy in NAFLD, metabolic diseases (obesity/ diabetes) and neurodegenerative diseases [7] with relevance to maintaining mitochondrial quality control and homeostasis has become a major criticism of clinical biochemistry detection (biomedical data). Monitoring of early disease progression by diagnostic tests is not connected to dysfunctional mitochondria and mitochondrial mass in cells and diseased tissues in global populations. Discoveries in medicine now identify the role of the heat shock gene Sirtuin 1 (Sirt 1) to be involved in toxic immune reactions, antimicrobial activity and mitophagy [8-10]. The nuclear receptor Sirt 1 is an NAD(+) dependent class III histone deacetylase protein that targets transcription factors to adapt gene expression to metabolic activity, insulin resistance, inflammation is the defective gene that determines mitochondrial survival in various chronic diseases [11-14]. Interactions between Sirt 1 and other anti-aging genes such as Klotho, p66Shc (longevity protein) and Fork head box proteins (FOXO1/ FOXO3a) have been associated with mitochondrial apoptosis and accelerated aging linked to global diseases [15]. The nuclear-mitochondria interaction [16] is important to cell survival in many tissues. Sirt 1' regulation of the nuclear-mitochondria interaction in cells is critical to prevent NAFLD with Sirt 1 repression involved in the induction of NAFLD and linked to obesity, diabetes and neurodegnenative diseases [16]. DNA methylation is a key epigenetic process involved in the regulation of nuclear gene expression and mitochondrial gene expression with programmed aging. Sirt 1 and its regulation of the nuclear-mitochondria interaction is now relevant to DNA methylation [17,18] with Sirt 1 inactivation involved in defective nuclear and mitochondrial DNA methylation (Figure 1) with relevance to the epigenetic aging clock, immune reactions, mitophagy and disease associated aging/Alzheimer's disease alterations [19-22]. Proteome blood clinical analysis is now an important diagnostic procedure in medicine with many existing proteomic biomarkers [23] possibly correlated with early

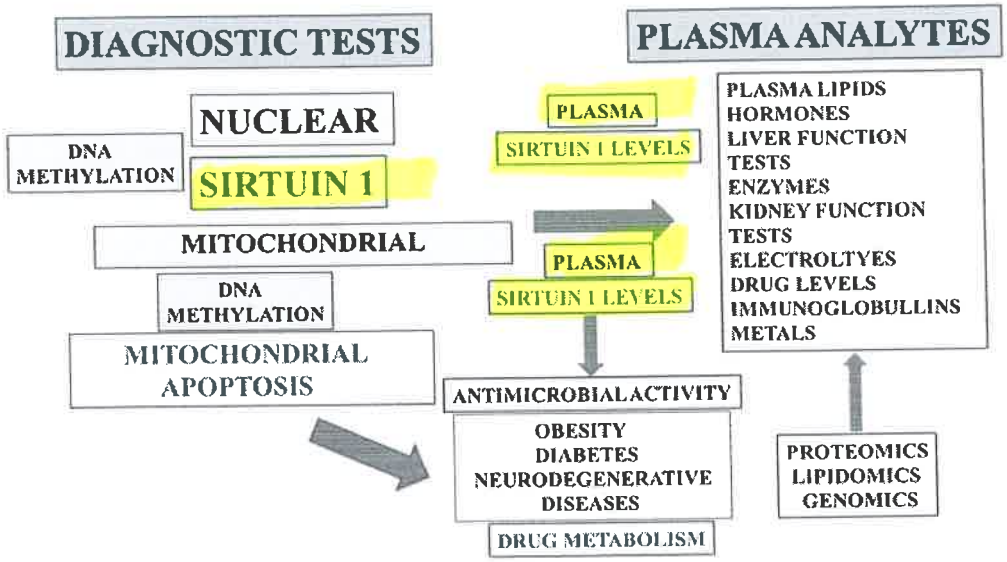

Figure 1. *Mitophagy exists as a major concern.*

disease progression in health and disease. Sirt 1 measurement in the plasma, cytoplasm and nucleus (Figure 1) is essential to determine mitochondrial apoptosis [24-27] when compared to the validity of various diagnostic tests and plasma analyte measurements [1-5]. Biomedical data that have promised detection of early disease progression have raised concerns with under-diagnosis of various chronic diseases associated with the increased prevalence of various global chronic diseases.

Conclusion

Mitophagy is a major concern with relevance to chronic diseases in spite of various plasma/serum clinical chemistry tests that may provide early diagnosis for the nature of disease. In health and disease mitochondrial apoptosis is responsible for apoptotic and necrotic death in various tissues associated with cardiovascular disease, NAFLD, obesity, diabsetes and neurodegenerative diseases. Discoveries identify the heat shock gene Sirt 1 to be defective with toxic immune reactions that determine mitochondrial survival, mitophagy and mitochondrial apoptosis. Sirt 1 inactivation in various global chronic diseases require Sirt 1 plasma analysis to determine effective cell nuclear-mitochondria DNA methylation in various cells and tissues that is not evaluated by existing biomedical data from existing clinical biochemistry diagnostic tests.

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Editorial

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The Future of Biomarkers Tests and Genomic Medicine in Global Organ Disease

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Keywords
Biomarkers, Diagnosis, Genomic, Immunometabolism, Mitochondria.

Abbreviations
NAFLD: Nonalcoholic fatty liver disease, MODS: Multiple organ disease syndrome, Sirt 1: Sirtuin 1, LPS: Bacterial lipopolysaccharides.

Editorial

Interests in global organ diseases have accelerated with links between nonalcoholic fatty liver disease (NAFLD) and various chronic diseases with relevance to the metabolic syndrome and neurodegenerative diseases. Early diagnosis of global organ disease involve genomic, lipidomic and proteomic biomarker tests that may diagnose early neuron dysfunction with the prevention of various organ diseases [1]. Diet and nutrition are closely linked to accelerated aging and may allow biomarker tests to provide adequate information with relevance to the immune system dysfunction and the severity of chronic diseases. In spite of various biomarker tests and analyte measurements for chronic diseases such as obesity and diabetes abnormal nuclear-mitochondria interactions [2] persist with inflammation involved in the induction of programmed cell death.

Various diagnostic technologies have been used with relevance to genomics, lipidomics and proteomics to generate heat maps [3-5] that may allow more sensitive interpretations of cell dysfunction. Analysis of plasma lipidomic and proteome heat maps in NAFLD, obesity and diabetes are required to determine relationship between these heat maps (lipid/protein interactions) with relevance to genomic heat maps. The diagnostic technologies encompass the genome, transcriptome, proteome and metabolome (central dogma of biology, Wikipedia) and determine the cell genome and transcription factor alterations with relevance to concentrations of plasma lipids and proteins [6]. The projected cost of plasma and cell biomarker analysis is expected to cost by the year 2012 approximately 52 billion dollars [7]. Major efforts with proteomic biomarkers have identified plasma protein panels to assess progression and severity of diseases with relevant proteomic biomarkers that delay the severity of progression from mild cognitive impairment to prodromal disease and dementia [8]. Lipidomics and genomics have become important as technologies that may supersede proteomic biomarker tests with the analysis of plasma ceramides and sphingolipids that may be relevant to single gene inactivation [1,9] and multiple organ dysfunction syndrome (MODS).

Interests in genomic tests and autoimmune disease have accelerated with Sirtuin 1 (Sirt 1) inactivation associated with immunometabolism defects and related to defective heat shock protein metabolism and natural killer cell activation [10-14] linked to NAFLD. Genomic biomarkers in predictive medicine [15] must now include nuclear, cytoplasmic and plasma Sirt 1 analysis to avoid expensive diagnostic technologies (Figure 1) with biomarker analysis that do not assess the severe progression of cell disease that involve mitochondrial apoptosis. Mitophagy is now relevant to various chronic diseases such as NAFLD, obesity, diabetes and Alzheimer's disease [16-18]. Diet and nutrition have become important to the immune system and mitophagy with the correct

consumption of fat critical to maintain the nuclear-mitochondria interaction [19] with the prevention of mitochondrial apoptosis and cell death.

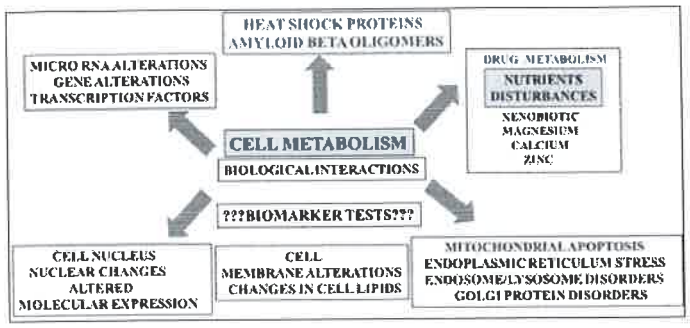

Figure 1: Various diagnostic technologies for biomarker analysis may not assess the severe progression of cell disease that involve mitochondrial apoptosis. Altered biological interactions, immune system dysfunction and cell lipid metabolism defects do not reflect the sensitivity of various biomarker test assays. Altered plasma micro RNA levels and cell transcription factors may not be connected to increased heat shock proteins that induce natural killer cell activation with mitochondrial apoptosis. Diagnostic technologies for biomarker analysis may now also need assays for LPS, xenobiotic, magnesium and calcium that are associated with nutritional disturbances.

Technologies that cost billions of dollars have become of major concern with relevance to inadvertent errors that may not allow early interpretations of disease progression that may be irreversible. In the developing world bacterial lipopolysaccharides (LPS) levels [20] should be carefully assessed to prevent repression of Sirt 1 with complete nitric oxide and immune dysregulation related to mitophagy, MODS and global organ disease [9,15,20]. Plasma heat shock protein analysis [14] is relevant to immune dysregulation and associated with inactivation of the heat shock gene Sirt 1 needs measurement to avoid unexpected errors with relevance to various biomarker tests (Figure 1). The relevance of LPS that may corrupt magnesium, calcium and albumin formulas may be require recalculation [15] with relevance to the biomarker test limitations with relevance to severity of inflammatory pathways for various chronic diseases [21]. Proteomic, lipidomic and genomic biomarker test should be carefully interpreted with relevance to individuals from the developed world that visit or stay in the developing world with mitophagy in these individuals associated with xenobiotic toxicity [22].

Conclusion

Diagnostic technologies for biomarker analysis have become important to the immune system and mitophagy to prevent early programmed cell death. Projected costs for biomarker analysis is expected to increase to billions of dollars in the next few years but altered biological and cell membrane interactions may not allow early diagnosis of immune system dysfunction related to early progression of global organ disease. In the developing world LPS and xenobiotic levels may be responsible for altered biological interactions and supersede diagnositic technologies for biomarker analysis. Inactivation of Sirt 1 by increased ceramide levels and nutritional disturbances may be responsible for increased inflammation (autoimmune disease) and mitophagy in NAFLD and global chronic disease.

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SIRT1 is a Useful Biomarker for High-Grade Dysplasia and Carcinoma in Barrett's Esophagus

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Abstract. The diagnosis of epithelial dysplasia and subsequent grading of the dysplasia in Barrett's esophagus (BE) are clinically significant for the patient's follow-up and management. However, histologic diagnosis for these lesions often proves challenging for general practicing pathologists and even GI pathologists. Certain biomarkers, such as p53 and racemase, have shown some value in diagnosing these lesions. We previously showed that SIRT1, the mammalian homologue of silent mating type information regulator 2 in budding yeasts, was over-expressed in colonic adenomas. The goal of this study was to investigate the value of SIRT1 in BE-related dysplasia. Twenty BE cases without epithelial dysplasia, 11 with low-grade dysplasia, 4 with high-grade dysplasia, and 8 invasive carcinomas were included in this study. Twenty-nine of 31 cases with no epithelial dysplasia or low-grade dysplasia showed weak nuclear staining at the base of the crypts, but the surface epithelium was negative in all cases. Ten of twelve cases with high-grade dysplasia or carcinomas had 2-3+ diffuse nuclear staining including the surface epithelium. Using 2+ surface nuclear staining as the cut-off, BE with high-grade dysplasia and carcinoma had significantly higher SIRT1 expression than BE with no dysplasia or low-grade dysplasia (p=0.0001). Therefore, SIRT1 appears to be a very promising biomarker in the diagnosis of BE with high-grade dysplasia and carcinoma. This is the first report using SIRT1 as an adjunctive marker on evaluation of BE-related dysplasia, but large-scale and prospective studies are needed to confirm and validate our findings.

Key words: SIRT1, biomarker, dysplasia, Barrett's esophagus.

Introduction

Pathologists face significant diagnostic challenges and controversies in the pathologic evaluation of Barrett's esophagus (BE) and Barrett's-related dysplasia [1-3]. The intraobserver and interobserver variations are significant for low-grade dysplasia [3-5]. In one US study, general pathologists had only poor to fair interobserver agreement for the diagnosis of low-grade dysplasia (κ=0.32), and the expert gastrointestinal pathologists did only slightly better [6]. A study from the Netherlands showed that 85% of low-grade dysplasia cases from general pathologists were downgraded to "no dysplasia" by expert gastrointestinal pathologists [7]. Pathologists could not do much better in separating high-grade dysplasia from intramucosal carcinoma and submucosal invasive adenocarcinoma. A recent study showed only fair overall agreement (κ=0.30) for these lesions [8].

Due to the significant intraobserver and interobserver variations in the diagnosis of dysplasia in BE and the significant implications for patient treatment and clinical follow-up based on the pathologic evidence of dysplasia and the grade of dysplasia, some biomarkers have been studied for their diagnostic and prognostic value in BE. Immunohistochemistry for p53 overexpression has been shown to be strongly correlated with dysplasia and is useful for high-grade dysplasia, but a high rate of false positives and false negatives has been reported [3,9,10]. Immunostaining for α-methylacyl-CoA-racemase has been shown to have high specificity for detection of dysplasia in Barrett's esophagus, but it requires confirmation in large studies [11,12].

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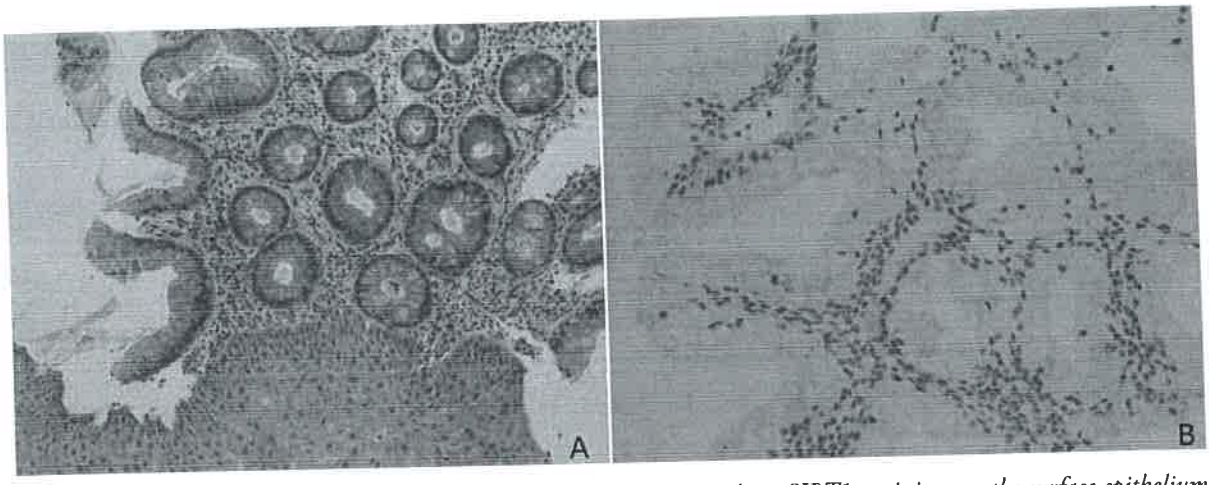

Figure 1. *Barrett's esophagus with no dysplasia shows negative nuclear SIRT1 staining on the surface epithelium (**1A:** H&E, 200X; **1B:** SIRT1 immunohistochemistry, 200X).*

SIRT1, a nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase, is significantly elevated in human prostate cancer, primary colon cancer, and skin cancers [13-15]. A previous study from our group showed a significant overexpression of SIRT1 in colonic tubular adenoma [16]. Due to the histologic similarity of Barrett's-related dysplasia and colonic adenoma, we evaluated the SIRT1 expression in Barrett's-related dysplasia in this study.

Materials and Methods

This study was approved by the Institutional Review Board (IRB) of LSUHSC-Shreveport. All esophageal biopsies or resections with diagnosis of BE with and without dysplasia and carcinoma received in the Department of Pathology at LSUHSC-Shreveport between January 2005 and March 2010 were retrieved from the pathology database. All cases of dysplasia and carcinoma were included if there was enough tissue for immunohistochemistry. Twenty cases of BE without dysplasia were randomly selected as a control group. BE was defined both by endoscopic abnormalities and histologic evidence of goblet cells, and dysplasia was classified as negative, indefinite, low-grade or high-grade.

Immunohistochemical staining for SIRT1 was performed with SIRT1 monoclonal antibody (DB083, 1:250 dilution) purchased from Delta Biolabs (Delta Biolabs, Gilroy, CA) according to the manufacturer's instructions using an automated immunostainer (Ventana, Rocklin, CA). The SIRT1 staining score was graded as 0-3 based on the nuclear staining intensity, and the staining patterns (diffuse, base, and surface epithelium) were also recorded. Fisher exact test was used for statistical analysis.

Results

Nineteen of twenty (19/20) cases of Barrett's esophagus without epithelial dysplasia showed negative to weak 1+ nuclear stain at the base of the crypts, and the surface epithelia were negative **(Figure 1 A&B)**. Only one case of Barrett's esophagus without dysplasia (1/20) had 2+ nuclear staining including the surface epithelium, and this patient had a previous diagnosis of low-grade dysplasia one year prior to the current specimen. Unfortunately, the lesional tissue from the previous biopsy was not available for SIRT1 immunohistochemical study. Ten of 11 cases of BE with low-grade dysplasia (10/11) had negative to weak 1+ nuclear stain at the base of crypts, and the surface epithelia were negative. One case of BE with low-grade dysplasia (1/11) showed 2+ nuclear staining including the surface epithelia **(Figure 2 A&B)**. Three of four (3/4) high-grade dysplasia and seven of eight (7/8) invasive adenocarcinomas (10/12) had 2-3+ diffuse and surface epithelial nuclear staining **(Figure 3 A&B)**. One high-grade dysplasia and one adenocarcinoma showed negative to weak 1+ nuclear staining. Using 2+ nuclear staining as the cutoff, BE with high-grade dysplasia and invasive carcinoma (10/12) had significantly higher SIRT1 expression than BE with no dysplasia or low-grade dysplasia (2/31) (p=0.0001). The results are summarized in **Table 1**.

Discussion

Barrett's esophagus is believed to be the major risk factor for the development of esophageal adenocarcinoma, and the incidence of adenocarcinoma of the esophagus continues to rise rapidly [17]. However, different definitions have been used in the literature. The guidelines from the American College of Gastroenterology for the definition of

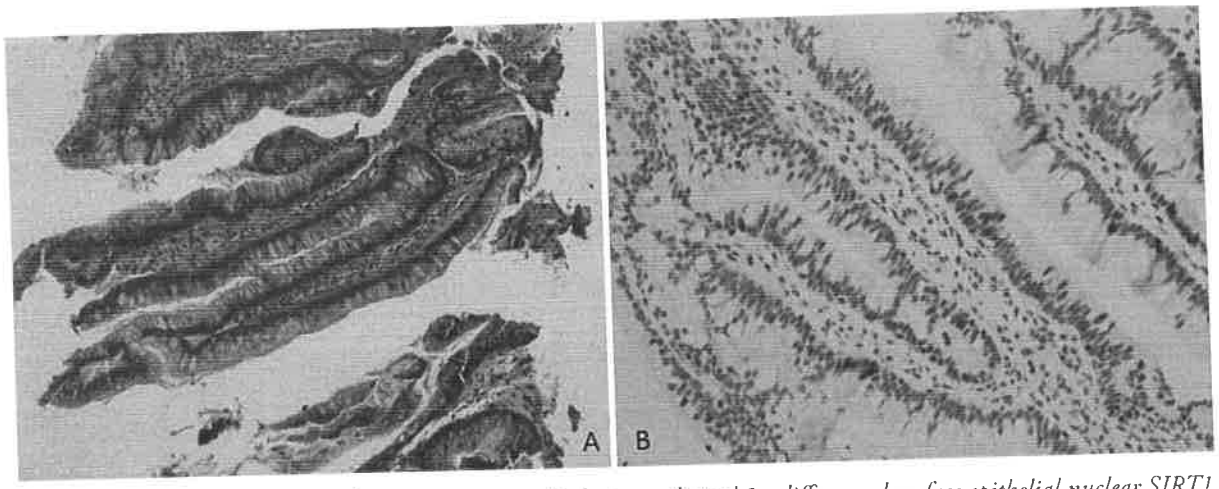

Figure 2. *A case of Barrett's esophagus with low-grade dysplasia showed 2+ diffuse and surface epithelial nuclear SIRT1 staining (**2A:** H&E, 200X; **2B:** SIRT1 immunohistochemistry, 200X).*

BE include an endoscopic abnormality and a histologic alteration characterized by the identification of goblet cells [17]. Many American pathologists have embraced the absolute necessity of identifying goblet cells in a biopsy specimen to make the diagnosis of BE. However, British gastroenterologists have consistently rejected this restrictive definition [18]. Recently, emerging data has shown that columnar-lined esophagus (CLE) with and without goblet cells has immunohistochemical and molecular similarities [1]. Several studies have also found a similar risk of progression in patients with and without goblet cells in CLE [19,20]. We should keep an open mind for these emerging data; however, "A change in the definition of BE to include patients with CLE without goblet cells would obviously have enormous clinical and economic implications" [1].

There are two classification systems used for dysplasia in Barrett's esophagus: the Vienna system and the Inflammatory Bowl Disease (IBD) system [3]. The IBD classification of dysplasia includes negative for dysplasia, indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia and adenocarcinoma (intramucosal or invasive). The Vienna classification includes negative for neoplasia/dysplasia, indefinite for neoplasia/dysplasia, non-invasive low-grade neoplasia (low-grade adenoma/dysplasia), non-invasive high-grade neoplasia (high-grade adenoma/dysplasia, non-invasive carcinoma, and suspicious of invasive carcinoma), and invasive neoplasia (intramucosal adenocarcinoma and submucosal carcinoma or beyond). The IBD system is used commonly in the USA, and some European and most far Eastern countries use the Vienna system. The World Health Organization proposed that the term "dysplasia" be replaced by "intraepithelial neoplasia", but this term has not been well used in literature [21].

According to the guidelines from the American College of Gastroenterology, the surveillance interval and the management of BE mainly depend on the histologic diagnosis of the dysplasia [17]. BE without dysplasia requires two follow-up esophagogastroduodenoscopies (EGD) with biopsy within 1 year and endoscopy every 3 years. BE with low-grade dysplasia requires repeat EGD with biopsy within 6 months and at 1-year intervals until no dysplasia is evident twice in a row. BE with high-grade dysplasia requires repeat EGD with biopsy to rule out esophageal adenocarcinoma within 3 months, endoscopic resection, and continued 3-month surveillance or intervention based on results and the individual patient. However, the interobserver variability is significant in diagnosis of Barrett's-related dysplasia, as mentioned earlier [3-5]. Expert pathologist confirmation for low-grade and high-grade dysplasia is recommended according to the guidelines from the American College of Gastroenterology, but the expert pathologists face similar challenges when diagnosing and grading Barrett's-related dysplasia [6].

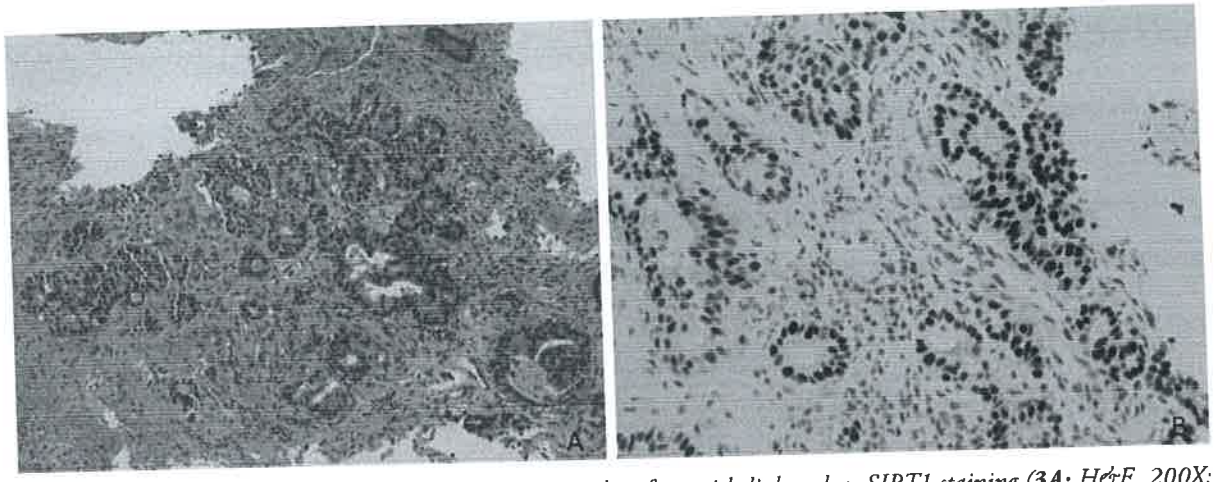

Figure 3. Invasive adenocarcinoma showed 3+ diffuse and surface epithelial nuclear SIRT1 staining (3A: H&E, 200X; 3B: SIRT1 immunohistochemistry, 200X).

Using some biomarkers may be necessary to achieve a better agreement and a more accurate diagnosis to guide patient management in Barrett's-related dysplasia. Nuclear DNA content abnormalities and loss of heterozygosity of p16 and p53 have some diagnostic value [9,10]. DNA content abnormalities have proven to be substantially useful in the difficult group of non-dysplasia BE and low-grade dysplasia with 5-year cumulative cancer incidence rates of 28% with DNA abnormalities compared to 0% without DNA abnormalities [10]. Despite the good results, aneuploidy/tetraploidy has not been widely used because of the technical challenges. LOH of p53 significantly increases the risk of progression to adenocarcinoma, but accurate evaluation of p53 LOH requires genotyping that is currently limited to the research setting [9]. Immunohistochemistry for p53 and racemase shows some promising results and is more practical from day to day. However, a significant rate of both false positives and false negatives is a problem for p53 immunohistochemistry, and large studies are needed to confirm the initial promising results of racemase [3,9-12].

Epigenetic modifications of proteins, histones, and chromatin play an important role in relating gene expression, cancer formation, and life span. Recent evidence indicates that epigenetic changes might 'addict' cancer cells to altered signaling during the early stages of tumor development [22,23]. SIRT1 plays a significant role in epigenetic modifications. SIRT1 modifies histones through the deacetylation of K26 in histone H1 (H1K26), K9 in histone H3 (H3K9), and K16 in histone H4 (H4K16) [24]. SIRT1 also deacetylases many non-histone proteins that are involved in cell growth, apoptosis, cell senescence, and tumorigenesis, including p53, forkhead class O transcription factor (FOXO), retinoblastoma protein (Rb), Ku 70, mismatch repair gene MLH1, and survivin, and results in an increased risk of cancer [16-18, 25,26]. Our previous study showed SIRT1 expression was significantly increased in colonic tubular adenoma, which indicates the possible roles of SIRT1 in the early tumorigenesis of colonic neoplasia [16]. In this current study, we observed that SIRT1 expression was significantly high in BE with high-grade dysplasia and invasive adenocarcinoma ($p=0.0001$). The SIRT1 staining patterns and intensity appear to be very useful in separating BE with high-grade dysplasia/carcinoma from BE with no dysplasia or low-grade dysplasia.

In summary, our study showed that SIRT1 is a useful biomarker in the diagnosis of BE with high-grade dysplasia and invasive carcinoma, and this is the first report using SIRT1 as an adjunctive marker on the evaluation of Barrett's-related dysplasia. We acknowledge the small data set in this study; large scale and prospective studies are needed to validate our findings.

Table 1. *SIRT-1 expression in the epithelium of BE, BE related dysplasia and invasive carcinoma*

Diagnosis	SIRT-1 0-1+	SIRT-1 2-3+	p value (group 1 vs group 2)
Group 1			
BE without dysplasia	19	1	
BE with low-grade dysplasia	10	1	
Group 2			0.0001
BE with high-grade dysplasia	1	3	
BE with invasive carcinoma	1	7	

SIRT-1: the mammalian homologue of silent mating type information regulator 2 in budding yeast; BE: Barrett's Esophagus.

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DELTA BIOLABS

DB083: SIRT1 (C19)

Background:

The Sir2 protein in yeast is known to function in transcriptional silencing processes through the deacetylation of histones H3 and H4 (1). The more recently described human homologue of Sir2, known as SIRT1, has been found to associate with the tumor suppressor protein p53 (1-3). SIRT1 binds and deacetylates p53 with specificity for its C-terminal Lys382 residue in response to the upregulation of promyelocytic leukemia protein (PML) nuclear bodies or oncogenic Ras (2&3). The deacetylation of p53 SIRT1 has been shown to negatively regulate p53-mediated transcription, preventing cellular senescence and apoptosis induced by DNA damage and stress (1-3).

Origin:

SIRT1 (C19) is provided as an affinity purified rabbit polyclonal antibody, raised against a peptide mapping to the carboxy terminal domain of human SIRT1.

Product Details:

Each vial contains 200 µg/ml of affinity purified rabbit IgG, SIRT1 (C19) DB083, in 1 ml PBS containing 0.1 % sodium azide and 0.2% gelatin.

Competition Studies:

A blocking peptide is also available, DB083P, for use in competition studies. Each vial contains 100 µg of peptide in 0.5 ml PBS with 0.1% sodium azide and 100 µg BSA.

Specificity:

SIRT1 (C19) is recommended to detect human SIRT1 in Western blotting, immunoprecipitation, and CHIP assays. Recommended Western blotting starting dilution 1:400.

Storage:

Store this product at 4° C, do not freeze. The product is stable for one year from the date of shipment.

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