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Review Article

Role of Glycomic Biological Age Markers in Health and Disease

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ABSTRACT

Chronological age is an imperfect tool for assessing healthspan and risk for diseases. As a result, biological markers of age become important components of personalized medicine. One of such markers, the plasma glycome, and especially Immunoglobulin G (IgG) N-glycosylation, is gaining attention due to its dynamic nature and involvement of genetics, environment, and lifestyle.

In this review, we summarize current knowledge about the role of glycomic biological age markers ("Glycan Age") in health and disease. Aging causes the progressive reduction in the levels of IgG galactosylation and sialylation with changes in fucosylation and bisection. Moreover, these structural changes do not only reflect the physiological decline, but also impact immune cell activity by changing the affinity for activating and inhibitory $Fc\gamma$ receptors and cause the shift from anti-inflammatory towards pro-inflammatory status resulting in sterile systemic low-level inflammation, called "inflammaging."

As a marker clinically, premature glycan aging becomes a strong predictor of disease outcomes in various disease categories. Glycan aging tends to occur several years prior to the onset of clinical symptoms in autoimmunity, heart diseases, metabolic syndromes, neurodegenerative conditions, and cancers, and works as an independent predictor of overall mortality. Importantly, glycan aging is a very manipulable clock; changes in endocrine status (perimenopause), lifestyle modifications, and therapies of longevity have been shown to effectively reverse this biological clock. Finally, it would be necessary to overcome the technical issues related to standardization and integrate glycomics into multi-omics clocks using machine learning approaches.

KEYWORDS:

• Glycan Age • Immunoglobulin G (IgG) • Inflammaging • Biological Age Biomarkers • Glycosylation

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INTRODUCTION

A paradigm shift is being witnessed in conventional geoscience from a focus on chronological age, that is, age based on the passage of time from birth, to biological age, that is, one's actual physiological age. Although chronological aging is a uniform process, biological aging is variable and determined largely by genetics, environment, and lifestyle.[1] Therefore, it becomes important to understand the disparity between these two types of ages as people with the same chronological age can have very different physiological states of being.[1]

In order to chart out these physiological pathways with precision, investigators have correlated the systemic alterations to the "hallmarks of aging" including cellular senescence, chronic inflammation, and disturbed inter-cellular communication. However, measuring these alterations demands powerful and sensitive molecular markers, which should be able to detect early signs of physiological deterioration well before the appearance of clinical manifestations.[1,2] Although some progress has been made in this direction in the form of epigenetic clocks and transcriptomic markers, there is a vital requirement for dynamic blood markers.[2]

The glycomes of cells, which include all the sugars, or glycans, attached to proteins and lipids, have turned out to be a highly sensitive post-translational measure of biological aging. Changes in the pattern of IgG glycosylation due to aging, including reduced levels of galactose and sialic acid and increased core fucosylation, serve as highly sensitive indicators of the presence of low-grade systemic inflammation and vascular dysfunction.[1,3] The main goal of the present review is a comprehensive assessment of the function of glycomic biological age markers in physiology and pathophysiology. This paper will analyse the current glycan clocks and their ability to predict different pathological conditions and application in personalized preventive medicine.

BIOCHEMICAL FOUNDA TIONS OF GLYCAN-BASED AGING CLOCKS

The glycosylation of Immunoglobulin G (IgG) constitutes the bedrock of systemic post-translational monitoring, making the N-glycome of the Fc region of IgG the unquestionable gold standard of glycomic biological age modelling. As the most abundant glycoprotein circulating in the bloodstream, IgG captures the genetic, environmental, and physiological changes in unique glycan structures that occur on the highly conserved Fc region. This structural information forms a very good dynamic indicator of systemic dysregulation and chronic inflammation. Thus, measuring IgG glycol profile is a much better gauge of biological robustness than chronological parameters.[4]

Increasing biological age leads to reproducible and specific structural changes within the IgG glycome actively participating in reprogramming of immune cells. These structural changes include a progressive reduction in terminal galactosylation, specifically resulting from a reduction in anti-inflammatory di galactosylated forms and the increase in pro-inflammatory a galactosylated (G0) forms. This process is additionally associated with an age-related decrease in the levels of terminal alpha2,6-sialic acid, further reducing anti-inflammatory properties and leading to increased siginalling for cell senescence. Simultaneously, changes in core fucose together with bisecting N-acetylglucosamine (GlcNAc) regulate IgG structural architecture leading to chronic low-grade sterile inflammation.[5]

The precise characterization of these minute age-related changes needs very advanced technologies for the analysis. Ultra-high Performance Liquid Chromatography is still the most important instrument for highly reproducible glycan separation, whereas Capillary Gel Electrophoresis coupled with Laser Induced Fluorescence provides high resolution profile. Also, the development of the modern MALDI-TOF MS allowed glycomic analysis because of linkage-specific stabilization and absolute quantification models. Thanks to these technologies, it is now possible to go from relative percentage profiles to absolute quantification, thus securing the medical application of the glycan aging clock.[6]

BIOLOGICAL MECHANISMS: FROM BIOMARKER TO FUNCTIONAL EFFECTOR

Age-related loss of terminal galactose and sialic acid residues of the fragment

crystallizable (Fc) region of immunoglobulin G (IgG) changes its tertiary structure, thus initiating self-amplifying glycan-inflammaging feedback mechanism. Physiologically, IgG in full sialylation and galactosylation form immune homeostasis.[7] Yet, the process of immunosenescence leads to the accumulation of agalactosylated forms, which turns the pool of IgG molecules into a pro-inflammatory molecule.[7,8] The glycomic clock mechanism is represented as Figure 1.

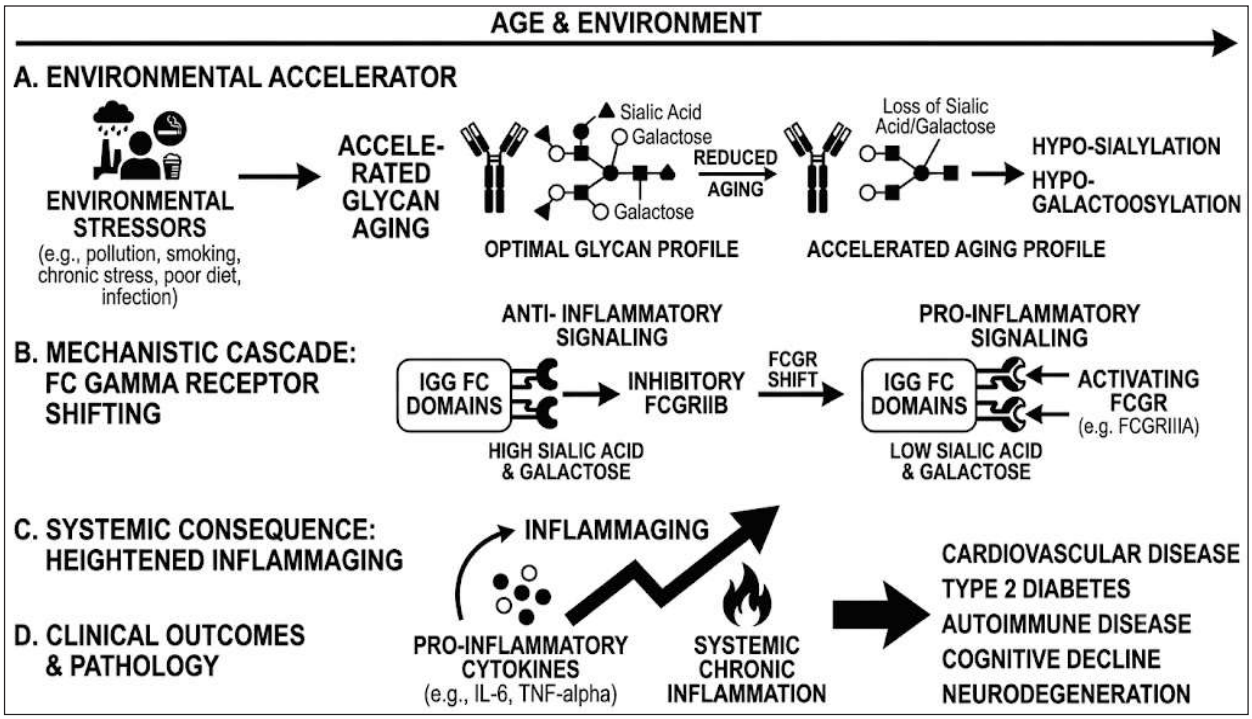

Figure 1: The Glycomic Clock Mechanism: Environmental Acceleration of IgG Glycan Aging and the Inflammaging Cascade

Pathogenesis of these abnormal glycoforms leads to significant changes in the binding of immunoreceptors via molecular dynamics. Indeed, the change in the structure of glycosylation site results in the increase in IgG binding ability to activating Fc gamma receptors (Fc gamma Rs) and decrease in IgG-Fc gamma RIIb and C-type lectins (such as DC-SIGN) interactions.[1,2] Thus, the downstream pathological effects such as complement activation and ADCC (antibody-dependent cellular cytotoxicity) are triggered, which lead to the development of chronic sterile low grade systemic inflammation.[8]

The basic structure of the glycan clock arises out of an intricate relationship between genetic inheritance and environmental factors. Though the narrow-sense heritability of the plasma N-glycomes is known to be about 39%, the predominant glycomic variation is governed by the lifetime exposome.[9] Negative environmental forces such as consumption of ultra-processed foods, chronic stress, smoking habits, and disruption of gut microbiome contribute to disruption of glycosylation pathway, thus increasing the biological clock independent of chronological aging.[8,9]

GLYCOMIC AGE MARKERS IN SPECIFIC DISEASE SPECTRUMS

In the case of autoimmune diseases and chronic inflammation, premature glycan aging emerges as a powerful predictor of systemic disease. Distortion of Immunoglobulin G (IgG) glycosylation, particularly the premature depletion of galactose and sialic acid moieties from the glycan structures, acts as a proxy of early immune dysfunction associated with Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Inflammatory Bowel Disease (IBD) (10). Importantly, the longitudinal studies of cohorts have shown that pro-inflammatory glycans may be detected years before any manifestation of the clinical symptoms.[4,10]

The acceleration of glycan aging is also connected with the structural and functional

mechanisms of development of cardiovascular and metabolic diseases. The pronounced modifications of the glycan composition of the circulating Immunoglobulin G (IgG) strongly correlate with the endothelial dysfunction, subclinical atherosclerosis, increased arterial stiffness and hypertension.[4,11] Furthermore, the chronic, sterile, low-grade inflammation that characterizes Type 2 Diabetes mellitus and morbid obesity leads to a particular agalactosyl expansion of glycans.[10] Thus, these examples show that the indices of glycomic aging effectively reflect the accumulated cardiometabolic stress and vascular damage, surpassing many classical indicators.[4,10]

Other than the inflammatory and metabolic pathways, the changes occurring in the glycome within a systemic context hold immense diagnostic value for oncologic and neurodegenerative diseases. The development of malignancies and senescence within the immune system result in profound changes, which are represented by the altered glycan signatures in the entire plasma glycome and tumor-specific IgG.[11] In parallel, in the spectrum of cognitive decline diseases such as Alzheimer's and vascular dementia, glycan markers are used as peripheral reflections of central neuroinflammation.[4,11]

CLINICAL INTERVENTIONS AND MODIFIABILITY OF THE GLYCAN CLOCK

Endocrine regulation plays a significant role in glycan clocks due to changes in levels of sex hormones. In particular, during the period of perimenopause, women undergo an exceptionally quick biological aging in terms of glycans due to fast decrease in anti-inflammatory immunoglobulin G (IgG) galactosylation and terminal sialylation.[10] However, the described phenomenon can be easily controlled since clinical studies show that hormone replacement therapy (HRT) with estradiol is able to halt and even reverse such negative glycomic changes.[6,10]

Moreover, along with hormonal changes, lifestyle modifications can play the role of non-medical methods of adjustment of the biological glycan clock. Metabolic disorders such as obesity and insulin resistance result in quickening of the process of aging in terms of glycan clock, however, a considerable weight loss that results from caloric restriction or bariatric surgery decreases the levels of pro-inflammatory agalactosylated (G0) forms.[10] Besides, regular physical exercises were shown to reduce the index of Glycan Age and decrease inflammation potential of IgG.[12]

Emerging strategies in therapy present revolutionary perspectives on how to rewind the glycan clock through chemical targeting. Early studies using targeted anti-inflammatory medications, novel longevity interventions such as senolytic drugs and metformin, and therapeutic plasma exchange (TPE) have shown amazing success at removing existing systemic dysregulation and rejuvenating the glycan structures.[6,10] Significantly, employing such glycan markers of aging presents unparalleled advantages in predicting medicine. They act as strong independent predictors of mortality risk, greatly surpassing the abilities of traditional clinical biomarkers for predicting longevity.[10]

Clinical Interventions and Modifiability of the Glycan Clock

The unique dynamic reactivity to hormonal changes makes the glycan clock different from fixed chronological clocks. Sex hormones have a powerful influence on Immunoglobulin G (IgG) glycosylation pattern, which is clearly demonstrated when the female goes through the process of menopause. The drastic drop of estrogen levels during the menopausal period provokes a rapid aging of the glycome due to the lack of anti-inflammatory galactosylated and sialylated structures. Strikingly, Estradiol administration within Hormone Replacement Therapy (HRT) is capable of completely stopping or even reversing this trend.[9]

It was shown that metabolic and dietary intervention can become a very efficient method of non-pharmacological regulation of the glycan clock. Lifestyle interventions aimed at fighting obesity and metabolic syndrome (caloric restriction, physical training, bariatric surgery) cause quick alterations in the IgG glycosylation pattern. Weight loss leads to suppression of systemic inflammation and results in a drastic decrease in the level of pro-inflammatory agalactosylated (G0) isoforms. This metabolic improvement contributes to the slowing down of the glycan biological age.[13]

New longevity therapies provide encouraging possibilities for the direct "undoing" of the glycan clock. The recent longitudinal studies have shown impressive

results achieved with the help of Therapeutic Plasma Exchange (TPE) and specific geroprotectors like metformin and senolytics in immune rejuvenation. TPE is effective in reducing pro-inflammatory circulating cytokines and immunoglobulins. It is known that the effects of TPE treatment are reflected in the rejuvenation of the IgG glycome at a rate of per month. Thus, the mentioned glycan aging biomarkers can be considered as strong independent predictors of mortality.[14]

CURRENT CHALLENGES, LIMITATIONS, AND FUTURE DIRECTIONS

However, although the enormous potential of glycan age markers for accurate diagnostics is evident, there are numerous technical difficulties that remain unresolved. One of the main technical obstacles related to standardization concerns switching from relatively percentage composition profiling to absolute quantification of glycan structures using large clinical samples to avoid the impact of changes in total levels of immunoglobulins . Moreover, confounding factors need to be identified and controlled for, which requires the current diagnostics approaches to be able to distinguish between acute systemic inflammation and true biological aging processes.[15,16]

In order to increase the accuracy of prediction, the field is rapidly advancing towards the multi-omic approach. Combination of highly dynamic plasma glycomic analysis with stable epigenetic (DNA methylation) clocks and digital health metrics generates an unprecedented synergy of clinical parameters.[3] Machine and deep learning algorithms allow the investigators to model the complex non-linear biological patterns in multidimensional networks and establish glycosylation pathways as stable molecular markers.[17]

Nevertheless, certain translational obstacles need to be overcome for such a broad application of the technology to take place. Dealing with rigorous processes related to gaining regulatory approval, showing cost-effectiveness, and clinical benefit in the long run are the key challenges in this regard. Overcoming these obstacles is crucial in order to apply the standardized glycan age test in personalized prevention.[18]

CONCLUSION

In summary, the nature of glycans in human senescence lies in their dual nature as exquisitely sensitive mirrors reflecting physiological degradation and active mediators of pathology at the same time. Far beyond being simple passive markers, changes in the structure of glycans – specifically the absence of terminal galactose and sialic acid modifications in immunoglobulin G molecules – actively trigger inflammation, thus causing "inflammaging" and the development of numerous pathologies.

In order to translate glycomics from basic research into clinical practice, we must now make a clinical effort. Therefore, we call for a last push towards comprehensive and longitudinal validation studies that would finally allow us to standardize these systems and set up clinical benchmarks for the glycomic platforms. In doing so, we will firmly ground glycomics in the realm of clinical health assessments.

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