Proinflammatory Glycomic Dysregulations Precede Cancer Onset During HIV Infection

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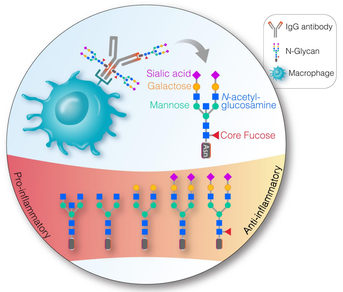
BACKGROUND



- Host glycomic alterations, in particular, **loss of galactose** (agalactosylation; measured as high levels of G-ratio and G0 glycan groups), on circulating IgG, drive inflammation and precede the onset of premature aging-associated diseases.
- We investigated whether glycomic alterations, in particular agalactosylation, precede the development of non-AIDS-defining cancers during antiretroviral therapy (ART)-suppressed HIV infection.

METHODS

- In a longitudinal case-control study, 104 plasma samples were collected between 13.8 and -0.8 years before the onset of cancer in 29 HIV+ ART+ cases; 10 with gastrointestinal (GI) cancers, 9 with skin cancers, and 10 with other non-AIDS-defining cancers.
- Control samples (121) were collected, at same time-points as cases, from 32 matched (for age at sample collection, sex, and ethnicity) HIV+ ART+ controls without cancers.
- IgG glycosylation was profiled using capillary electrophoresis, and markers of inflammation were measured by multiplex cytokine arrays.

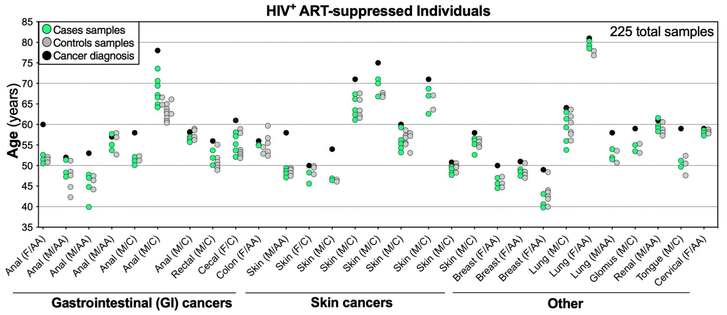


Figure. 1. Plasma samples collected and studied from cases (HIV+ ART-suppressed with cancers) and age, gender, and ethnicity matched controls (HIV+ ART-suppressed without cancers). F= Female; M= Male; AA= African American; C=Caucasian.

Premature-aging-associated glycomic dysregulations and pro-inflammatory responses may precede the onset of non-AIDS-defining cancers, especially inflammation-associated cancers, such as gastrointestinal cancers, during ART-suppressed HIV infection.

RESULTS

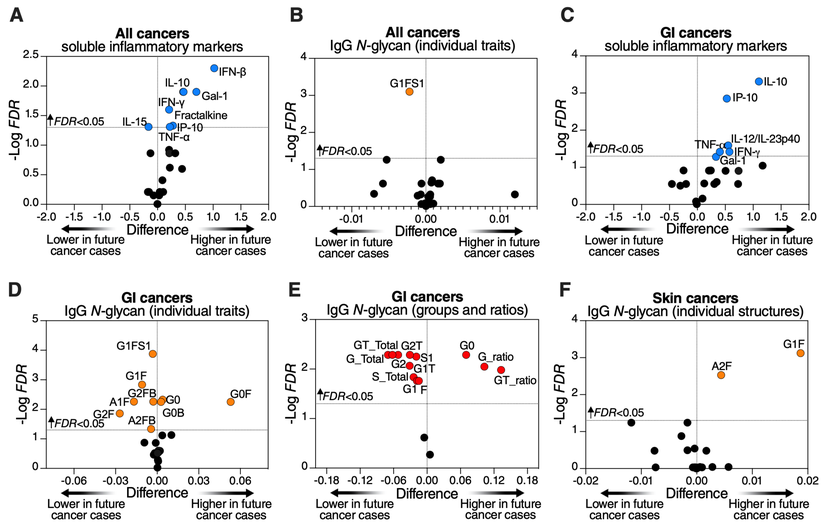


Figure. 2. IgG glycans and soluble inflammatory markers differentiate controls from cases with GI cancers. Volcano plots showing factors differentiating controls from cases before cancer onset. (A) soluble markers using samples from all cancers. (B) IgG glycans (individual traits) using samples from all cancers. (C) soluble markers using samples from GI cancers. (D) IgG glycans (individual traits) using samples from GI cancers. (E) IgG glycans (grouped and ratios) using samples from GI cancers. (E) IgG glycans (individual traits) using samples from skin cancers. FDR was calculated using the Benjamini-Hochberg method.

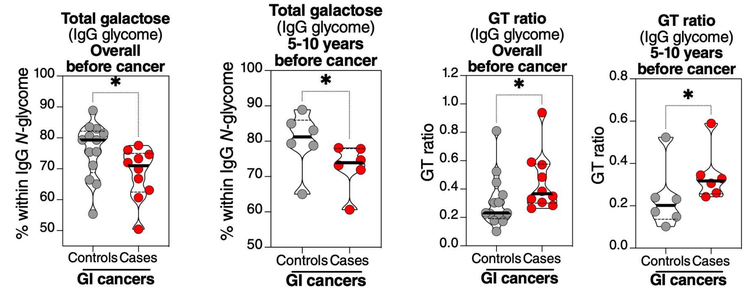


Figure. 3. Loss of galactose differentiates controls from cases 5-10 years before GI cancers onset. Levels of galactose or loss of galactose (GT ratio) measured either as as average across the study period or average between 5-10 years before cancer onset compared between cases and controls. Mann–Whitney U test

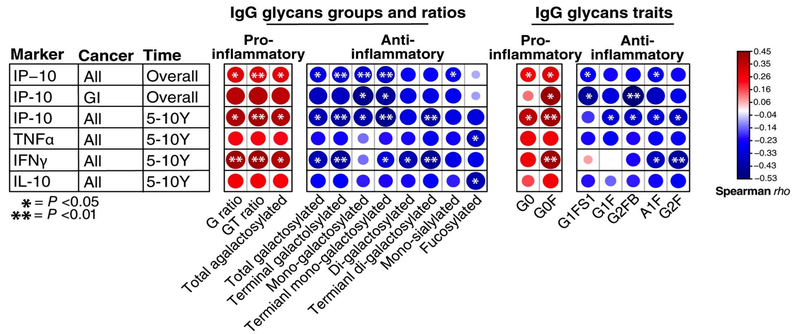


Figure. 4. IgG glycans correlate with inflammatory markers. A matrix showing the correlations between IP-10 (average across the study period in all patients; average across the study period in GI cancer cases; average 5-10 years before cancer onset in all cancer), TNFα, IFNγ, and IL-10 and levels of pro- and anti-inflammatory glycans. Spearman r correlations. Red = positive correlation and blue is a negative correlation. The size and color shade of the circles reflect the strength of the correlation.

CONCLUSIONS

- Our exploratory study suggests that premature-aging-associated glycomic dysregulations and pro-inflammatory responses may precede the onset of non-AIDS-defining cancers, especially inflammation-associated cancers such as GI cancers, during ART+ HIV infection.
- Potential glycomic and inflammatory pathways fostering cancer progression, during ART-suppressed HIV infection, warrant further investigation into their prognostic and functional significance.

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