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AIDS 2017, **31**:2311–2315

Predictive value of galectin-1 in the development and progression of HIV-associated lymphoma

At HIV-1 infection, the binding of the viral envelope proteins to $CD4^+$ is essential for viral transmission, and this process is facilitated by interaction with the highly conserved host lectin, galectin-1 (Gal-1) [1–3]. Within the tumor microenvironment, Gal-1 is expressed by both tumor and stromal cells where it promotes tumor immune escape and favors hypoxia-driven angiogenesis [4–6]. In sporadically occurring Hodgkin lymphoma, high Gal-1 expression at diagnosis is associated with poorer treatment response [7], and high soluble Gal-1 (sGal-1) correlates with adverse disease characteristics [8]. Previous studies have shown that targeted inhibition of Gal-1 prevents tumor-induced immunosuppression [9,10] and inhibits tumor growth and metastasis in various tumor models [6,11–13].

Recently, we published a proteomic profiling study of pretreatment serum samples from HIV-infected patients, identifying several differentially expressed proteins associated with lymphoma development [14]. In this cohort, we have now evaluated serum levels of sGal-1 and correlated this with clinical parameters, including lymphoma development. In addition, we have investigated the intratumoral expression and prognostic value of Gal-1 in HIV-associated lymphomas, and, for comparison, sGal-1 serum levels in 30 healthy blood donors [15]

Circulating sGal-1 levels were measured using a time-resolved immunofluorometric assay and immunohistochemistry and the evaluation of tumoral Gal-1 expression were performed as described previously [7,14,15].

Pretreatment sGal-1 serum levels were assessed in 19 HIV-positive individuals at time of HIV diagnosis. There were no sex-related differences ($P = 0.450$) and sGal-1 levels neither correlate with peripheral $CD4^+$ cell count nor with viral load at HIV diagnosis ($\rho = -0.491$ $P = 0.852$ and $\rho = -0.009$ $P = 0.974$, respectively).

HIV-infected individuals had significantly lower levels of sGal-1 compared with healthy controls (43.6 vs. 84.9 ng/ml; $P < 0.001$; Fig. 1a). Within the entire study cohort (healthy controls and HIV-infected individuals), those patients who would later develop lymphoma also had significantly lower levels of sGal-1 at time of HIV-diagnosis (Fig. 1b; $P = 0.016$). There was no significant difference in sGal-1 within the HIV cohort (Fig. 1c, $P = 0.130$).

A cut-off value of 2.4 ng/ml generated by receiver operating curve (ROC) analysis separated HIV-infected individuals who later developed lymphoma from the remaining cohort of HIV patients and controls with a specificity of 82% and a sensitivity of 100%. Based on this cut-off value, 13 (31%) HIV-infected patients were allocated to the low sGal-1 group, including all future lymphoma patients ($N = 5$).

Tumoral Gal-1 expression correlated positively with a proinflammatory signature of the microenvironment, including the macrophage marker CD68, the cytotoxic markers CD8 and granzyme B, as well as the activation marker CD30 [CD68 ($\rho = 0.740$; $P < 0.001$), CD8 ($\rho = 0.379$; $P = 0.027$), granzyme B ($\rho = 0.579$; $P < 0.001$) and CD30 ($\rho = 0.467$; $P = 0.006$)]. Clinical features of the cohort included in the tissue microarray have been described previously [14].

Gal-1 was widely expressed in all lymphoma subtypes. Based on a ROC generated cut-off value for high vs. low intratumoral Gal-1 expression, 59% ($N = 10$) of diffuse large B-cell lymphoma (DLBCL) patients had a high level of intratumoral Gal-1 expression (>24.8% positive cells). In the total lymphoma cohort (all diagnoses), two-thirds of the patients ($N = 22$; 65%) were high expressers. This latter group more often had nodal disease and B-symptoms ($P = 0.006$). Gal-1 did not correlate with tumoral Epstein–Barr virus (EBV) status, EBV latency type, international prognostic index (IPI), clinical stage, or cell of origin.

In HIV-associated DLBCL, patients with higher levels of intratumoral Gal-1 expression had a significantly better outcome with a 5-year overall survival of 70.0% (95% confidence interval 32.9–89.2%) vs. 14.3% (95% confidence interval 0.7–46.5%). In a multivariate analysis, adjusting for IPI and rituximab treatment, both Gal-1 expression ($P = 0.021$) and IPI ($P = 0.049$) retained an independent prognostic value.

HIV infection has a profound influence on the host immune system including altered cytokine and protein expression years prior to lymphoma diagnosis [14,16–18]. Gal-1 is secreted by most immune cells [19] and the significantly lower levels of sGal-1 in newly diagnosed HIV-infected individuals (compared with healthy controls), as found in our study, may reflect the dramatically altered immune constitution of these patients. This may lead to a proinflammatory although nonefficient T-cell response, ultimately leading to lymphoma development.

We found a relatively high intratumoral expression of Gal-1 in our cohort of HIV-associated DLBCL, as

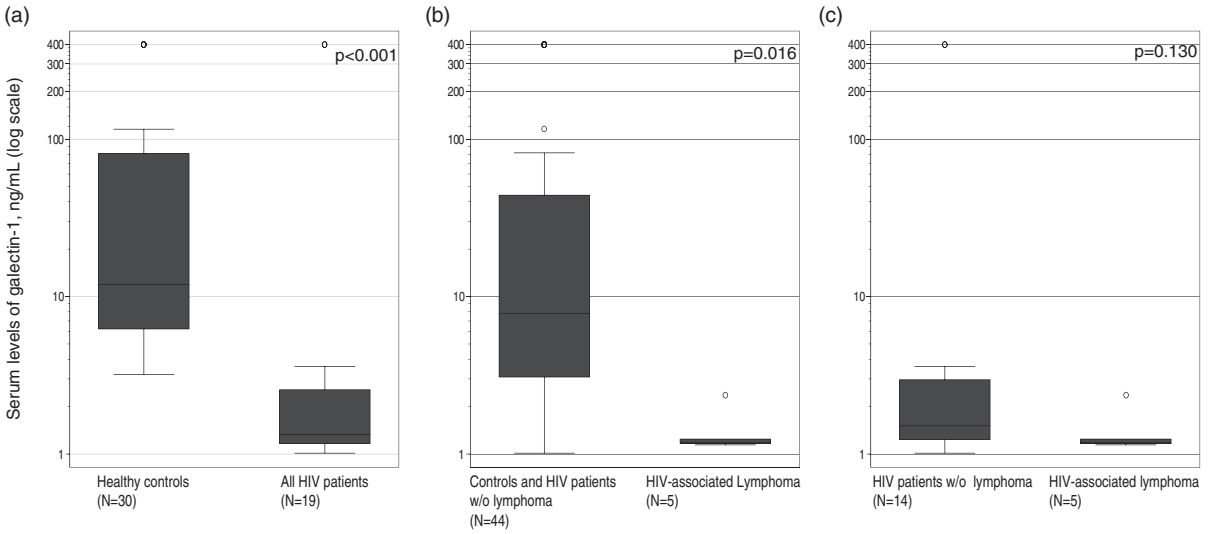

Fig. 1. Serum galectin-1 (Gal-1) levels in HIV-infected individuals and controls. The line indicates the median and the box indicates the 25th and 75th percentiles. Whiskers are upper and lower adjacent values. (a) HIV-infected individuals had significantly lower levels of soluble Gal-1 at the time of HIV diagnosis compared with healthy controls ($P < 0.001$). (b) Soluble Gal-1 at the time of HIV diagnosis in HIV-infected individuals with subsequent lymphoma compared with the remaining cohort (healthy controls and HIV-infected individuals without lymphoma) ($P < 0.016$). (c) Differences in Gal-1 serum levels in HIV-infected individuals who did or did not develop lymphoma ($P < 0.130$).

compared with the immunocompetent setting [20]. This may partly reflect different evaluation techniques, but inherent disparities in lymphoma microenvironment may also be involved [21,22]. Gal-1 is largely produced by macrophages [23]. The correlation between high Gal-1 expression and improved outcome in HIV-associated DLBCL may therefore be explained by a higher level of macrophages because they have been shown to improve the efficacy of antibody-driven immunotherapy [24].

In conclusion, the results of our study indicate that Gal-1 is significantly associated with risk of lymphoma in HIV-infected individuals and may represent an attractive future target for the management of HIV-associated lymphoma.

Acknowledgements

The authors wish to thank Erik Hagen Nielsen, Vibeke Ellerup Jensen, and Kristina Lystlund Lauridsen for expert technical assistance, and Betina S. Sørensen for facilitating access to healthy donors samples.

Conceived and designed the study: M.Ø.V., M.L., C.S.L., F.d'A. Provided study material: G.A.R., I.P., G.P., C.S.L., M.B.M., K.B., S.H.D. Performed the experiments: R.H., M.L. Analyzed data: M.Ø.V., M.L., B.H., P.W.D. Wrote the paper: M.Ø.V. and M.L. Final editing and approval of the manuscript: all authors.

The work was supported by unrestricted grants from Dagmar Marshalls Foundation, Manufacturer Einer Willumsen's Memorial Foundation, The Harboe Foundation, The Krista and Viggo Petersens Foundation, Fonden til Lægevidenskabens fremme, Director Emil C. Hertz and his wife Inger Hertz Foundation, The Foundation of 17 December 1981, Architect Holger Hjortenberg and wife Dagmar Hjortenberg's Foundation; Frits, Georg, and Marie Cecilie Glud's Foundation, Danish Diabetes Academy supported by the Novo Nordisk Foundation, Inger and Max Wørzner's Memorial Foundation, and The MEMBRANES Center at Aarhus University.

Conflicts of interest

There are no conflicts of interest.

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Received: 14 May 2017; revised: 24 July 2017; accepted: 8 August 2017.

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DOI:10.1097/QAD.0000000000001622