INFECTIOUS AGENTS AND CANCER

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TNFAIP3(A20) genetic alterations in AIDS-related lymphomas

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From 12th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI)
Bethesda, MD, USA. 26-27 April, 2010

Background

AIDS-related lymphomas (ARLs), which include Burkitt lymphoma and diffuse large B cell lymphoma (DLBCL), are a heterogeneous group of lymphoproliferative disorders that occur in the setting of HIV-mediated immune suppression. A subset of cases are associated with Epstein-Barr virus (EBV) infection. EBV expresses latent viral oncoproteins that constitutively activate the transcription factor NF-κB, a potent inducer of genes involved in promoting B cell survival and proliferation [1].

In immunocompetent individuals, lymphomas that are not associated with EBV can also display increased NF-κB activity, and recent reports have described mutations in regulators of NF-κB. One of the frequently mutated regulatory genes is TNFAIP3, which encodes A20, a ubiquitin modifying enzyme involved in the termination of NF-κB signaling. Mutations resulting in the inactivation of A20 have been found in a significant proportion of marginal zone lymphomas [2], classical Hodgkin's lymphomas and primary mediastinal B cell lymphomas [3], and DLBCLs [4]. In ARL the role of NF-κB activation and the incidence of mutations in A20 have not been described.

Materials and methods

We evaluated archival formalin-fixed paraffin-embedded tissue samples of AIDS-related lymphoma for genetic alterations in A20. Tissue was collected through an international collaboration between Weill Cornell Medical College in New York, NY, and Siena University in Siena, Italy. A tissue microarray with 48 cases of ARL was prepared, and characterization of viral status and lymphoma subtype were determined by immunohistochemistry and in situ hybridization for Epstein-Barr encoded RNA (EBER). Fluorescent in situ hybridization (FISH) was used to evaluate for genomic deletions in A20, and translocations of cMYC, BCL-2, and BCL-6. Direct sequencing of the coding region of A20 was performed to evaluate for additional mutations.

Results

FISH was performed on 48 cases of ARL. Of 21 cases with successful hybridization loss of heterozygosity at the A20 locus was observed in 6 cases (28%). Cases with A20 deletion included three diffuse large B cell lymphomas, two Burkitt lymphomas, and one Burkitt-like lymphoma. Two cases were positive for EBER but all were negative for latent membrane protein-1 (LMP-1). Partial sequencing of approximately 70% of the A20 coding regions in 23 cases did not reveal additional mutations.

Conclusions

A20 may represent a tumor suppressor gene in a subset of AIDS-related lymphomas. Inactivation of A20 may be an alternative mechanism of NF-κB upregulation in the absence of LMP-1.

Acknowledgements

This article has been published as part of *Infectious Agents and Cancer* Volume 5 Supplement 1, 2010: Proceedings of the 12th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI). The full contents of the supplement are available online at http://www.biomedcentral.com/1750-9378/5?issue=S1.

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Published: 11 October 2010

References

1. Keller SA, Hernandez-Hopkins D, Vider J, Ponomarev V, Hyjek E, Schattner EJ, Cesarman E: **NF-kappaB is essential for the progression of KSHV- and EBV-infected lymphomas in vivo.** *Blood* 2006, **107(8)**:3295-3302.
2. Novak U, Rinaldi A, Kwee I, Nandula SV, Rancoita PM, Compagno M, Cerri M, Rossi D, Murty VV, Zucca E, *et al*: **The NF-{kappa}B negative regulator TNFAIP3 (A20) is inactivated by somatic mutations and genomic deletions in marginal zone lymphomas.** *Blood* 2009, **113(20)**:4918-4921.
3. Schmitz R, Hansmann ML, Bohle V, Martin-Subero JI, Hartmann S, Mechtersheimer G, Klapper W, Vater I, Giefing M, Gesk S, *et al*: **TNFAIP3 (A20) is a tumor suppressor gene in Hodgkin lymphoma and primary mediastinal B cell lymphoma.** *J Exp Med* 2009, **206(5)**:981-989.
4. Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, Bertoni F, Ponzoni M, Scandurra M, Califano A, *et al*: **Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma.** *Nature* 2009, **459(7247)**:717-721.

doi:10.1186/1750-9378-5-S1-A82
Cite this article as: Giulino *et al.*: TNFAIP3(A20) genetic alterations in AIDS-related lymphomas. *Infectious Agents and Cancer* 2010 **5**(Suppl 1): A82.

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