Activating Mutations in MYD88 and CD79B Are Predictive of Response to Ibrutinib in ABC-DLBCL Tumors

Poster 2759

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Abstract

Background. DLBCL is the most common form of non-Hodgkin's lymphoma (NHL) consisting in 2 subtypes: the activated B cell-like (ABC) and the germinal center B cell-like (GCB). ABC-DLBCL is more difficult to treat and is characterized by the presence of a diverse range of activating mutations, such as in the CD79B and Bruton's tyrosine kinase (BTK), in the B-cell receptor (BCR) signaling pathway and in the MYD88 gene, encoding for an adapter for Toll-like receptors. Activation of BCR signaling is required for disease maintenance. The activating mutation L265P in MYD88 turns on the BCR pathway (29% of ABC-DLBCL), driving the disease. DLBCLs carrying the L265P mutation are responsive to ibrutinib (a BTK inhibitor) in the clinic[1,2]. While a proportion of DLBCL patients with MYD88-L265P mutation is wild type for CD79B, the majority of patients (21% of total ABC-DLBCL) are double mutant (MYD88-L265P and CD79B-Y197N), suggesting an oncogenic cooperation between the two genes. It remains unclear whether the single/double mutants differ in their molecular pathogenesis as well as in their response to ibrutinib. This study set to investigate which genotypes are the most predictive of the response to ibrutinib.

Methods. We created a panel of 20 DLBCL patient derived xenografts (PDXs). We transcriptome-sequenced 6 of them and categorized them into ABC or GCB subtypes according to their gene expression profile[2,3], and CD79B/MYD88 mutations. We then tested them for response to ibrutinib.

Results. Our panel of DLBCL-PDX include:

- Models double mutant for MYD88-L265P and CD79B-Y197N (LY2298, LY2264)
- Models with single MYD88-L265P mutation (LY0257)
- Models with MYD88 wild type (LY2345, LY2214, LY2266)

Wild-type/single mutant models did not respond to ibrutinib, but double mutations did, suggesting distinct molecular oncogenic mechanisms.

Conclusion. Consistently with recent clinical data[1] our study shows that the concomitant presence of a mutated form of CD79B and MYD88 confers sensitivity to ibrutinib, suggesting that the mutational status of both genes could be used as a biomarker predictive of response.

References

1. Wilson, W.H., *et al.* Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nature medicine* (2015).
2. Wright, G., *et al.* A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 9991-9996 (2003).
3. Gutierrez-Garcia, G., *et al.* Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Blood* **117**, 4836-4843 (2011).

Results

ID	Gender	Age	Clinical Diagnosis
LY0257	Female	NA	Non-Hodgkin lymphoma (Diffused large B cell); IHC results: CD20(+), CD45RO(-), CD3(-), CD15(-), CD79α(+), CD30(-), CK(-), CD56(-).
LY2214	Male	67	Non-Hodgkin lymphoma (Diffused large B cell); IHC results: CD3(-), CD45RO(-), CD20(+), CD79α(+), Ki-67(80%), CD10(-),CD30(-), ALK(-), Bcl-6(-), MUM1(-)
LY2266	Male	67	Non-Hodgkin lymphoma (B cell lymphoma with plasma cell differentiation). IHC results: CK(-), CD20(+), CD3(-), CD79α(+), Ki-67(40%), CD5(-), CyclinD1(-), CD138(+/-), CD56(-), CD10(-), Bc1-6(-), Pax-5(+), MUM1(+/-), CD45RO(-)
LY2298	Female	64	Non-Hodgkin lymphoma B cell lymphoma of right forehead; CD20(++), CD79a(+), Ki-67(+ 80%), CD56(-), CD3(-), CD45RO(-), NSE(-), GFAP(-), Syn(-), S-100(-)
LY2264	Male	61	Non-Hodgkin lymphoma (diffuse large B cell lymphoma). IHC results: CD3(-), CK(-), CD20(+), Vim(+/-), CD79α(+/-), CD45RO(-), Ki67(80%), CD30(-), HMB45(-), Mart-1(-), Pax-5(+), Bc1-6(+), EMA(-), CK7(-), P63(-), ALK(-), CD10(-).
LY2345	Female	56	Non Hodgkin lymphoma (consider large B cell lymphoma). IHC result: CD3(-), CD45Ro(-), CD20(+), CD79a(+), Pax-5(+), CD5(+/-), CD10(+), BCL-6(-), CyclinD1(-), MUM1(+).

Table 1. Patients Information and Diagnosis

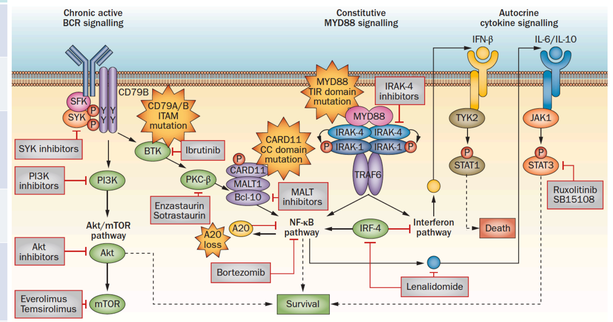

Figure 1. BCR/MYD88 Signaling Pathway

ID	Subtype	MYD88	CD79B	CARD11	Chromosomal translocation/ gene fusion	CD20/19/ 79a IHC	Ibrutinib
LY0257	ABC	L273P	WT	WT	(Chr3)BCL6-IGHM-(Chr14)	+/+/+	resistant
LY2214	GCB	WT	WT	WT	(Chr14)-IGHG1-MYC(Chr8)	+/+/+	resistant
LY2298	ABC	L273P	Y197N	WT	(Chr3)BCL6-IGHM-(Chr14)	+/+/+	sensitive
LY2266	ABC/GCB	WT	WT	WT	(Chr3)BCL6-IGHM-(Chr14)	+/+/+	resistant
LY2264	ABC	L273P	E191A/Y196S	WT	(Chr3)BCL6-IGHM-(Chr14)	+/+/+	sensitive
LY2345	ABC	WT	WT	WT	(Chr3)BCL6-IGHM-(Chr14)	+/+/+	r?

Table 2. Genetic Characterization and Pharmacological Responses of 6 DLBCL-PDXs

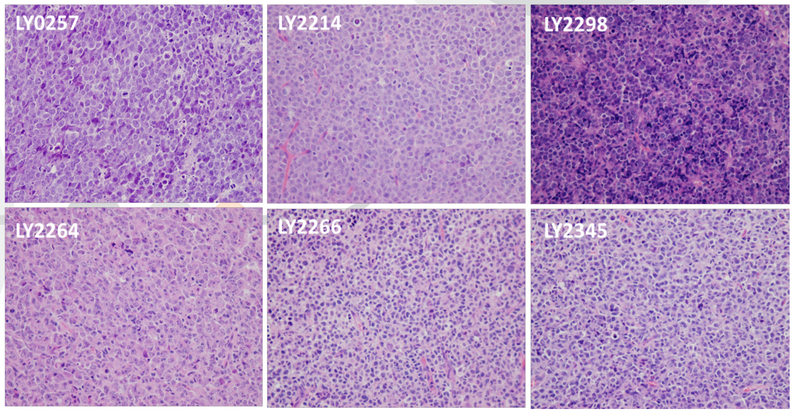

Figure 2. H&E Staining of DLBCL-PDXs

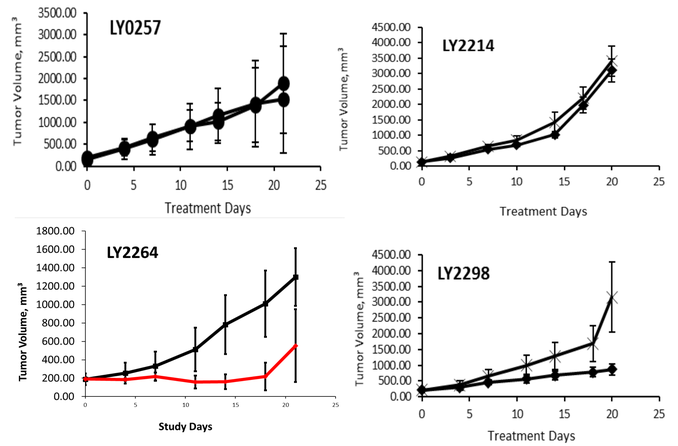

Figure 3. Response to Ibrutinib in DLBCL PDX Models

Conclusions

1. We generated a panel of DLBCL-PDXs
2. Our PDX models differ in the mutational status of MYD88 and CD79B
3. Double mutants models are sensitive to ibrutinib, while MYD88 mutation alone or MYD88 wild type confers resistance to treatment