A20 inactivation in ocular adnexal MALT lymphoma

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ABSTRACT

Recent studies showed A20 inactivation by deletion, mutation and promoter methylation in ocular adnexal mucosa-associated lymphoid tissue lymphoma. However, the incidences of A20 abnormalities and their clinical impact remain for the most part unknown. It is also unknown whether ABIN-1 and ABIN-2, the components of the A20 NF-κB inhibitor complex, are inactivated by genetic changes in ocular adnexal mucosa-associated lymphoid tissue lymphoma. A total of 105 cases were investigated for A20 mutation/deletion, *ABIN-1/2* mutation, *MALT1* and *IGH* involved translocation. Somatic mutation was seen frequently in *A20* (28.6%) but rarely in *ABIN-1* (1%) and *ABIN-2* (1%). *A20* mutations were significantly associated with A20 heterozygous deletion, and both were mutually exclusive from the *MALT1* or *IGH* involved translocations. A20 mutation/deletion was also significantly associated with increased expression of the NF-κB target genes *CCR2*, *TLR6* and *BCL2*. The cases with *A20* mutation/deletion required significantly higher radiation dosages to achieve complete remission than those without these abnormalities.

Key words: A20, ABIN, ocular adnexal MALT lymphoma

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Introduction

MALT lymphoma is genetically characterized by recurrent *t(11;18)(q21;q21)/API2-MALT1*, t(1;14)(p22;q32)/*BCL10-IGH*, t(14;18)(q32;q21)/*IGH-MALT1* and t(3;14)(p13;q32)/*FOXP1-IGH*.[1] BCL10 and MALT1 are critical components linking the antigen receptor signaling to the canonical NF-κB activation pathway. Expression of BCL10, MALT1 or API2-MALT1 both *in vitro* and *in vivo* causes NF-κB activation.[1] By analyses of the gene expression profiles, we showed that the NF-κB target genes *CCR2*, *TLR6*, *BCL2* and *CD69* were highly expressed in MALT lymphoma with the above translocations.[2]

The above translocations occur frequently in MALT lymphoma of the stomach and lung, but rarely in those of the ocular adnexa, salivary glands and thyroid.[1] By genomic profiling of translocation negative ocular adnexal MALT lymphoma (OAML), we and others identified *A20* as the target of 6q23.3 deletion.[3-5] Subsequent studies demonstrate that *A20* is also inactivated by somatic mutation and promoter methylation in several lymphoma subtypes.[6-10] Based on a small cohort of OAML, we previously showed that complete A20 inactivation was associated with poor lymphoma-free survival.[11]

A20 is a *global* inhibitor of the NF-κB activation pathway and requires its binding partner, ABIN-1/2/3, to function as an NF-κB inhibitor.[12] We previously showed that *ABIN-1* and *ABIN-2* were also inactivated by somatic mutation in gastrointestinal diffuse large B-cell lymphoma (GI-DLBCL).[13] It is still to be investigated whether *ABIN-1/2* are also mutated in OAML, and whether A20 inactivation impacts on NF-κB activities and clinicopathological presentation.

Design and Methods

Patients and tissue materials

We investigated a total of 105 cases of OAML from the Eye and ENT Hospital, Shanghai. The local ethical guidelines were followed for the use of archival tissues for research with the approval of the

The online version of this article has a Supplementary Appendix. This article is dedicated to Professor Rongjia Chen.
**YB and NZ contributed equally to this manuscript.*
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institution's ethics committees. The diagnosis of OAML was made according to the 2008 WHO classification. Staging was performed by physical examination and CT or MRI scan. The majority of the patients were treated by radiotherapy with Cobalt-60 γ-ray, or deep X-ray or high energy X-ray. A daily radiotherapy dose of 1.8-2.0 gray (Gy) was used with a total dose ranging from 18 Gy to 54.2 Gy (mean 40.6 Gy). The daily dose was determined according to the site and size of the lymphoma, while the total dose was essentially determined by the treatment response. After the first course of radiotherapy, treatment response was routinely assessed by physical examination and CT or MRI scan and, when necessary, a further course of radiotherapy was given.

Microdissection, DNA extraction, PCR and sequencing, FISH, A20 promoter methylation analysis, quantitative RT-PCR, NF-κB reporter assay, immunoprecipitation and statistical analysis were all essentially performed as previously described,[13] and the experimental conditions are described in the *Online Supplementary Appendix and Tables S1 and S2*).

Results and Discussion

A20 *genetic abnormalities in OAML*

A20 deletion was found in 9 of 105 (8.6%) OAML including 2 cases showing homozygous deletion, while *TNFA/B/C* gain was seen in 8 of 105 (7.6%) cases (*Online Supplementary Figure S1 and Table S3*). There was a significant association between *A20* deletion and *TNFA/B/C* gain (P=0.014; Table 1). A total of 37 mutations were seen in 30 of 105 (28.6%) cases, with 7 cases each harboring two mutations (Figure 1A, *Online Supplementary Table S3 and Figure S2*). There was a significant association between A20 mutation and heterozygous deletion (P=0.006, Table 1, *Online Supplementary Table S3*). Pyrosequencing showed promoter methylation in one of 105 (1%) cases, which also displayed an *A20* mutation but not deletion (*Online Supplementary Table S3*).

Among the 37 *A20* mutations identified, the majority (89.2%) would produce truncated proteins due to out-frame insertion/deletion (n=21), nonsense mutation (n=11) or mutation in the splicing site (n=1), and the remaining 4 mutations (10.8%) were missense changes (Figure 1A, *Online Supplementary Table S3*). Of the 30 cases with A20 mutation, 29 harbored at least one mutation that resulted in a truncated protein product. These mutations are very similar in nature to those reported recently (Figure 1A) and would most likely impair A20 function.[6-10] Recent studies have consistently shown that the frameshift and nonsense mutations seen in the *A20* gene were of somatic origin.[6-10,13] Given this, and the fact that 29 of 30 cases showing *A20* mutation in this study contained at least one frameshift or nonsense mutation, we performed germline mutation analysis only in the single case showing a sole missense mutation. The missense mutation in this case was confirmed to be a germline change.

The incidence (28.6%) of *A20* mutation in this series of OAML from Shanghai was higher than those from the UK and the USA (17%)[11] and from Japan (16%),[7] while the incidence of *A20* deletion (8.6%) in this study was lower than those from the UK and the USA (17%)[3,11] and from Japan (21%).[7] Using pyrosequencing, we had previously demonstrated *A20* promoter methylation in 7 of 27 (26%) cases from the UK and the USA,[11] but in only one of 105 (1%) cases in this study. Variable frequencies of *A20* promoter methylation were also seen in DLBCL. By methylation specific PCR, Honma *et al.* showed *A20* promoter methylation in 41.6% of ABC-DLBCL,[10] while by pyrosequencing, we demonstrated *A20* promoter methylation in only 1.4% of GI-DLBCL.[13] The variable frequencies of *A20* abnormalities seen from different studies may be due to several factors including the limited number of cases studied, differences in the sensitivity of the methods used, and possible variations among the different ethnic patient populations investigated.

ABIN-1/2 *mutation in OAML*

A total of 7 *ABIN-1* mutations were seen in 7 of 105 (6.7%) cases. They include 6 missense mutations downstream of AHD4 (n=1), upstream of AHD3 (n=3), within AHD3 (n=1) and NBD (n=1), and a frameshift insertion (n=1) within the Src kinase phosphorylation motif (YPPM) (Figure 1B, *Online Supplementary Table S3*). With the exception of R263W, a germline change in GI-DLBCL,[13] all other mutations found in this study were novel. In 4 cases, it

Table 1. Correlation analysis of A20 genetic abnormalities.

	A20 inactivating mutation			*A20* deletion		
	Positive	Negative	*P*	Positive	Negative	*P*
Age						
< 60	13	42	0.332	4	51	0.475
≥ 60	12	22		4	30	
Sex						
Female	5	22	0.211	2	25	1.000
Male	20	42		6	56	
Site						
Conjunctiva	3	12	0.296	1	14	0.446
Lachrymal gland		2	12		0	14
Orbit	14	25		5	34	
≥ 2 sites	6	15		2	19	
Eye side						
Single	23	53	0.337	8	68	0.598
Bilateral	2	11		0	13	
Clinical stage						
IE	24	64	0.281	8	80	1.000
IIE	1	0		0	1	
TNF copy number gain						
Negative	21	61	0.094	5	77	**0.014**
Positive	4	3		3	4	
MALT1 copy number gain						
Negative	21	55	1.000	5	71	0.089
Positive	4	9		3	10	
MALT1 translocation						
Negative	25	62	1.000	8	79	1.000
Positive	0	2		0	2	
IGH translocation						
Negative	25	61	0.556	8	78	1.000
Positive	0	3		0	3	
ABIN-1 somatic mutation						
Negative	24	63	0.485	8	79	1.000
Positive	1	1		0	2	
ABIN-2 somatic mutation						
Negative	25	62	1.000	8	79	1.000
Positive	0	2		0	2	
A20 heterozygous deletion						
Negative	20	63	**0.006**	-	-	-
Positive	5	1		-	-	

Statistical significance was calculated using Fisher's Exact Test (two-sided).

was possible to investigate the origin of these mutations. The frameshift insertion was shown to be a somatic event, while S140T, P267L and D566W were shown to be germline changes.

A total of 13 *ABIN-2* mutations were seen in 10 of 105 (9.5%) cases and they were made up of 3 recurrent missense mutations: Q249H upstream of AHD1, E255K within AHD1, and A364T downstream of the UBAN domain (Figure 1C, *Online Supplementary Table S3*). In 3 cases, E255K and A364T occurred concurrently, while all the remaining cases harbored only one mutation. In 9 cases, it was possible to investigate the origin of these mutations. With the exception of case 40, in whom A364T was not detected in the normal DNA, all other mutations were

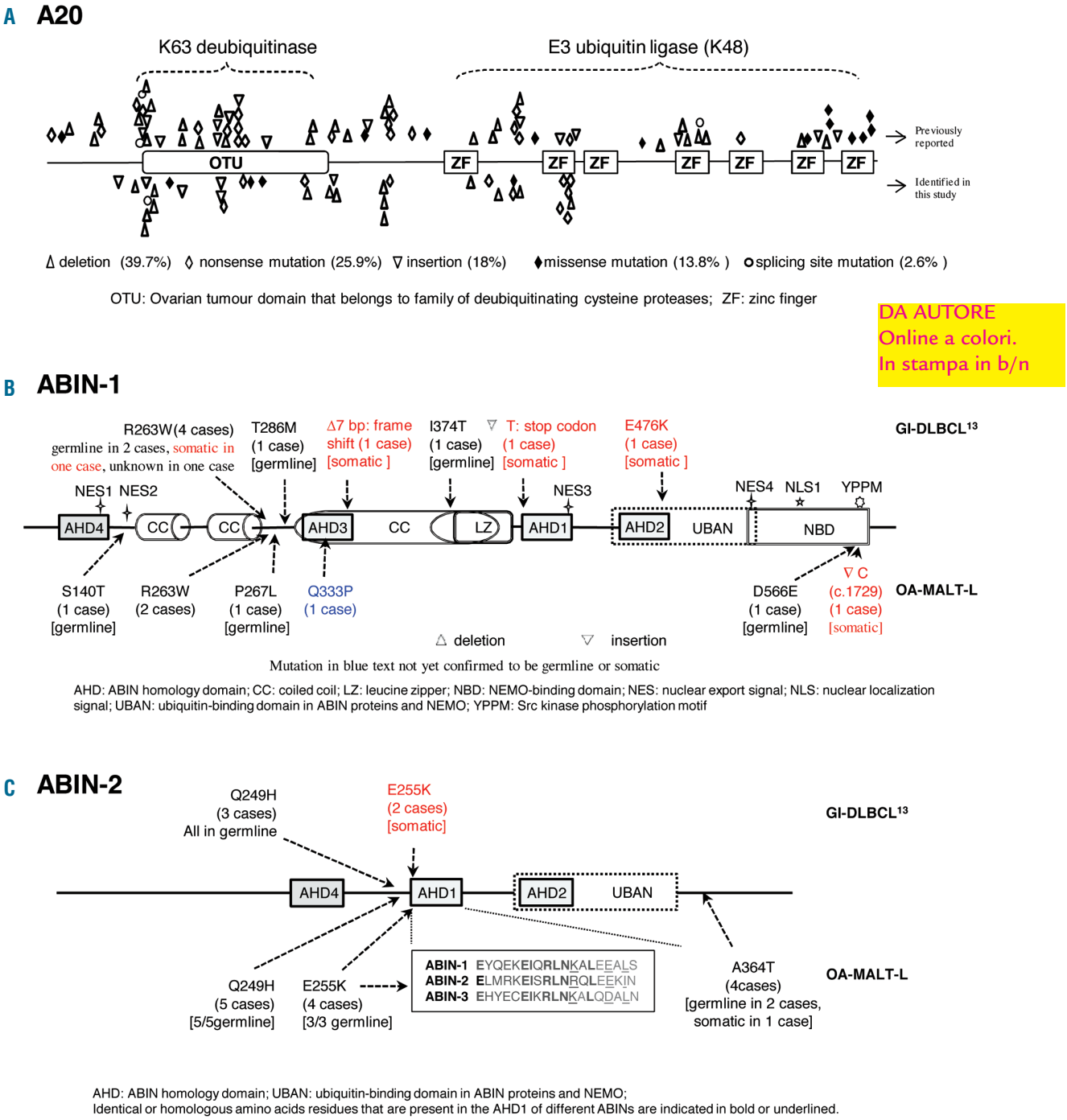

Figure 1. **The distribution of mutations in *A20*, *ABIN-1* and *ABIN-2* in ocular adnexal MALT lymphoma. The *A20* mutations seen in ocular adnexal MALT lymphoma are similar in nature to those reported in DLBCL, Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma and the vast majority are frameshift or nonsense mutations, and thus would impair A20 function.[6-10] The mutations seen in ocular adnexal MALT lymphoma are biased towards the N-terminus. Unlike *A20*, *ABIN-1* and *ABIN-2* are rarely affected by somatic mutation in ocular adnexal MALT lymphoma. Nonetheless, a high proportion of these mutations are within or adjacent to a functional domain.**

shown to be germline changes.

There was no statistical difference in the incidence of the above *ABIN-1* and *ABIN-2* germline mutations between Chinese patients with OAML and a healthy Han Chinese population sequenced by the 1000 genome project (*Online Supplementary Table S4*).

To examine the functional consequence of *ABIN-1* and *ABIN-2* mutations, we first investigated the ability of these mutants to repress NF-κB activation by TNFα in HEK293 cells using a reporter assay, but found no evidence of defect (*Online Supplementary Figure S3*). Given that Abin-1 and Abin-2 deficiency mice studies showed only a small role for these proteins in the suppression of NF-κB signaling,[14,15] it may be difficult to demonstrate the effect of loss of function of ABIN-1/2 by reporter assay due to the presence of other redundant family members. We, therefore, investigated the impact of *ABIN-1/2* mutations on their protein interaction where indicated.

Among the 6 *ABIN-1* mutations identified, 5 were non-recurrent and all occurred in regions poorly characterized in function. Therefore, these were not pursued for further functional characterization. Of the 3 recurrent *ABIN-2* mutations, E255K and Q249H were recurrent. E255K involved a conserved residue in AHD1 that is important for A20 binding, and our previous study had demonstrated that this mutant was defective in A20 binding although not in NF-κB inhibition by a reporter assay.[13] Q249H occurred in the region (amino acids 194-250) upstream of AHD1 which was responsible for TPL2 binding.[16] We, therefore, further investigated the capacity of these ABIN-2 mutants to bind A20 and TPL2 by immunoprecipitation. As expected, both E255K and Q249H showed a reduced capacity in A20 and TPL2 binding (*Online Supplementary Figure S3*), suggesting that these mutations might be pathologically relevant. Interestingly, recent studies have shown a strong link between *A20* and *ABIN* polymorphisms and a range of chronic inflammatory disorders, including systemic lupus erythematosus and rheumatoid arthritis.[17-22] Whether the above *ABIN-1/2* germline mutations predispose to lymphoma development still needs to be investigated.

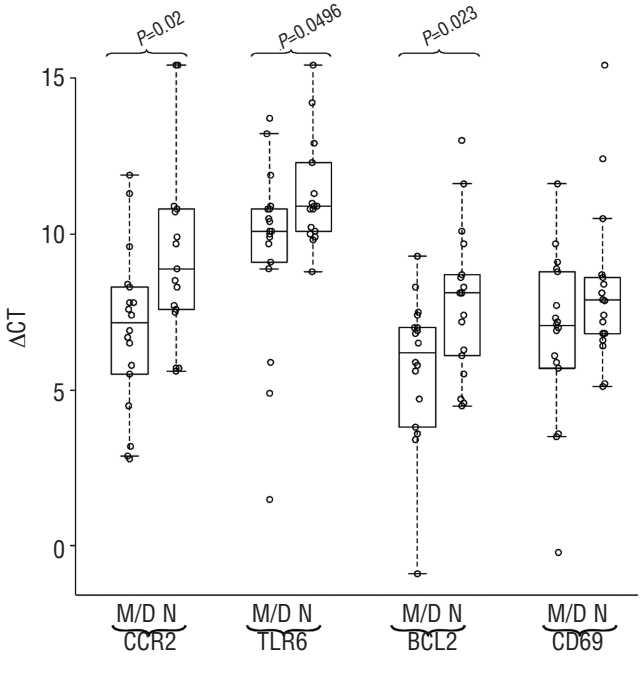

Figure 2. Increased expression of NF-κB target genes in ocular adnexal MALT lymphoma with *A20* inactivating mutation/deletion. The expression of NF-κB target genes *CCR2*, *TLR6*, *BCL2* and *CD69* was measured by qRT-PCR in 18 cases with *A20* inactivating mutation with or without *A20* deletion, and 17 cases without any evidence of *A20*, *ABIN-1/2*, *MALT1* and *IGH* genetic abnormalities. The expression level of *CCR2*, *TLR6* and *BCL2*, albeit not *CD69*, was significantly higher in cases with A20 inactivating mutations/deletion than those lacking these abnormalities. M/D: *A20* inactivating mutation /deletion; N: no *A20*, *ABIN-1/2*, *MALT1* and *IGH* genetic abnormalities.

A20 inactivation correlates with increased expression of NF-κB target genes

Previous analyses of gene expression profiles of MALT lymphoma showed that the NF-κB target genes *CCR2*, *TLR6*, *BCL2* and *CD69* were highly expressed in cases with chromosome translocation.[2] To investigate whether *A20* inactivation by mutation/deletion leads to enhanced NF-κB activities, we measured the expression of the above NF-κB target genes in 18 cases of OAML with *A20* inactivating mutation and 17 cases without any evidence of *A20*, *ABIN-1/2*, *MALT1* and *IGH* genetic abnormalities by quantitative RT-PCR. The expression of *CCR2*, *TLR6* and *BCL2*, although not CD69, was significantly higher in cases with *A20* mutation than those without *A20* genetic abnormalities (Figure 2).

Correlation of A20 genetic abnormalities with clinicopathological parameters

There was no association among *A20* somatic mutation/deletion, *ABIN-1* and *ABIN-2* somatic mutation. T(11;18)(q21;q21)/*API2-MALT1* and t(14;18)(q32;q21)/*IGH-MALT1* were each detected in a single case, while IGH involved translocation with unknown partners was seen in 5 cases. None of these translocation positive cases showed any *A20*, *ABIN-1* and *ABIN-2* genetic abnormalities.

Clinical follow-up data were available in 103 cases (range 12-83 months, median 43 months) and the majority (n=88) were treated by radiotherapy alone. All patients showed favorable treatment response and none showed lymphoma relapse or lymphoma related death. Comprehensive correlation analyses revealed that the cases with *A20* mutation or deletion (range 28.8-53.6 Gy, median 43.4 Gy) required significantly much higher total radiation dosages than those without the *A20* abnormalities (range 18-51.4 Gy, median 39.6 Gy) to achieve complete remission (P=0.049).

Based on a small cohort of OAML from the UK and the USA, we previously showed that complete A20 inactivation was significantly associated with a poor lymphoma free survival.[11] In line with this, our present study demonstrated a significant association between *A20* mutation/deletion and the need for higher total radiation dosages to achieve complete remission. Although the cases in both studies were primarily treated by radiotherapy, there is an important difference in the total radiation dosage used between the two studies. In the previous study, the cases were treated with a total radiation dosage typically around 30 Gy,[23,24] while the cases in the present study were treated with an average total dosage of 40.7 Gy. The use of a higher radiation dosage gives better local control and few lymphoma relapses, but this is frequently associated with a wide range of side effects.[23,24] Not sur-

prisingly, none of the cases in this study showed lymphoma relapse.

In summary, we confirmed that *A20* mutations were significantly associated with *A20* heterozygous deletion and both were mutually exclusive from the *MALT1* and *IGH* involved translocations. Importantly, we have made the following novel observations. Firstly, *A20* mutation/deletion was significantly associated with an increased expression of NF-κB target genes; Secondly, the OAML with *A20* mutation/deletion required significantly higher radiation dosages than those without the *A20* abnormalities to achieve complete remission. Finally, *ABIN-1* and *ABIN-2* were rarely targeted by putative inactivating mutations.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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