Smit *et al.*, 2003). At present, the expression of AID in mantle cell lymphoma, which is derived from naïve B cells or an intermediate cell type between naïve and GC cells (Kolar *et al.*, 2007), is controversial (Babbage *et al.*, 2004; Greeve *et al.*, 2003; Klapper *et al.*, 2006; Smit *et al.*, 2003).

Of note, AID is constitutively expressed in lymphoid crisis in chronic myelogous leukemia (CML) and in Ph1+ pre-B acute lymphoblastic leukemia (ALL), both of which carry a t(9;22) translocation (Feldhahn *et al.*, 2007; Klemm *et al.*, 2009). These studies indicate that AID can be expressed not only in GC-derived B-cell lymphomas, but also in leukemias and lymphomas derived from B cells at various stages of differentiation.

4. AID'S POTENTIAL IMPORTANCE IN HUMAN B-CELL MALIGNANCIES

The presence of AID in a variety of human B-cell malignancies supports the assumption that AID plays a critical role in their initiation or progression. However, the AID levels expressed in these malignancies do not always correlate with the SHM level in the IgV gene or in oncogenes (Heintel *et al.*, 2004; McCarthy *et al.*, 2003; Pasqualucci *et al.*, 2004; Smit *et al.*, 2003). Moreover, AID expression is not always associated with ongoing mutations (Lossos *et al.*, 2004; Pasqualucci *et al.*, 2001, 2004; Smit *et al.*, 2003), although a clear association is observed in LPHL (Greiner *et al.*, 2005; Hardianti *et al.*, 2004b; Mottok *et al.*, 2005). The dissociation between AID expression and SHM activity can be explained at least in part by two possibilities: (1) the SHM machinery or AID itself is functionally impaired in tumor cells; or (2) AID may introduce mutations at earlier stages of the disease, but in later stages, AID may be shut off.

Nevertheless, AID expression is correlated with a poor prognosis in several human B-cell lymphomas and leukemias. As mentioned above, AID is associated with UM B-CLL, which has a poorer prognosis than M B-CLL (Heintel *et al.*, 2004; McCarthy *et al.*, 2003). High AID expression is restricted to a tumoral cell subpopulation with ongoing CSR and associated with aberrant SHM in the *c-myc*, *Pax5*, and *RhoH* genes. It is also associated with the transformation into a more aggressive lymphoma, which supports a potential role of AID as a new prognostic marker for B-CLL (Palacios *et al.*, 2010; Reiniger *et al.*, 2006).

In addition, significantly higher AID expression has been observed in a subgroup of DLBCL cases with a significantly poorer prognosis (Lossos *et al.*, 2004; Pasqualucci *et al.*, 2004). DLBCLs are categorized into three subgroups based on their gene expression profiles: the GC B-cell-like (GCB), activated B-cell-like (ABC), and type III DLBCL subgroups. The ABC subgroup has a poorer survival rate (Alizadeh *et al.*, 2000; Rosenwald *et al.*,

2002) and significantly higher AID levels than the other subgroups, although AID is highly expressed in all three subgroups (Lossos *et al.*, 2004; Pasqualucci *et al.*, 2001). Similarly, the association between AID and a poor prognosis was examined in primary cutaneous large B-cell lymphomas (PCLBCLs), which are divided into two main groups: primary cutaneous follicle center lymphoma (PCFCL), which is indolent, and PCLBCL, leg type (PCLBCL-leg), which has an intermediate prognosis (Willemze *et al.*, 2005). Aberrant SHM in the *Bcl6*, *Pax5*, *RhoH*, and/or *c-myc* genes was observed in cases of both PCFCL and PCLBCL-leg, and the AID expression level was significantly higher in PCLBCL-leg than in PCFCL (Dijkman *et al.*, 2006). This observation is consistent with the fact that PCFCL and PCLBCL-leg gene expression profiles are similar to those of GCB and ABC DLBCL, respectively (Hoefnagel *et al.*, 2005).

Finally, two out of seven FL cases with clinical and histological progression showed elevated AID expression and the selective outgrowth of AID-expressing clones during the transformation into DLBCL, suggesting that AID is involved in the transformation from indolent FL to aggressive DLBCL (Smit *et al.*, 2003). These observations suggest that AID may play a role in tumor evolution, and that AID may be useful as a new prognostic marker in certain human B-cell malignancies. In Ph1+ ALL and in the lymphoid blast crisis of CML that carries t(9;22), it is hypothesized that Bcr-abl kinase, which is derived from t(9.22), activates AID, and that AID subsequently introduces mutations into various oncogenes, resulting in clonal evolution. There is considerable interest in treatment with Imatinib, an abl kinase inhibitor. The first molecularly targeted Imatinib therapy dramatically improved the prognosis of Ph1+ ALL and CML. However, *bcr-abl* kinase domain mutations cause resistance to Imatinib, especially in the T315I leukemic clone, which is resistant to all abl kinase inhibitors. AID is involved in generating the T315I mutation in *bcr-abl* (Feldhahn *et al.*, 2007; Gruber *et al.*, 2010; Klemm *et al.*, 2009). Splicing variants have also been identified in Ph1+ ALL (Iacobucci *et al.*, 2010). Further analyses of the molecular mechanisms underlying these mutations and their clinical relevance are required.

C. Normal and Pathogen-Induced AID Expression

1. PATHOGEN-INDUCED AID EXPRESSION

Association studies of AID expressed in various pathogen-induced tumors have clarified its involvement in tumorigenesis. In humans, AID is abundantly expressed in EBV-positive BL cells (Table V). This is probably due to the expression of LMP1 on the cell surface, which mimics continuous CD40

Table V Pathogen-Induced Human Malignant Tumors

Pathogen	Type of cancer	Origin	AID expression	Inducer
HTLV-1	ATL		+	Tax[a]
EBV	BL	GC B cell	+	LMP1[b]
	CHL	GC B cell	–	
	Gastric cancer	Gastric epithelial cells	?	
	Nasopharyngeal carcinoma	Epithelial cells	?	
HCV	Hepatoma	Hepatocyte	+	TGF-beta signaling[c]
	DLBCL	GC B cell	+	NF-κB signaling[d]
H. pylori	Gastric cancer	Gastric epithelial cells	+	NF-κB signaling[e]
	MALT lymphoma	Marginal zone B cells	?	
Papilloma virus	Cervical cancer	Cervical epithelial cells	?	

ATL, acute T-cell lymphoma/leukemia; BL, Burkitt lymphoma; CHL, classical Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; GC B cell, germinal center B cell
[a]Ishikawa *et al.* (2011).
[b]Epeldegui *et al.* (2007).
[c]Kou *et al.* (2007).
[d]Machida *et al.* (2004).
[e]Matsumoto *et al.* (2007).

signaling stimulation. More recently, many tumor-causing viruses have been shown to induce AID expression in both B and non-B cells. AID is frequently expressed in adult T cell leukemia cells caused by HTLV-1 infection (Ishikawa *et al.*, 2011). The HTLV-1 Tax oncogene, when overexpressed in T cells, activates the *Aicda* gene in a CREB- and NF-κB-dependent manner (Ishikawa *et al.*, 2011; Nakamura *et al.*, 2011). Tumorigenesis occurs in transgenic mice for Tax or bZIP, which are HTLV-1 oncogenes; it will be interesting to test whether AID is required for this T-cell tumor (Satou *et al.*, 2011; Yamazaki *et al.*, 2009). Hepatitis C virus (HCV) also induces AID. HCV hepatocyte and B cell infection induces AID via NF-κB signaling (Endo *et al.*, 2007; Machida *et al.*, 2004). Increasing epidemiological evidence has highlighted the close correlation between HCV infection and B-NHL (de Sanjose *et al.*, 2008; Turner *et al.*, 2003). Thus, it is tempting to hypothesize that the upregulation of AID in HCV infected B cells is at least partly responsible for HCV related DLBCL lymphomagenesis. Further, *H. pylori*, a gastric cancer-causing agent, also induce AID in the gastric epithelium (Matsumoto *et al.*, 2007). Kim *et al.* (2007) reported that 73 of 186 sporadic

gastric cancers examined expressed AID. The majority of pathogens known to induce tumors are connected with AID expression. AID expression has also been reported in colitis-associated colorectal cancers (Endo *et al.*, 2008), in epithelial breast cancer cell lines (Babbage *et al.*, 2006), in hepatoma (Kou *et al.*, 2007), and in cholangiocarcinoma (Komori *et al.*, 2008). It is not known whether the papilloma virus, which causes cervical cancer, induces AID; this has not yet been studied.

2. REGULATION OF AID EXPRESSION

It is important to understand how AID is regulated. How is AID restricted to B cells? How can AID be expressed in infected non-B cells? Tran *et al.* (2010) extensively analyzed the promoter *Aicda* in CH12F3-2 cells. Evolutionary conservation reveals four candidate regions for regulatory elements within and surrounding the *Aicda* locus. The R1 region located 5′ to the transcription initiation site contains Sp and HoxC4-Oct binding elements, which have relatively weak activity (Park *et al.*, 2009; Tran *et al.*, 2010; Yadav *et al.*, 2006). The R2 region located in intron 1 contains the Pax5 and E2A elements, which are the most important B cell-specific transactivation motifs. The most striking feature in the R2 region is the presence of negative regulatory elements that may be responsible for suppressing the *Aicda* expression in non-B cells. Transgenic analysis showed that the R3 region located further downstream of the *Aicda* locus has transactivation activity (Crouch *et al.*, 2007). However, in an *in vitro* luciferase assay system, the locus did not show clear activity (Tran *et al.*, 2010). It was recently reported that BATF, which may directly regulate *Aicda* expression, binds to the R3 region (Ise *et al.*, 2011). The R4 region, located further upstream of the R1 region, contains multiple elements that respond to exogenous stimulation, such as NF-κB, STAT6 (which responds to IL-4), and Smad3/4 (Tran *et al.*, 2010). Estrogen has been reported to enhance *Aicda* expression, but whether it regulates *Aicda* directly or indirectly is still contradictory (Mai *et al.*, 2010; Pauklin *et al.*, 2009). Further, recent studies have shown another layer of AID expression regulation by microRNA-155 (Dorsett *et al.*, 2008; Teng *et al.*, 2008).

Qin *et al.* used genetic marking to examine cell lineages that had experienced AID expression. Transgenic *Aicda-cre* BAC mice were crossed with Rosa26 reporter mice (R26R or Rosa-tdRFP) (Kwon *et al.*, 2008; Qin *et al.*, 2011) to create a system that marks any cell that has expressed AID. This sensitive method substantially marked not only B-lineage cells, but also T-lineage cells. In particular, $CD4^+$ T cells were consistently marked and accumulated with age; by 18 months of age, up to 25% of these cells were marked as having experienced AID expression (Qin *et al.*, 2011). These cells exhibited an effector-memory phenotype, producing IL-10 and IFN-γ. Marked cells were generated by adoptively transferring naïve $CD4^+$ T cells

into a T cell-deficient host, suggesting that specific environmental stimuli may be involved in AID expression in T cells. However, because AID-experienced $CD4^+$ T cells can be generated in a B cell-deficient background, a germinal center environment is not essential (Qin *et al.*, 2011). An AID-experienced population was observed in the natural killer cell fraction, as well (Qin *et al.*, 2011). These results indicate that AID can be expressed in non-B lineage cells even under normal conditions. Thus, it is reasonable to imagine that chronic infection may induce AID expression even in nonlymphoid cells.

V. CODA

An evolutionary consideration of the AID mechanism reveals that AID shares its DNA cleavage mechanism with several types of genome instability mechanisms such as TAM and triplet contraction/expansion, which depend on Top1 nicking activity. These mechanisms also share a dependency on transcription, and probably on non-B structural formation induced by excessive negative supercoil. This indicates that AID does not necessarily uniquely target Ig genes. Many genes that form transcription-induced non-B structures could be candidates for AID targeting, but this requirement is not sufficient, because the AID-induced DNA cleavage also depends on chromatin H3K4me3 modification. In fact, even this mark may not be sufficient and other modifications may be required. This dilemma which has arisen when AID was introduced in vertebrates appears to be resolved at least in part by dual restriction of AID target; non-B structure and chromatin modification; while AID probably took advantage of transcription-induced genome instability to amplify immunoglobulin at the somatic level, it was almost impossible to limit its target. Therefore, AID expression was limited rather strictly to B cells. Nonetheless, AID expression is not absolutely regulated; recent studies clearly indicate that many pathogens can activate AID in non-B cells.

However, AID activation alone is not sufficient for tumorigenesis. This is seen in the fact that tumors do not develop until at least a few months after transgenic AID-induced tumorigenesis; in fact, most viral or pathogenic tumorigenesis takes years. It is possible that AID introduces mutations in various target genes, including oncogenes, while virus infection makes target cells immortal and induces AID activation. The immortalization gradually accumulates AID-induced mutations, and eventually tumor cells are selected and quickly expand. It is therefore reasonable for vertebrates to take advantage of AID-enabled immune diversification in spite of the tumorigenesis risks. Since SHM is acutely required to prevent infection, we have to accept the long-term risk of tumorigenesis.

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血液疾患・免疫疾患における エクソソームの役割

Role of Exosome in Hematological / Immune Disorder

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血液疾患・免疫疾患においても，他の疾患と同様，エクソソームは診断マーカーとして期待され，精力的に研究が行われている．さらに最近，デコイエクソソームを介したリンパ腫の抗体療法逃避機構や，1型糖尿病マウスにおけるエクソソーム単独での炎症惹起など，興味深い知見も得られてきた．本稿では，血液疾患・免疫疾患におけるエクソソームの役割について最近のトピックを紹介しながら，エクソソームを標的とした治療法開発の可能性について解説する．

key words　デコイエクソソーム，Mφ，炎症

はじめに

エクソソームは早くからワクチンとしての効果が期待され，これまでに多くの研究が行われてきた．さらにはドラッグデリバリーのキャリアとしても近年精力的に行われている（黒田氏らの稿参照）．本稿では，血液疾患の1つである悪性リンパ腫，またEB（Epstein-Barr）ウイルス（以下，EBV）感染および自己免疫疾患におけるエクソソームの役割について最近のトピックを紹介する．

Ⅰ 血液疾患・免疫疾患における診断マーカーとしてのエクソソーム

近年，エクソソーム研究があらためて脚光を浴びた1つの理由はエクソソーム中にmiRNAが内包されていることが明らかになったからであるが，エクソソーム内外の分泌性miRNAが診断マーカーになることはこれまでにも多く発表されている．特に，がんの早期診断マーカーとしての有用性については数多く報告されており，本邦からも急性白血病において先進的な仕事が発表された[1]．

これに対してまだ多くの自己免疫疾患において有効な初期病変の鑑別に役立つ診断マーカー，病勢を示す生物学的指標は見つかっておらず，後れをとっている感は否めない．だが，自己免疫疾患においても体液中のエクソソームを標的とした診断マーカーの探索が有用と考えられている．現在のところ，簡便に検体採取ができるというメリットから，自己免疫腎疾患について尿中エクソソームを用いた診断マーカー探索が精力的に行われている．腎疾患の多くはタンパク尿，血尿を初期症状とするものが多いが，鑑別診断には人体に侵襲的な腎生検が必要となるからである．IgA腎症や膜性腎症もそのような初期症状を呈するが，両者の鑑別診断マーカーになりうる尿中エクソソームマーカーとしてaminopeptidase N, vasorin precursor, α 1-antitrypsin, ceruloplasminなどが報告されている[2]．

ネフローゼ症候群の予後マーカーになりうるエクソソーム内包タンパク質の検討も行われた．ネフローゼ症候群では初期に大量のタンパク尿が認められるが，大半はステロイド治療が奏功し，予後良好である．しかし，中にはステロイドに対して抵抗性を示す症例もある．そこで，すでに腎臓の足細胞の障害を反映するマーカーとして報告されていた尿中エクソソーム中のWt1についてステロイド抵抗性との因果関係が調べられたが，残念ながら因果関係は認められなかった[3]．

Ⅱ デコイエクソソームを介したリンパ腫の抗体療法逃避機構

多くのB細胞性非ホジキンリンパ腫（B-NHL）では，正常B細胞同様にCD20の発現が認められる．これを標的とする抗ヒトCD20ヒト・マウスキメラ型モノクローナル抗体リツキシマブ単独，または併用化学療法などが標準的治療法の1つとしてすでに確立されている．リツキシマブは標的細胞に対して殺細胞作用を有するが，その機序としては主に，①補体依存性細胞傷害作用（CDC），②抗体依存性細胞傷害作用

可能性は十分にある．単一分子による細胞間コミュニケーション手段の存在は，これまでの概念を大きく展開・発展させる可能性がある．今後の詳細な研究が待たれる．

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