ANTICANCER DRUGS

Assault on MALT1

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Activated B cell-like diffuse large-B cell lymphomas (ABC-DLBCLs) are aggressive lymphomas that are characterized by nuclear factor-κB (NF-κB) hyperactivation, which is often mediated by the upstream proteolytic activity of mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1). Two new studies have identified small-molecule inhibitors of MALT1 that show anticancer activity *in vitro* and *in vivo*.

Although a peptide-based inhibitor of MALT1 exists, its poor pharmacological properties have motivated the search for alternative, small-molecule, inhibitors. Nagel *et al.* and Fontan *et al.* engineered dimeric, active forms of MALT1, and they collectively screened almost 65,000 compounds for their ability to inhibit the MALT1-mediated cleavage of a fluorescent reporter peptide. Following various validation studies, Nagel *et al.* focused on phenothiazines, particularly mepazine and thioridazine, and Fontan *et al.* focused on a novel compound that they termed MALT1 inhibitor 2 (MI-2).

In ABC-DLBCL cells, these molecules impaired cleavage of MALT1 substrates and decreased NF-κB signalling and target gene expression, which was consistent with MALT1 inhibition.

Both groups found that their compounds induced apoptosis in ABC-DLBCL cell lines at low micromolar concentrations. Importantly, this cytotoxicity was not seen in DLBCL cells of the germinal centre B cell-like (GCB) subtype, implying that these compounds achieve selectivity for ABC-DLBCL cells. However, not all ABC-DLBCL cell lines were responsive: Fontan *et al.* found that a subset of ABC-DLBCL cell lines with MALT1-independent NF-κB activation were resistant, and Nagel *et al.* induced resistance by expressing a mutant form of IKKβ that activates NF-κB signalling. This indicates that, if these compounds are used clinically, the lymphomas should be verified as being MALT1-dependent, because intrinsic or acquired resistance can occur through lesions downstream of MALT1 that activate NF-κB signalling.

Turning to more physiological settings, both groups found that their inhibitors could slow the growth of established MALT1-dependent ABC-DLBCL xenografts, but that the effects on GCB-DLBCLs or on normal tissues were minimal. Furthermore, both groups showed that primary human ABC-DLBCL samples underwent apoptosis in response to MALT1 inhibitors *ex vivo*.

Despite many shared biological outcomes of these compounds, the authors showed that they function by distinct biochemical mechanisms, which may affect their future use. MI-2 is an irreversible, covalent inhibitor of MALT1 with an apparent ability to accumulate inside cells, which might result in sustained MALT1 inhibition. By contrast, mepazine and thioridazine are reversible MALT1 inhibitors, and previous clinical experience of these drugs for neurological symptoms might facilitate their adoption in cancer trials. Finally, it will be interesting to see whether MALT1-targeted agents, alone or in combination, can be developed to achieve the regression of established ABC-DLBCLs (or any other MALT1-dependent cancer types) in mice and humans.

Darren J. Burgess
Assistant Editor,
Nature Reviews Cancer *and* Nature Reviews Genetics

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ORIGINAL RESEARCH PAPERS Nagel, D. *et al.* Pharmacologic inhibition of MALT1 protease by phenothiazines as a therapeutic approach for the treatment of aggressive ABC-DLBCL. *Cancer Cell* **22**, 825–837 (2012) | Fontan, L. *et al.* MALT1 small molecule inhibitors specifically suppress ABC-DLBCL in vitro and in vivo. *Cancer Cell* **22**, 812–824 (2012)