KINASE INHIBITORS

A molecular target for myelodysplastic syndromes

> A small-molecule inhibitor of IRAK1 inhibited NF-κB activation and selectively induced a cytostatic effect in MDS cell lines.

Inhibition of interleukin-1 receptor-associated kinase 1 (IRAK1) could be a new therapeutic approach for myelodysplastic syndromes (MDSs).

MDSs comprise a diverse group of blood disorders characterized by a deficiency in the production of myeloid lineage cells. They are also known to predispose the patient to acute myeloid leukaemia. Treatment options for MDSs are limited and although cure can be achieved through stem cell transplants, this is not suitable for all patients.

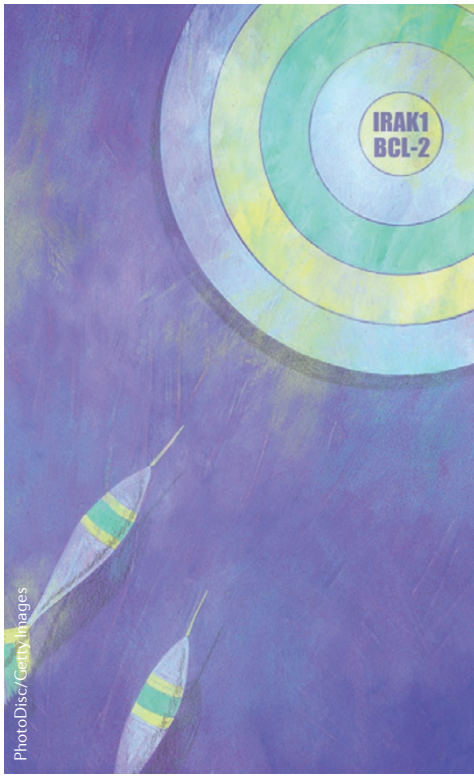
Previous studies showed that the innate immune system is implicated in the pathophysiology of MDSs, and that IRAK1 — a serine/threonine kinase in the pathway leading to activation of the transcription factor nuclear factor-κB (NF-κB) — is a key protein in this system. Consequently, Starczynowki and colleagues investigated whether IRAK1 could represent a druggable target in innate immune signalling in MDSs.

First, they confirmed that IRAK1 is overexpressed and activated in MDS $CD34^+$ bone marrow cells compared with normal cells. Furthermore, high levels of IRAK1 expression correlated with reduced overall survival. Then, the authors showed that a small-molecule inhibitor of IRAK1 (IRAK-Inh; previously developed for the treatment of autoimmune disease) inhibited NF-κB activation and selectively induced a cytostatic effect in MDS cell lines.

In mice bearing an MDS patient-derived cell line xenograft, intraperitoneal injection of IRAK1-Inh reduced the level of engrafted cells in peripheral blood, whereas untreated mice developed disease.

The effects and specificity of IRAK-Inh were validated by knocking down IRAK1 with a specific short hairpin RNA (shRNA) in MDS cell lines. Interestingly, as well as inducing cytostatic effects, knockdown of IRAK1 also induced a greater degree of apoptosis than IRAK-Inh. Gene expression analysis revealed that pharmacological inhibition of IRAK1 led to an upregulation of pro-apoptotic genes, but also to an unexpected compensatory upregulation of anti-apoptotic genes (such as those belonging to the BCL-2 family). By contrast, knockdown of IRAK1 with the shRNA did not result in a compensatory upregulation of anti-apoptotic genes. The authors suggest that this might explain the reduced capacity of IRAK1-Inh to induce apoptosis. Indeed, an increase in BCL-2 expression was seen in the MDS cell lines tested, which was not observed when IRAK1 was knocked down with the IRAK1-specific shRNA.

Following up these observations, a small-molecule BCL-2 inhibitor (ABT-263) was evaluated for its effects on MDS cell lines and patient-derived cells. Interestingly, co-treatment of cells with IRAK1-Inh and ABT-263 led to synergistic effects on cell growth and survival compared with when cells were treated with each inhibitor alone. Moreover, co-treatment of mice bearing an MDS patient-derived cell line resulted in greater survival (43 days) compared with those treated with individual drugs (~35 days).



Together, these data provide a molecular basis to target IRAK1, and BCL-2, to treat MDSs.

Man Tsuey Tse

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