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In This Issue

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Receptor tyrosine kinase inhibitor beneficial in infectious disease Receptor tyrosine kinase inhibitors (RTKIs) are routinely used to treat several forms of cancer, but whether they would be effective therapeutics for the treatment of infectious diseases has not been determined. In this issue (1204–1216), Dalton and colleagues have started to address this question, showing that the broad-spectrum RTKI sunitinib maleate (Sm) blocks several symptoms of disease in mouse models of visceral leishmaniasis, a neglected tropical disease caused by the protozoan parasites Leishmania donovani and L. infantum. Specifically, administration of Sm prevented the vascular remodeling and progressive splenomegaly associated with experimental visceral leishmaniasis and restored splenic microarchitecture. Despite these effects on symptoms, Sm treatment alone did not cause a reduction in tissue parasite burden. However, sequential administration of Sm and a conventional antileishmanial drug led to effective parasite clearance with ten-fold less of the conventional drug than normally required to achieve this effect. The authors therefore suggest that using an RTKI prior to administration of conventional drugs might be clinically useful in the treatment of visceral leishmaniasis as well as other diseases involving lymphoid tissue remodeling, including cancer. miR-31 an oncomir in the lung MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression at the posttranscriptional level in both healthy and malignant tissues. Liu and colleagues therefore set out to […]

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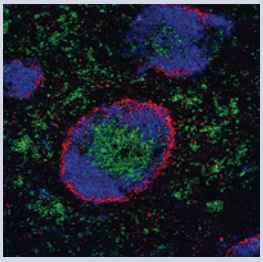
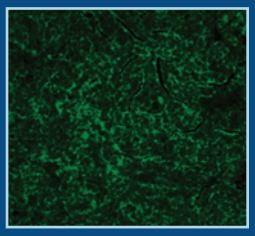


Receptor tyrosine kinase inhibitors (RTKIs) are routinely used to treat several forms of cancer, but whether they would be effective therapeutics for the treatment of infectious diseases has not been determined. In this issue (1204–1216), Dalton and colleagues have started to address this question, showing that the broad-spectrum RTKI sunitinib maleate (Sm) blocks several symptoms of disease in mouse models of visceral leishmaniasis, a neglected tropical disease caused by the protozoan parasites *Leishmania donovani* and *L. infantum*. Specifically, administration of Sm prevented the vascular remodeling and progressive splenomegaly associated with experimental visceral leishmaniasis and restored splenic microarchitecture. Despite these effects on symptoms, Sm treatment alone did not cause a reduction in tissue parasite burden. However, sequential administration of Sm and a conventional antileishmanial drug led to effective parasite clearance with ten-fold less of the conventional drug than normally required to achieve this effect. The authors therefore suggest that using an RTKI prior to administration of conventional drugs might be clinically useful in the treatment of visceral leishmaniasis as well as other diseases involving lymphoid tissue remodeling, including cancer.

Overcoming multidrug resistance in ALL

A strong predictor of poor outcome in children with acute lymphoblastic leukemia (ALL) is resistance to first-line cytotoxic chemotherapeutics, in particular glucocorticoids. One possible way to overcome this drug resistance is to promote the induction of cell death pathways. Bonapace and colleagues have now shown that this approach could work: subcytotoxic concentrations of obatoclax, a drug thought to promote cell death by antagonizing BCL-2 family members, resensitized multidrug-resistant childhood ALL cells to glucocorticoids and other cytotoxic agents in vitro (1310–1323). This reversal of glucocorticoid resistance occurred through rapid activation of autophagy-dependent necroptosis. Execution of cell death required the autophagy regulators beclin-1 and ATG-7 as well as the necroptosis regulators receptor-interacting protein (RIP-1) kinase and cylindromatosis (turban tumor syndrome) (CYLD). Interference with each of these regulators prevented the in vitro sensitization to glucocorticoid by obatoclax completely. Importantly, in vivo combination of obatoclax and dexamethasone markedly delayed progression to leukemia in mice xenografted with leukemic cells from patients with multidrug-resistant ALL. Further, as obatoclax had broad in vitro chemosensitizing activity, the authors suggest that their data provide the rationale for translating their approach into the clinic to treat multidrug-resistant ALL.

miR-31 an oncomir in the lung



MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression at the posttranscriptional level in both healthy and malignant tissues. Liu and colleagues therefore set out to identify the miRNAs that are overexpressed in lung cancer and to determine whether any of these function as oncogenic miRNAs (oncomirs) (1298–1309). Initial miRNA microarray expression profiling, real-time RT-PCR, and in situ hybridization indicated that miR-136, miR-376a, and miR-31 were all overexpressed in mouse and human malignant lung tissue compared with paired normal tissue. Importantly, knockdown of miR-31 repressed the in vitro growth of mouse and human lung cancer cell lines and reduced the in vivo tumorigenicity of mouse lung cancer cell lines. Further bioinformatic and in vitro analyses provided a potential mechanism by which modulation of miR-31 expression levels could affect lung cancer cell growth: miR-31 repressed expression of the tumor-suppressor genes large tumor suppressor 2 (*LATS2*) and PP2A regulatory subunit B alpha isoform (*PPP2R2A*). As miR-31 and these target mRNAs were inversely expressed in human lung cancers, the authors conclude that their data have clinical relevance and that miR-31 acts as an oncomir in lung cancer by repressing expression of specific tumor suppressors.

Sealing the deal to block heart failure in dystrophic dogs

Duchenne muscular dystrophy (DMD) is caused by lack of the cytoskeletal protein dystrophin, which leads to muscle membrane instability. While the hallmark of DMD is progressive skeletal muscle wasting, heart failure is emerging as a leading cause of death for individuals with DMD, and there are currently no effective therapies for this fatal clinical consequence of DMD. But now, Townsend and colleagues have found that chronic intravascular infusion of membrane-sealing poloxamer blocks advanced heart disease in the golden retriever muscular dystrophy (GRMD) model of DMD (1140–1150). Of particular relevance to this effect, poloxamer limited myocardial fibrosis and prevented left ventricular remodeling. Further analysis revealed a cellular basis for the more severe heart disease in the dog model of DMD compared with the mouse model. Dystrophic canine myocytes had substantially lower cellular compliance than dystrophic mouse myocytes, as a result of a lack of upregulation of the dystrophin homolog utrophin. Direct application of poloxamer to dystrophic canine cardiac myocytes restored their compliance to normal. The authors therefore suggest that membrane-sealant therapy could provide a new approach to treating DMD heart disease.