CANCER

Potential new role for antimalarial agents in the treatment of gastrointestinal stromal tumors

New findings indicate that the success of imatinib mesylate treatment for gastrointestinal stromal tumors (GISTs) could be improved by giving it in combination with an antimalarial agent, such as chloroquinone or quinacrine.

The treatment of metastatic GISTs was transformed by imatinib—a small molecule inhibitor of the KIT receptor tyrosine kinase. "However, we were struck by the fact that less than 2% of GISTs regress completely after treatment with imatinib, leaving variable numbers of quiescent GIST cells," explain Brian Rubin and Jayanta Debnath, the study's corresponding authors. To prevent clinical progression of quiescent GIST cells, imatinib must be taken indefinitely, but chronic therapy can lead to development of acquired imatinib resistance.

"We were motivated to try to understand how GIST cells enter into a state of quiesence instead of dying," say Rubin and Debnath. Evidence suggests that autophagy—a lysosomal self-digestion process that allows energy and nutrient recycling during periods of starvation or stress—promotes survival of tumor cells in response to chemotherapy. The researchers hypothesized that autophagy facilitates GIST cell survival in response to treatment with imatinib.

To try to understand the processes involved, Rubin, Debnath and colleagues adopted a multifaceted approach. Novel isogenic cell lines (two sensitive and one resistant to imatinib) were developed and used to confirm that imatinib is not effective at killing GIST cells, but that it induces reversible quiescence and autophagy. Autophagosome formation, a hallmark of autophagy, was then shown to occur in resected GIST samples taken from patients who had been treated briefly with imatinib (for 3, 5 or 7 days) and to correlate with a decrease in cell death.

The reasearchers also used RNAi to knockdown two vital autophagy regulators and found that this promoted the death of imatinib-treated GIST cells. Finally, Rubin, Debnath and colleagues studied the effect of treatment with imatinib plus lysosomotrophic antimalarial agents, which block the final stages of autophagic degradation. Combination treatment promoted cell death whilst abrogating imatinib resistance in both an imatinib-sensitive cell line and an imatinib-sensitive mouse xenograft model.

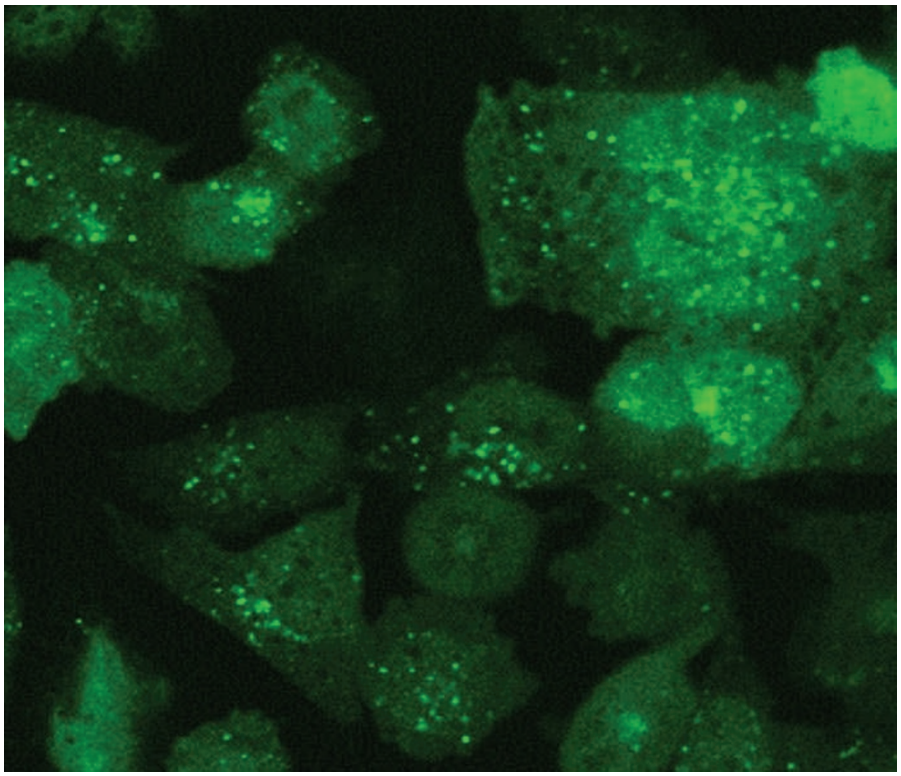
"Our study is the first study to show conclusively that autophagy facilitates GIST cell survival after treatment with imatinib. It is also the first study to demonstrate that inhibition of autophagy synergizes with imatinib in the treatment of GIST."

The authors are currently working towards understanding how autophagy is activated by inhibition of KIT and whether autophagy contributes to survival of GIST stem cells. They are confident that it should be relatively straightforward to investigate the effects of combination therapy with imatinib plus an autophagy inhibitor in a clinical trial. Autophagy inhibitors have been used in the clinic in the form of antimalarial agents for many years and have well-understood toxicity profiles.

Rubin and Debnath hope their work will now "encourage industry to develop better and more targeted autophagy inhibitors for use in cancer therapy".

Natalie J. Wood

GFP-microtubule-associated protein light chain 3 puncta, representing autophagosomes, detected in GIST cells 8h after treatment with imatinib. Courtesy of B. Rubin and J. Debnath.



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