Thyroxine: MIFfed about sepsis

By Michael J. Haas, Senior Writer

A U.S. research team has shown that D-thyroxine, an old hyperlipidemia drug from **Abbott Laboratories**, promotes survival in mouse models of sepsis by inhibiting the proinflammatory cytokine MIF.¹ The team is planning a clinical trial of the drug to treat sepsis, but a better approach may be to develop thyroxine analogs.

Macrophage migration inhibitory factor (MIF) plays a key role in sepsis pathogenesis, and high serum levels of MIF in severe sepsis are associated with poor outcomes.² Additionally, sepsis patients often have low serum levels of the thyroid hormone L-thyroxine (levothyroxine; T₄), and these low levels are associated with severe disease and poor prognosis.³

Based on those two observations, a team led by Yousef Al-Abed hypothesized that MIF and L-thyroxine directly interact in sepsis. Supporting this hypothesis was a previous study by study by Al-Abed and colleagues at **Yale School of Medicine** showing that thyroxine shared a structural feature with a small molecule MIF antagonist called ISO-1.⁴

Al-Abed is professor of medicinal chemistry and director of the laboratory of medicinal chemistry at **The Feinstein Institute for Medical Research** and professor of molecular medicine at the **Hofstra North Shore-LIJ School of Medicine at Hofstra University**.

Now, his team has shown that high serum levels of MIF correlate with low L-thyroxine levels in severe sepsis patients and in rat models of the indication.

Molecular modeling and *in vitro* binding assays showed that the two isomers of thyroxine—the hormonally active L-thyroxine and the hormonally inert D-thyroxine (dextrothyroxine; D-T₄)—bound the same catalytic domain on MIF to inhibit its proinflammatory activity.

As a hormonally inert compound would clearly be preferable in sepsis, the team turned to D-thyroxine and showed the molecule increased survival in mouse models of sepsis compared with vehicle.

In 1967 Abbott received **FDA** approval for D-thyroxine to treat hyperlipidemia and marketed the drug as Cholestyramine dextrothyroxine sodium to treat the indication. The product was later discontinued. The company was not available to disclose the year and reason for the discontinuation.

Al-Abed told *SciBX* that D-thyroxine was a more attractive clinical candidate than ISO-1 or other MIF antagonists identified by his group "because it has already been used in humans, so in principle we should be able to run a clinical trial very soon."

Data were published in the *Proceedings of the National Academy of Sciences*. The team also included researchers from **North Shore University Hospital** and **The Translational Genomics Research Institute**.

"The biology of MIF as a critical component in inflammation has been studied for a long time, but the utility of targeting it" to treat cancer, autoimmune disease and other inflammatory indications has not always been clear from preclinical studies, said Randall Riggs, president and CEO of MIF inhibitor company **Advanced Cancer Therapeutics LLC**. "This *PNAS* paper shows one way to harness MIF therapeutically."

Advanced Cancer has MIF antagonists in preclinical development to treat cancer, autoimmune disease and age-related macular degeneration (AMD).

More modes

Researchers contacted by *SciBX* said the results add to the evidence that MIF could be targeted to treat sepsis, but the consensus was that other MIF antagonists might be safer and more effective than D-thyroxine.

However, Al-Abed and Paul Davis noted that D-thyroxine might have a second mode of action in sepsis—inhibition of integrin $\alpha_v\beta_3$ -mediated inflammation—that could give its analogs an advantage over therapies targeting only MIF.

Davis is director and senior scientist at **Ordway Research Institute** and senior associate dean for clinical research and professor of medicine at **Albany Medical College**.

Indeed, Davis said reports from other groups have shown that inhibiting integrin $\alpha_v\beta_3$ (CD51/CD61) has an anti-inflammatory effect in sepsis, and studies published by his research groups at Ordway and Albany

Medical College have shown that L-thyroxine can bind integrin $\alpha_v\beta_3$ to promote the production of proinflammatory cytokines in cancer cells.⁵

"Ordway also has some unpublished data supporting the idea that D-thyroxine blocks the proinflammatory action of L-thyroxine on the integrin," he said.

Thus, Davis speculated that in sepsis, D-thyroxine might "prevent L-thyroxine from promoting inflammation or possibly exert an anti-inflammatory effect of its own."

He said this possibility could be tested in sepsis models with the research compound tetrac—a thyroxine analog that blocks the interaction of L-thyroxine and integrin $\alpha_v\beta_3$ —to see whether the compound mimics the action of D-thyroxine.

Davis did caution that at the doses used to treat hyperlipidemia, D-thyroxine has known side effects on the cardiovascular system, liver and kidneys. Moreover, the dose of D-thyroxine in the team's murine sepsis studies "is more than 100-fold the daily dose recommended for human subjects with hyperlipidemia," he said. Thus, Davis thinks D-thyroxine is more of a lead compound than a clinical candidate.

"Medicinal chemistry may permit remodeling of the compound's iodothyronine skeleton to maintain MIF inhibitory activity yet yield more favorable side-effect and dosing profiles," he said.

"Ordway also has some unpublished data supporting the idea that D-thyroxine blocks the proinflammatory action of L-thyroxine on [integrin $\alpha_v\beta_3$]."

**—Paul Davis,
Ordway Research Institute**

Eric Morand, cofounder and CSO of MIF inhibitor company **Cortical Pty. Ltd.**, agreed. “The potential off-target effects of D-thyroxine could be problematic compared with a more potent and highly selective small molecule MIF inhibitor,” he said.

Cortical has oral MIF antagonists in lead optimization to treat rheumatoid arthritis (RA), lupus and other chronic inflammatory diseases.

Cortical CEO Nicole Fowler added: “Once we have Phase II data in hand for these indications, it would be interesting to explore the potential of our MIF antagonists to treat sepsis” and other acute indications for which MIF has been validated as a target.

Trial and tribulations

Al-Abed said unpublished data from his group have shown tetrac also binds to MIF, which would make it difficult to use the compound—as Davis proposed—to determine whether D-thyroxine has one or two modes of action. “But I am open to discuss these issues and future experiments” with Davis, he said.

Meanwhile, Al-Abed and colleagues are planning a Phase I trial of D-thyroxine to treat sepsis. He acknowledged that a new dosing study would be necessary but declined to disclose details about the trial design.

The Feinstein Institute holds a patent on the findings reported in the paper and the IP is available for licensing, Al-Abed said.

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