THE SHORT ANSWER

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Exploiting Innate Immune Cell Activation of a Copper-Dependent Antimicrobial Agent during Infection.

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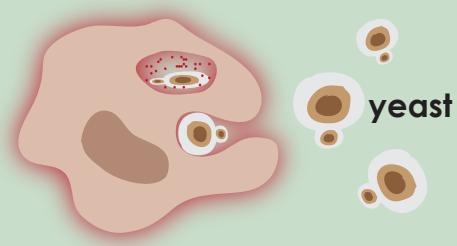
BACKGROUND:

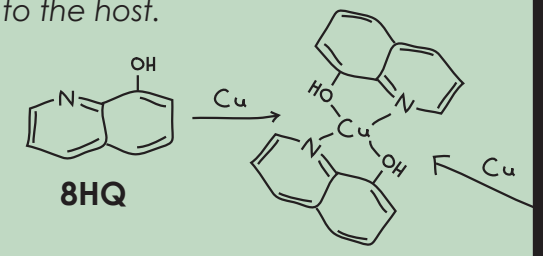
In addition to H_2O_2, NO, lytic enzymes, etc., Cu is also used in macrophage phagolysosomes to destroy microbes such as bacteria and fungi. However, many pathogens have Cu resistance mechanisms.



activated macrophage

HYPOTHESIS:

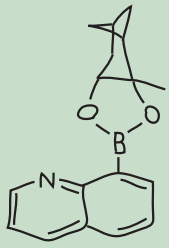
A small-molecule copper chelator may be used to enhance the killing of pathogens if it can increase Cu in the phagolysosome and overcome Cu detox mechanisms, without being toxic to the host.



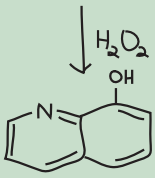
8HQ

Great candidate, but toxic to host macrophages!

APPROACH:



QBP



8HQ

QBP is non-toxic to the host, and should only convert to 8HQ in the presence of H_2O_2 (found in the phagolysosomes of activated macrophages, right where 8HQ is needed). QBP treatment should kill the yeast Crypotococcus neoformans, without killing macrophages.

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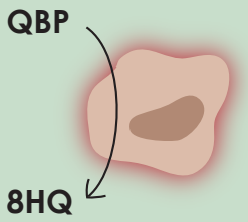
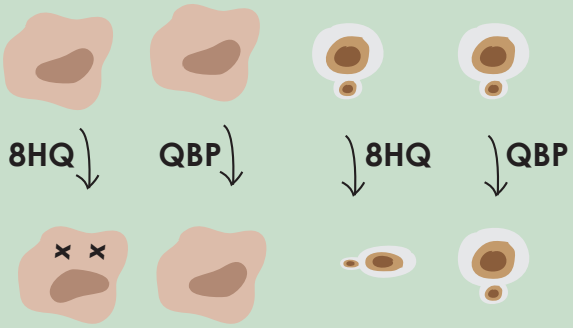
EVIDENCE:

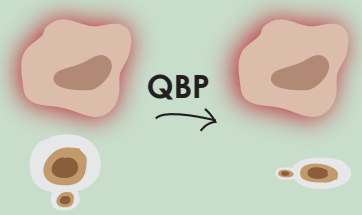
Activated macrophages convert QBP to 8HQ.



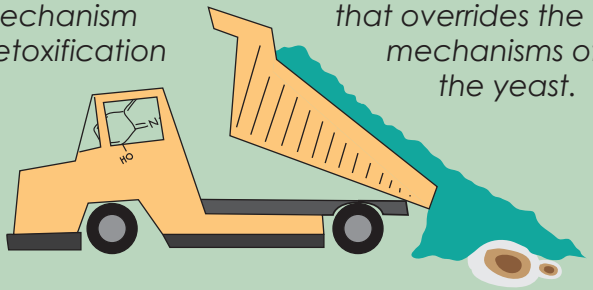
QBP by itself is not toxic to naive (not activated) macrophages or Neoformans crypococcus, while 8HQ is toxic to both.



QBP plus activated macrophages leads to killing of Neoformas crypococcus. Under these conditions, and presumably due to localization in phagolysosomes, there is no loss of viability to the macrophages.



C. neoformans treated with 8HQ and Cu wound up with about 40 times (40 times!) more cell-associated Cu than if treated with Cu alone. Data support a Cu-shuttling mechanism that overrides the detoxification mechanisms of the yeast.



Mice infected with C. neoformans and then treated with QBP had a decreased fungal burden compared to untreated mice,*

UNTREATED

*I feel awesome, except that my mouth tastes like a roll of pennies.***

QBP-TREATED

*Fungal Burden would be a great name for a band

**not an actual side effect as far as anyone knows, though fighting infection does lead to higher serum Cu.

CONCLUSIONS:

I love this idea - it is what chemical biology is all about. QBP is basically a prodrug that is only processed to the toxic form in a location that is designed to kill pathogens. It enhances a normal antibiotic pathway by flooding pathogenic cells with Cu to bypass the native Cu detoxification pathway. They also show 8HQ to have broad spectrum antimicrobial activity, including against the dreaded Staphylococcus aureus!