

A CF IL-8 transgenic mouse model for the in vivo long-term monitoring of the anti-inflammatory role of metallo-protease inhibitors and antibiotics with mechanisms of action similar to that of azithromycin

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Background. The possibility of monitoring the inflammatory response in a IL-8 transgenic WT and CFTRknockout (CF), non invasive, animal model has been demonstrated in a previous project conducted by us [1, 2].

Hypothesis and objectives In the past project we shown that the antibiotic azithromycin causes a significant decrease of the lung inflammation in that is capable of inhibiting the synthesis of bacterial virulence factors. Azithromycin is extensively used in cystic fibrosis as an anti-inflammatory molecule but several cases of azithromycin resistance have been reported [1-2], especially in patients using the drug for long times. It seems then important to identify other therapeutic agents to be used in nonresponding patients.

Methods We have used the IL-8 transgenic CF mouse model to monitoring the expected significant reduction of the pro-inflammatory response induced by Pseudomonas metalloproteases (MPs) by using protease inhibitors such as Galardin and other approved drugs for human use, namely Marimastat and the antibiotic Doxycycline. As an alternative or complementary approach it has been also analyzed the possible anti-inflammatory activity of antibiotics with a mechanism of action similar to that of AZM and used in CF such as claritromycin (CLAR) and tobramycin (TOB).

Results In this study, it has been demonstrated that Galardin and Marimastat, but not Batimastat or doxycycline, have inhibitory activity against the pro-inflammatory MPs released by P. aeruginosa during growth thus causing a decrease of lung inflammation in WT and CF mice. A significant reduction of pulmonary inflammation in CF mice has been also obtained by growing Pseudomonas aeruginosa in the presence of sub-MIC doses of clarithromycin, and antibiotic with a mechanism of action similar to that of azithromycin. Clarithromycin in fact is capable of blocking the synthesis of several Pseudomonas virulence factors, namely pyoverdine, pyocyanin and metalloproteases. The transgenized IL-8, CF mouse model has been further validated in this study.

Spin-off for research & clinical purposes The model reveals an interesting tool to the monitoring of the inflammatory process in CF induced by infective and non-infective causes and to test in vivo the antibacterial/anti-inflammatory effect of candidate molecules to be used in cystic fibrosis. Its use allowed us to uncover the anti-inflammatory properties of three drugs already in clinical use for purposes other than treating lung inflammation.

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References

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