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Mycobacteria in the Literature: Report 01-2016

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RNA signature for assessment of future tuberculosis risk

Zak DE, Penn-Nicholson A, Scriba TJ, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet. 2016 Jun 4;387(10035):2312–22. doi: 10.1016/S0140-6736(15)01316–1.

Treatment of latent tuberculosis infection (LTBI) is neither feasible nor recommended in countries where tuberculosis is endemic. Current commercially available blood testing cannot distinguish latent TB from active TB, nor does it determine who is at risk for developing reactivation of latent tuberculosis. Identifying patients at risk for progressing from latent to active disease however, may be helpful in targeting prophylactic treatment and thus assisting in the fight against the global TB epidemic. Berry and colleagues previously described a gene signature that could differentiate active TB infection from LTBI. [1] Zak and colleagues aimed to identify a gene signature that could identify healthy individuals at risk for developing tuberculosis for up to 2 years.

In this prospective cohort study, the investigators enrolled 6363 HIV-negative individuals aged 12–18 years from the South African adolescent cohort study (ACS) and assessed them every 6 months for 2 years. They identified 46 people who progressed to active TB infection and 107 matched controls. Participants were randomly assigned to either a training set or a test set. The training set was used to develop a tuberculosis risk signature by mining a whole blood sequencing dataset, which was cross-validated. The signature was composed of 16 genes, which became more expressed as the tuberculosis diagnosis approached. The predictive potential of tuberculosis progression in the training group found a sensitivity of 71.2% at 6 months, 62.9% at 6–12 months at a specificity of 80.6%, and 47.7% at 12–18 months before TB diagnosis. The tuberculosis risk signature was then applied to a qRT-PCR platform and used to predict TB risk in the test set. The sensitivity was 66.1% and specificity was 80.6% in the 12 months preceding TB diagnosis.

The investigators went on to apply the tuberculosis risk signature to predict TB risk in other HIV-negative cohorts including 4466 individuals in South Africa and Gambia, aged 10–60 years with a sputum spear positive household contact. They were followed for 2 years. Sensitivity of the risk signature was 53.7% and specificity was 82.8% in the year preceding TB infection.

Given the increase in gene expression as active TB diagnosis approached, the gene signature was also used to determine individuals with active TB infection from those LTBI and uninfected controls in other studies of HIV-uninfected South African adults, and found to have an 87% sensitivity and 97% specificity. Furthermore, gene expression was found to decrease over time when applied to those being treated for active TB over 6 months.

These results show promise in the area of blood-based gene signatures to identify individuals at risk for developing active TB infection. Further studies are necessary to determine whether this platform would be useful in other populations, particularly in those with HIV or other co-infections, where a tremendous burden of disease exists.

Reference

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Outcomes and prognosis of patients with macrolide-resistant pulmonary mycobacterium avium complex lung infection

Morimoto K, Namkoong H, Hasegawa N, et al. Macrolide-Resistant Mycobacterium avium Complex Lung Infection: An Analysis of 102 Consecutive Cases. Ann Am Thorac Soc. 2016 Aug 11 doi: 10.1513/AnnalsATS.201604–246OC.

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Treatment Mycobacterium avium complex (MAC) becomes extremely challenging in the face of macrolide-resistance. The 2007 ATS and IDSA statement compared management of these infections to that of multidrug resistant tuberculosis (MDR-TB). [1] Randomized controlled trials studying the efficacy of second line agents for pulmonary MAC are difficult to conduct given the heterogeneity of patients. Morimoto and colleagues aimed to describe the factors associated with development of macrolide resistance, as well as the outcomes and prognosis of individuals with macrolide resistant pulmonary MAC.

In this retrospective observational study, 102 cases of macrolide—resistant MAC lung disease were reviewed between 2005 and 2013. Cases were identified in 3 tertiary hospitals in Toyo and one hospital from Aichi prefecture. MDR-TB cases were also reviewed from Fukujuji Hospital for comparison of survival rates. Of the 102 cases, 90 met criteria. A majority of patients were women with lower BMIs and a median age of 68 years at the confirmation of macrolide resistance. The disease type was evenly distributed among nodular, fibrocavitary, and complex pulmonary disease. The rate of inappropriate first line treatment was high (58.9%) including clarithromycin monotherapy, clarithromycin plus a fluoroquinolone, and treatments without ethambutol. Adverse effects of treatment were common, including ethambutol (34.4%), rifampin (17.8%), aminoglycosides (7.8%), fluoroquinolones (5.6%) and clarithromycin (4.4%). Surgeries were performed on 12.2% of patients. The majority (63.3%) of patients showed worsened radiographic findings, 22.2% were unchanged, and only 16.7% were improved.

Multiple logistic regression analysis was done to stratify factors that were associated with better prognosis including demographics, disease type, discontinuation of clarithromycin, and addition of another treatment: fluoroquinolone, rifabutin, an aminoglycoside, and surgery. Surgery was correlated with improved outcomes (adjusted OR = 5.81) but this was not statistically significant. Only the combination of an aminoglycoside plus surgery had a significant association with a better prognosis (OR 29.1, $p = 0.01$). The five year survival was 71%, and similar to the 75% survival rate of MDR-TB.

Although this study has limitations of being a retrospective observational study, it highlights the contribution of inappropriate treatment prior the detection of macrolide-resistant MAC pulmonary disease. There are several reasons for this including treatment of other comorbidities, such as bronchiectasis, for which macrolides are often used for antiinflammatory purposes. Furthermore, ethambutol drug toxicity often prevents patients from receiving first line therapy. The improved outcomes in patients treated with surgery, particularly in combination with aminoglycosides, confirms what other investigators have shown. [2,3] Larger controlled trails are needed to better identify more optimal treatment regimens, and novel drugs are desperately needed in the hopes of offering better outcomes for these difficult to treat cases.

References

[1] Griffith D.E., Aksamit T., Brown-Elliott B.A., Catanzaro A., Daley C., Gordin F., et al. An Official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367–416.

[2] Shiraishi Y. Surgical treatment of nontuberculous mycobacterial lung disease. Gen Thorac Cardiovasc Surg 2014;62:475–480.

[3] Mitchell J.D. Surgical approach to pulmonary nontuberculous mycobacterial infections. Clin Chest Med 2015;36:117–122.

Broad range PCR for nontuberculous mycobacteria detection

Scoleri GP, Choo JM, Leong LE, et al. Culture-independent detection of nontuberculous mycobacteria in clinical respiratory samples. J Clin Microbiol. 2016 Sep;54(9):2395–8. doi: 10.1128/JCM.01410–16.

With increasing immunosuppressive therapies for treatment of malignancies and inflammatory disorders, rates of nontuberculous mycobacterial infections have been on the rise. Although positive acid fast staining on specimens can identify the presence of mycobacterial organisms early, it is not sensitive, nor can it distinguish between species. Current identification methods rely heavily upon culture growth, which can take days to weeks, delaying early treatment initiation in most cases. PCR probes have been developed to distinguish tuberculosis from other nontuberculous mycobacteria (NTMs); however a rapid screen that can detect presence of several NTM organisms would be of great benefit. Scoleri and colleagues describe a TaqMan quantitative PCR assay for detection of a large range of NTM species from respiratory samples.

The investigators developed an assay using 116 available heat-shock protein 65 (hsp65) NTM gene sequences, including the 56 NTM species known to cause respiratory infection. They went on to test the assay's ability to identify NTM species from several known isolates, including 15 NTM strains and negative controls consisting of 15 other NTMs, 9 TB strains, other respiratory pathogens, and human DNA. Sensitivity was assessed by dilutions methods using M. abscessus DNA. The assay was validated using 42 clinical respiratory samples, including sputum and BAL samples, from individuals with suspected NTM infection. Of these specimens, 8 were found to be culture-positive for NTM species and these were conformed confirmed by qPCR and DNA sequencing. Species identified included M. avium, M. abscessus, M. intracellulare, M. massiliense. Three samples were culture negative and qPCR positive. These included a case with high levels of H influenza growth, one who had received prior therapy for another NTM species, and one sample that was "insufficient for adequate assessment."

This study shows great promise in the development of a rapid assay for detection of clinically relevant NTM species. A limitation to this study includes small sample size. The investigators acknowledge that PCR assays detect viable and nonviable bacterial cells; therefore a positive result may not necessarily be indicative of infection. Further studies are needed to validate this assay. Areas for future research include application to other non-respiratory samples and assessment of other NTM species implicated in non-pulmonary disease.