Systems and Synthetic Biology Seminar mini workshop

3/9 (Fri) 15:30 - 17:30 D105 seminar room

Potentiating TB drug action through metabolic meddling

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The long-term goal of my research program is to develop innovative strategies to circumvent shortcomings in tuberculosis (TB) therapy. Currently, my lab is focused on understanding the metabolic basis for susceptibility, resistance and tolerance of *Mycobacterium tuberculosis* to various antimicrobial agents. As part of these studies, we have been using a combination of genetic and biochemical approaches to characterize the metabolic impact of the first-line drug pyrazinamide (PZA) and the second-line drug para-aminosalicylic acid (PAS) on *M. tuberculosis*. While both of these drugs have been in clinical use for TB therapy for over 60 years, we are just now beginning to unravel the mechanisms governing their anti-mycobacterial action. With these findings, we are exploring ways of potentiating the action of these drugs and re-sensitizing resistant isolates.

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Structure of bacterial metabolic pathway and anti-tubercular drug synergism
(細菌の代謝経路から読み解く抗菌薬相乗効果のメカニズム)

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Mycobacterium tuberculosis (Mtb) is the causative agent for tuberculosis (TB). Although effective TB drugs are available, 1.5 million TB related deaths still occur annually. TB treatment remains challenging because it requires a minimum of six months of chemotherapy and the treatment is not fully effective in preventing subsequent relapse of disease. As such, treatment failure is common and has fueled the emergent spread of drug resistant strains of Mtb that threaten the efficacy of the existing treatment. Some antimicrobial drug combinations show strongly synergistic effects where the combined inhibitory activity is far greater than the sum of individual activities. However, in most cases, the mechanistic basis for synergism is not apparent. The goal of our study is to understanding the fundamental mechanisms that govern antimicrobial synergy to facilitate the rational design of novel synergistic anti-tubercular drug combinations.

We revisited the widely assumed mechanism of synergy between trimethoprim (TMP) and sulfamethoxazole (SMX). These drugs are known to act by targeting sequential steps in the biosynthetic pathway for the essential cellular cofactor, tetrahydrofolate (THF), where SMX inhibits the production of the THF precursor dihydropteroate (DHPte) and TMP competitively inhibits the conversion of dihydrofolate (DHF) to THF. Consequently, SMX potentiates TMP activity by limiting de novo production of DHF and this mono-potentiation mechanism is widely accepted as the basis for synergy between these drugs. We demonstrated that this model is not sufficient to explain the strong degree of synergism between TMP and SMX. Using a multidisciplinary approach, we characterized a functional metabolic feedback loop in which THF is critical for production of the DHPte precursor dihydropterin pyrophosphate (DHPPP). Importantly, we revealed that TMP potentiates SMX activity ultimately through the inhibition of DHPPP synthesis. Collectively, the study indicates that the potent synergy between TMP and SMX is driven by mutual potentiation of the action of each drug on the other. These findings highlight the importance of metabolic pathway structure in understanding antimicrobial drug interactions and will enable the identification of additional pathways that can be explored for potently synergistic anti-tubercular drug targets.

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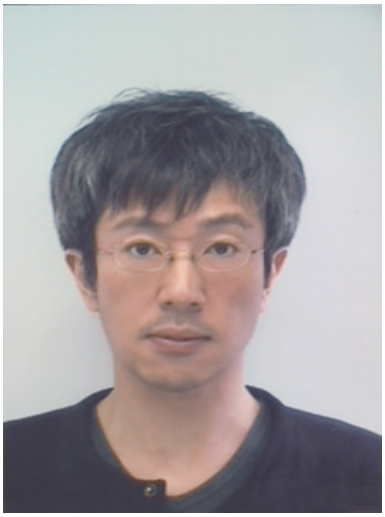

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非結核性抗酸菌の全ゲノム情報に基づく分子疫学研究が目指すもの

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結核菌とらい菌以外のマイコバクテリウム属細菌によって引き起こされる感染症は非結核性抗酸菌症（NTM 症）と呼ばれ、代表的なものに *Mycobacterium avium complex* (MAC) に分類される環境常在菌の感染を原因とする肺疾患、肺 MAC 症がある。肺 MAC 症は近年、基礎疾患を持たない中高年の女性の間で急増している。せきや血痰が続く病気で、抗菌薬による治療が基本だが、完治させることは難しい。肺 MAC 症を含めた NTM 症の発生件数は、先進国の中では日本が最も高い。それにもかかわらず、日本に分布する MAC と欧米に分布する MAC の遺伝的な違いはほとんど議論されてこなかった。今回、私たちは MAC の代表的なメンバーである *M. avium subsp. hominissuis* (MAH) の集団レベルでの比較ゲノム解析と遺伝的集団構造解析を行い、日本に分布する MAH 系統のゲノムの特徴を見出すことに成功した。さらに、MAH のゲノム情報が増加したことで、MAH のゲノム進化のパターンが結核菌とどのように異なっているのかも検証できた。本稿では、MAH のゲノム研究から得られた思いがけない発見の幾つかを紹介する。また、本研究は、日本医療研究開発機構（AMED）のプロジェクトの一部として実施しているものであるので、本プロジェクトの現状と進捗、そして目指す方向性を紹介したい。

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