部門公開セミナー

Ageing men, their selfish testes, new mutations and human disease

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Although new mutations are necessary to fuel evolution, our genomes are under strong selective pressure to faithfully transmit genetic information across generations, a role assumed by the germline. However, very little is known about how cell fate decisions in the germline are regulated in order to control mutation rates. In humans, it is now well-established that most new point mutations (>85%) originate from the father and increase in frequency at the rate 1-2 mutation/paternal year, suggesting that they arise as replication copy-errors during spermatogenesis.

We have previously described a mechanism which predicts that certain pathogenic mutations hijack the homeostatic mechanisms of sperm production to their own advantage. This process called 'selfish selection' was originally proposed to explain the paternal age-effect and high birth prevalence observed for some Mendelian disorders, such as Apert syndrome (FGFR2) or achondroplasia (FGFR3). It relies on principles similar to oncogenesis to explain why these mutations occur spontaneously at levels up to 1000-fold higher than the background rate.

I will summarise our current understanding of *de novo* mutations in humans and their importance for human disease and genome heterogeneity. I will then describe the data that have led to the discovery of the selfish selection process and the strategies we recently developed for visualizing 'selfish' clones directly within human testes and identify new pathogenic mutations. Finally, I will speculate on the broader implications of selfish selection and the importance of the regulation of spermatogenesis for human disease, genome diversity and evolution.

Seminar will be given in English.

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