Molecular mechanisms and population dynamics of drug-tolerant persisters

PhD admissions | Jan 2022

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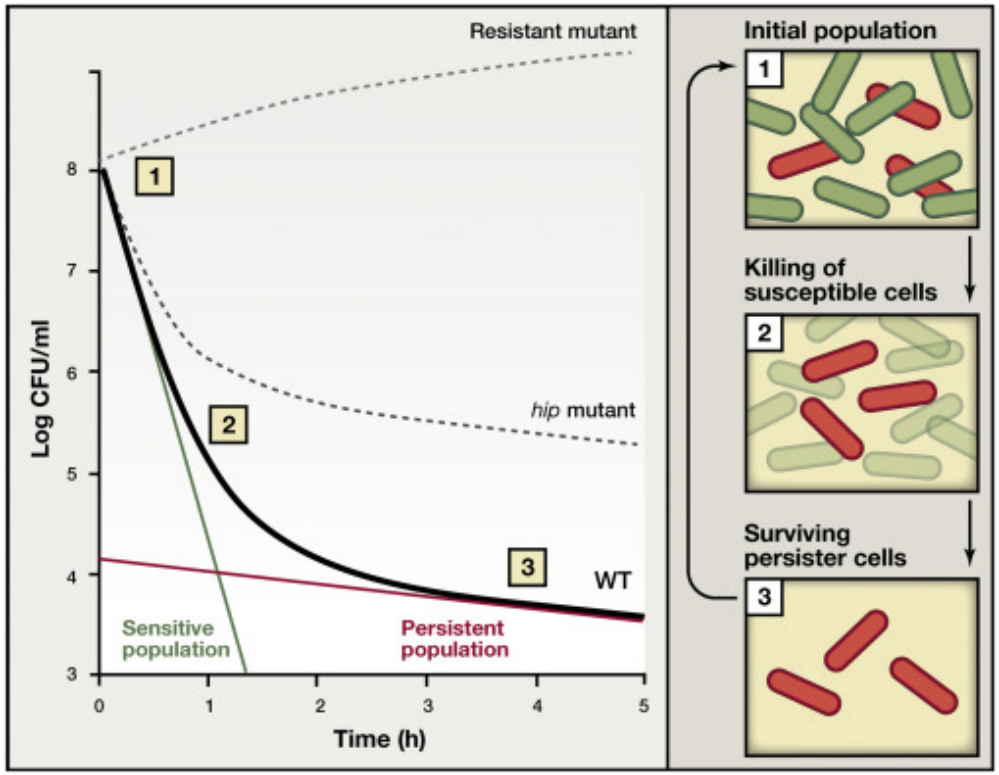
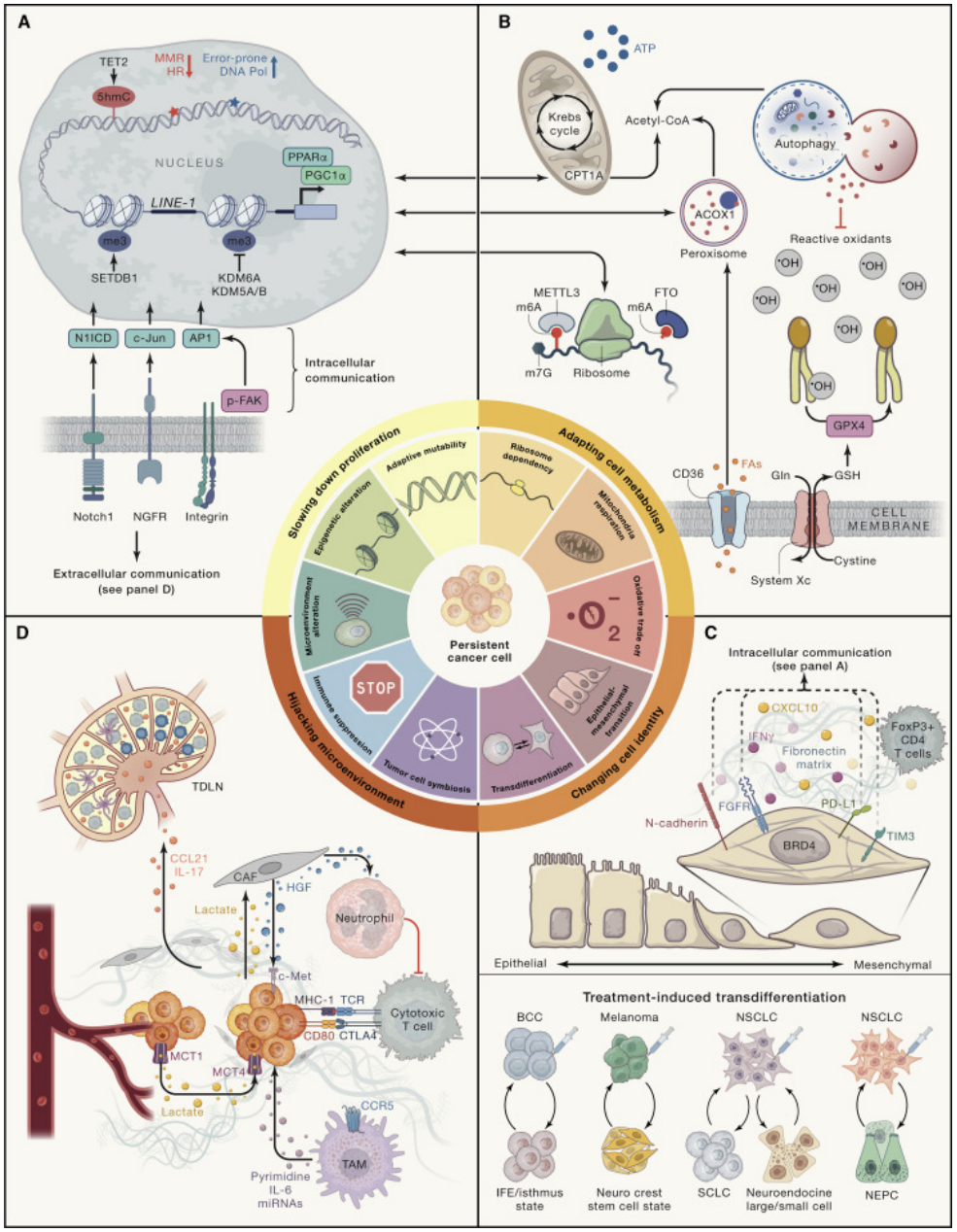
Drug-tolerant persisters (DTPs)



Maisonneuve & Gerdes, Cell 2014

- DTPs: A subpopulation of isogenic cells (bacterial or cancer) that can survive many therapeutic attacks by switching reversibly to a slow-cycling state
- DTPs reported initially in 1940s in bacterial population
- DTPs also seen in lung cancer, melanoma, colorectal cancer
- DTPs can act as long-term reservoirs for genetic resistance too

Mechanisms of DTPs



Shen *et al.* Cell 2020

DTPs can adapt to environmental fluctuations through various epigenomic, transcriptional and metabolic reprogramming events.

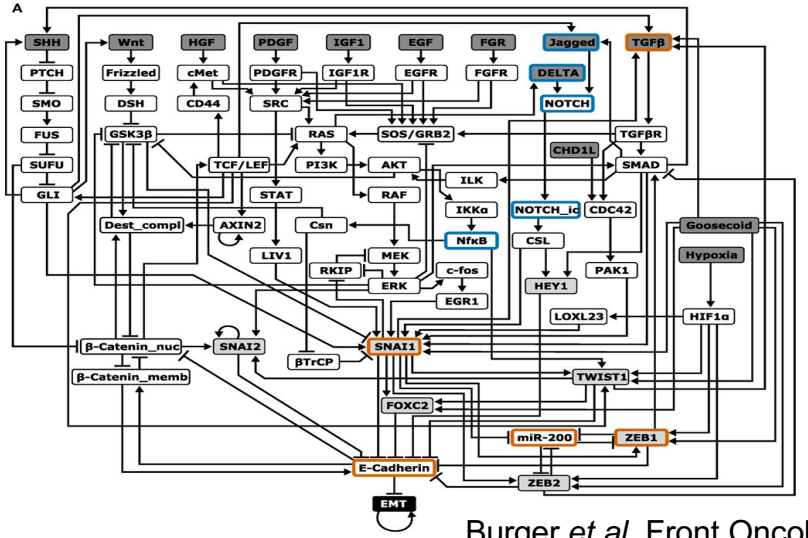
DTPs can expand into a colony, thus driving short-term and long-term resistance to various drugs.

However, a systems-level understanding of the intracellular and population-level dynamics of DTPs in bacterial and cancer cells remains unclear.

A systems-level understanding means…

1. Realizing that integrating different parts can lead to novel behaviors/functions, i.e. whole is greater than sum of its parts

2. Being able to predict the behavior of the system in varied conditions



Burger *et al.* Front Oncol 2017

We can mathematically model these biological networks to achieve a systems-level understanding, similar to that attained for engineered systems as shown above

Questions of interest

Through integrating systems-level approach integrating data-based (statistical) and mechanism-based (mathematical) models, we will answer the following set of questions:

- What regulatory networks underlie the formation of DTPs in bacterial and cancer cells?
- What are the emergent dynamics of the underlying networks that help cells adapt to stress at different time scales?
- Can ‘drug holidays’ or other sequential/adaptive therapy regimens be proposed to prevent or delay the formation of DTPs, based on a better mechanistic understanding?

Tools and techniques used

- Mathematical modeling of biological regulatory networks
- Simulating a set of ordinary (and/or partial) differential equations
- Analyzing experimental high-throughput and population dynamics data

Required background

- Basic understanding of ordinary differential equations and nonlinear dynamics (or the self-driven will to acquire them)
- Keen interest in pursuing interdisciplinary research (i.e. reading literature in systems biology and drug resistance in mycobacterium tuberclosis and cancer)
- **Note:** Students from physics/chemistry/mathematics/engineering background are welcome too, provided they show interest in acquiring the relevant understanding of biology

Further reading

- Mishra R, Kohli S, … **Singh A**. Targeting redox heterogeneity to counteract drug tolerance in replicating *Mycobacterium tuberculosis*. ***Sci Transl Med.*** 11 (518): aaw6635

- Sahoo S, Mishra A… **Jolly MK**. A mechanistic model captures the emergence and implications of non-genetic heterogeneity and reversible drug resistance in ER+ breast cancer cells. ***NAR Cancer*** 3 (3): zcab027