APPLICATIONS AND CASE STUDIES

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Malaria:
Plasmodium falciparum life traits within its two hosts

Geneviève Milon

* Comparative biology : apicomplexa to know parasites (some are long-lived extracellularly
unikonts " " animals

- p.f. asexual, then sexual developmental stages in red blood cells
1 male gametocyte → 8 gametes in 10 min ! this exflagellation takes place in gut lumen of Anopheles
commitment to sexuality first, then sexual activity in Anopheles
↳ in human

- 1. delivery of gametocytes in RBC
2. exit of sporozoites
} within the insect host and vector
Anopheles hosting p.f. very sensitive to fungi.

- collect Anopheles isofemales and feed them with gametocyte-containing blood
many don't show p.f. development : gene-controlled parasite development.
↳ proteins with leucine-rich repeats block it

- motility (actin-dependent) : apicomplexan gliding motility
in parasite : 80% G-actin (monomeric) 20% F-actin (filamentous)
studies in livers in mice : at 40 h merozoite-loaded hepatocytes, attached
at 46 h " " " , detached!
the hepatocytes anti-apoptotically reprogrammed to cross blood wall vessel
then pro-apoptosis changes and blurb formation to penetrate vessel,
and release of parasites ensues.
remodeling of tight junction, detachment, and migration act in concert here.

- invasion of the red blood cells
nowadays, technology has mastered maturation from CD34 marrow stem cells to RBCs.
synchronous, no need for spleen, donut / disk shape. (nucleated → nucleus-free cells)
in the future : plasmodium studies in reticulocytes in vitro!

Case studies - 2.

cortical membrane and cytoskeleton are "lumped", hard to distinguish in RBC.
some mutations in RBC protect against malaria : Duffy blood group negativity
some enzymes
structure haemoglobin variants

Sickle-cell disease could result from numerous mutations.
sickle-trait : one allele of the β-globin gene
cytoskeleton - adhesive property would lead to ingestion by macrophages early.
the parasite could lose this trait to produce and multiply progeny...

- in less than 25 s, very fragile merozoites enter RBCs.
band 3 is well expressed and detectable even after invasion by parasites.
gliding motility and active motility both rely on actin-myosin interactions
and membrane receptors.
RBC : erythrocyte binding proteins family identified
actin, myosin, TRAP, EBA, GAP45-MTIP, aldolase : how do they work together?

in the ring stage, RESA protein in infected RBCs
RSP2 in non-infected RBCs
} contribute to abnormal mechanical properties of RBCs

RESA : last segment of β-spectrin
interaction / dimerization with α-spectrin

- novel adhesive properties of p.f.-infected RBCs from Duffy binding proteins.
in spleen, are senescent and p.f.-harboring cleared ?
unique blood circulatory systems without endothelial cells !
are RBCs even deforming / changing shape upon exiting vessels in spleen?
young ≠ senescent RBCs (CD 47 disappears, interactions with SIRP α ↓)
↳ phagocytosed by macrophages.

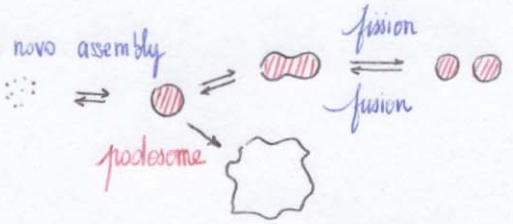
Case studies - 3.

Cell adhesion and motility

Paul Matsudaira

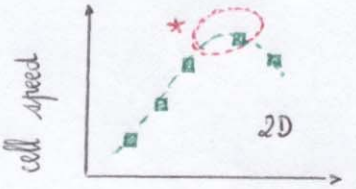
- cell movement is a product of net force
  1. protrusion, 2. attachment, 3. contraction, 4. detachment.
  very dynamic cells.
  self-assembly of the cytoskeleton drives the membrane forward (actin subuni
  daughter adhesions fragment from mother adhesion sites. (protesomes)
  chart the life history of these adhesions: form, grow larger, then split / bran
  microtubule stability influences dynamics of cell adhesion
  frequency of fragmentation / fusion (↗ if demecolcine, ↘ if paclitaxel)
  lifetime of adhesions (other way around)
  stabilizing or destabilizing microtubules prevent migration.

- cell adhesion dynamics



cell movement = balance* between adhesion and contraction

- cells move in 3D matrix:
  - pore size
  - stiffness of matrix
  - adhesiveness of matrix
  - components of underlying matrix



a biochemical & biomechanical basis for computational modeling:
cell folding / cell state approach
speed is an integrative read-out of multivariate system (adhesiveness, stiffness)
now balance between Fn density and number of integrins
cell speed shifts to lower ligand density as receptor binding is blocked: stiffness matters
matrix concentration & stiffness depends on pore size, pore/fiber density, f. thickn
ligand concentration can be controlled independently of matrix concentration.