Virus Infection, Chronic Inflammation and the Biology of Kaposi's Sarcoma

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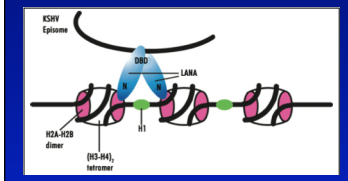
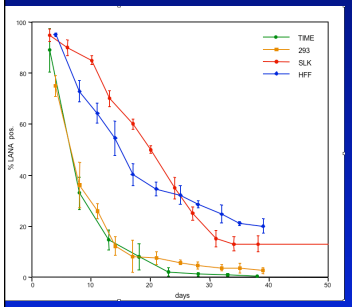
LANA: a latent protein that functions in episome maintenance



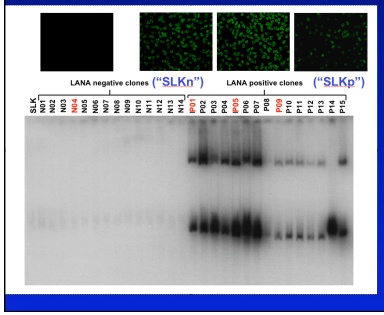
– *(Ken Kaye, Rolf Renne, Erle Robertson)*

But: this mechanism is inefficient, and KSHV latency is relatively unstable

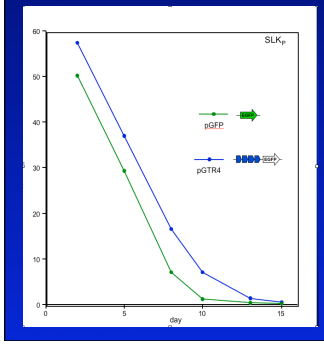
Loss of KSHV episomes from *de novo*-infected cells



Single cell clones derived from infected SLK cells



KSHV episomes are lost from SLKp cells



Summary: latency instability

- Newly established latent KSHV infection is unstable
- Proliferation leads to episome loss
  - In vivo counterpart: KS spindle cells
- Rare cells undergo episome stabilization
  - In vivo counterpart: PEL cells
- Stabilization is epigenetic and acts *in cis*

Tumor virology dogma

- Latency program does the work of tumorigenesis by stimulating proliferation and extending cell survival
- Lytic program doesn't contribute to cancer, because lytically infected cells die
  - (early, accessory role in virus spread)

Clinical medicine provides a seminal clue: ganciclovir and KS risk

	n	new KS
Placebo	122	11.3%
Oral GCV	123	2.7%
IV GCV	132	1.5%

Martin, NEJM 340:1063 (1999)

Ongoing lytic replication is continuously necessary for KS development!

How might lytic replication contribute to KS?

- If latency is not immortalizing: allow replacement of dying cells
- If latency is not stable: allow rescue of uninfected segregants
- Produce paracrine factors that promote inflammation or angiogenesis

Lytic functions with paracrine activity

v-MIPs (3)	Inflammation, angiogenesis?
v-IL6	B cell survival, angiogenesis
v-GPCR	VEGF induction

Pat Moore, John Nicholas, Enrique Mesri,

Summary

- KSHV latency program can promote inflammation, cell survival and possibly proliferation
  - But the effects are modest by comparison with known tumor viruses
- KSHV lytic replication is continuously required for KS development
  - Regenerates latently infected cells lost to cell death or instability
  - Provides paracrine signals for inflammation & angiogenesis

Some clinical inferences…

- Would prolonged treatment of established KS with GCV result in remissions?
- Is the linkage of KS to HIV caused by the loss of immune control of lytic infection?

And medicine continues to provide new clues to KS biology…

- Recent trials show rapamycin is very effective in treatment of post-transplant KS
- What is the role of the mTOR pathway in KS biology - and how is this influenced by KSHV infection?

"THE WORK OF THE RIGHTEOUS IS DONE BY OTHERS"
--TALMUD

- Many thanks to:
  - My students and postdocs over the past 15 years: *none of this would be possible without you.*
  - My many colleagues and competitors in the field: *you have set the bar very high*.