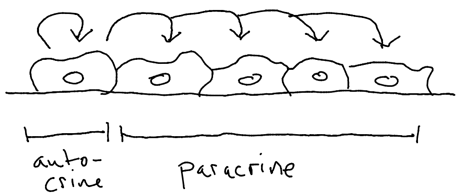
Part II-2: Receptor mediated Response to Growth factors

Thursday, April 16, 2020 12:26 PM

Knauer et al., 1984; Lauffenburger, ch. 6.1, ch. 3.2

1. Phenomenon

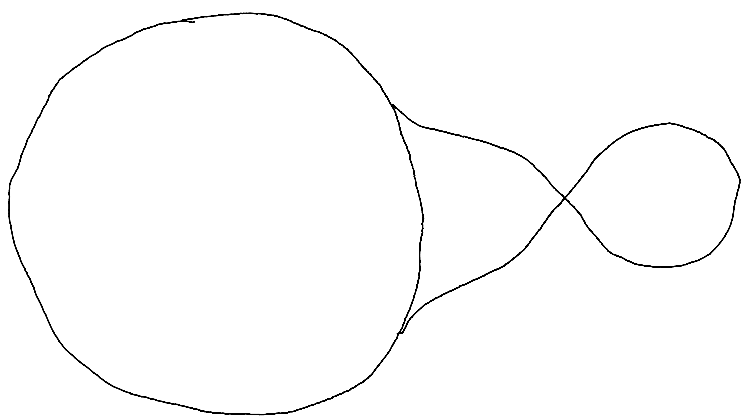


- Signals = soluble species, typically proteins
  e.g. growth factors
  cytokines

2. Controlled behavior - proliferation:

   Mammalian cells have highly regulated proliferation. Somatic cells (dedicated, adult cells) only proliferate under highly specific conditions.

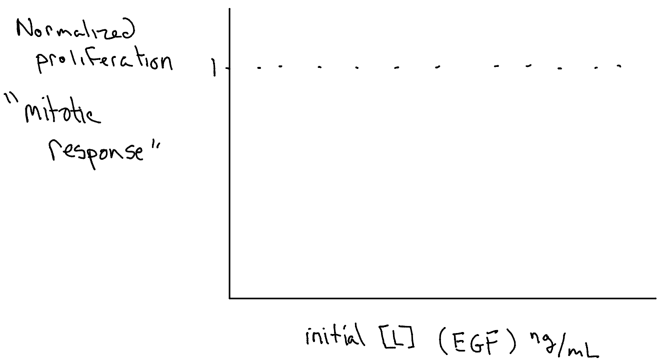
   <u>Cell cycle</u>: Phenomenological description of cellular states



V, C, R = control points

C = "competence"; requires, e.g., platelet-derived growth factor (PDGF)
V = "entry point"; requires, e.g., epidermal growth factor (EGF)
R = check before synthesis (S); requires, e.g., insulin-like growth factor I (IGF-I)

3. Observation (Knauer et al., 1984):



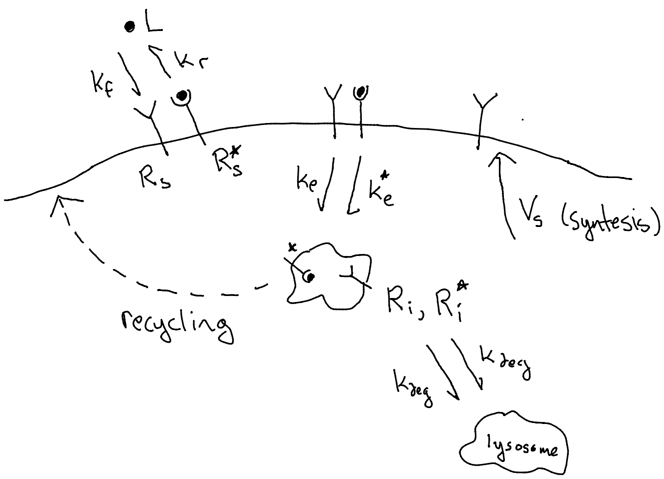
EGF binds EGF-receptor (EGFR), a receptor-tyrosine kinase

Observation:

Hypothesis: mitotic rate proportional to concentration of bound EGF
(EGFR and ligand bound complexes "limiting reagent"

Modeling implications:
=> We only need a model of binding and regulation of signal level
=> Ignore details of signal transmission from activated receptor to gene regulation

4. Model:



R_s = inactive surface recep.
R_s^* = active " "
R_i = inactive internal recep
R_i^* = active " "

Mass Balances:

free surface receptor: $$\frac{dR_s}{dt} = -k_f L R_s + k_r R_s^* - k_e R_s + V_s \qquad (1)$$

bound surface receptor: $$\frac{dR_s^*}{dt} = k_f L R_s - k_r R_s^* - k_e^* R_s^* \qquad (2)$$

total internal receptor: $$\frac{dR_i^T}{dt} = k_e R_s + k_e^* R_s^* - k_{deg} R_i^T \qquad (3)$$

$$R_i^T = R_i^s + R_i^*$$

internal active receptor : $\frac{dR_i^*}{dt} = k_e^* R_s^* - k_{deg} R_i^*$ (4)

@ S.S. :

(1) – (3) $\Rightarrow$ $R_s^* = \frac{K_{ss} L}{1 + K_{ss} L} \left(\frac{V_s}{k_e^*} \right)$; K_{ss} [=] effective binding const. (5)

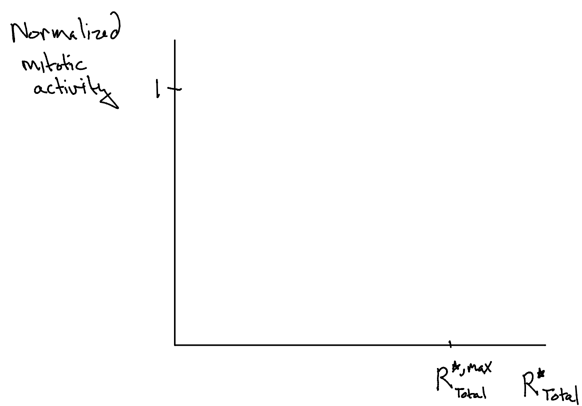
$$= \frac{k_e^* k_f}{k_e (k_r + k_e^*)}$$

(4) + (5) $\Rightarrow$ $R_i^* = \frac{k_e^*}{k_{deg}} R_s^*$ (6)

(5) + (6) $\Rightarrow$ $R^*_{Total} = R_s^* + R_i^*$

$$= \left(\frac{1}{k_e^*} + \frac{1}{k_{deg}} \right) \left(\frac{K_{ss} L}{1 + K_{ss} L} \right) V_s \qquad (7)$$

Check hypothesis (compare model and experiment):



• $R^{*,max}_{Total}$

$\Rightarrow$ $\frac{\text{mitotic rate}}{\text{max rate}} = \gamma \cdot R^*_{Total}$; γ