C. Cell-Matrix Interactions

A. How cells pull onto and deform the matrix to which they attach themselves.

B. Cell-matrix interactions control the spontaneous closure of wounds in organs.

C. <u>What happens when regeneration is induced?</u>

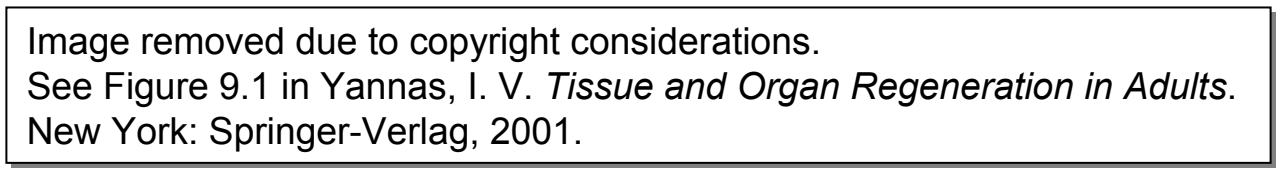
C. What happens when regeneration is induced?

- **Closure of a defect by contraction (and scar synthesis) appears to block regeneration in the adult.**
- **Certain ECM analogs that selectively lock contraction have been shown to induce partial regeneration in adults (skin, peripheral nerves, conjunctiva).**
- **Under the same conditions, neither addition of growth factors nor of cell suspensions have blocked contraction nor have they induced regeneration.**

Hypothesis: Regeneration requires selective blocking of contraction.

A brief review of the obvious effects of closure by contraction

Isolated cell (fibroblast) contracts surface of thin silicone film, floating on oil. Buckling results.



Burn patient has experienced closure by contraction of massive wounds in neck

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Closure of dermis-free defect by contraction induces scar synthesis

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See Figure 9.4 in [Yannas].

natural light

polarized light

Cell capsule round regenerated nerves

4-mm gap

Normal rat sciatic nerve

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See Figure 10.7 in [Yannas].

8-mm gap

Regenerated across 0-mm gap

Contractile cells (brown) ensheathe regenerating stump of transected rat sciatic nerve

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See Figure 4.6 in [Yannas].

near original proximal stump

near original distal stump

Partly regenerated rat sciatic nerve. Tubulated in silicone tube.

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See Figure 4.5 in [Yannas].

cross-section shows thick sheath of contractile cells

Hypothesis: Regeneration requires selective blocking of contraction.

Evidence supporting hypothesis (Chap. 8):

- **Decrease in C coincided with increases in R (C and R are terms in defect closure rule).**
- **Delay in contraction kinetics coincided with induced regeneration.**
- **Suppression of closure by contraction (C) in spontaneously healing defects coincided with increased regeneration (R).**
- **Scar was abolished when contraction was inhibited.**
- **Suppression of contraction did not suffice to induce regeneration.**
- **Specificity of contraction blocking by ECM analogs.**

Table 8.1. Decrease in C coincided with increases in R (C and R are terms in defect closure rule).

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See Table 8.1 in [Yannas].

Normal

Regeneration of conjunctival stroma following blocking of contraction of fully excised stroma

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Untreated defect

Treated with DRT

Table 8.2. Delay in contraction kinetics coincided with induced regeneration.

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- **Suppression of closure by contraction (decreased C) in two spontaneously healing defects coincided with increased regeneration (R).**

A. <u>Tadpole development</u>:

$\rightarrow$ Increasing development

[41,0,59]$\rightarrow$[62,0,38]$\rightarrow$[66,0,34]$\rightarrow$[90,0,10]

B. <u>Rabbit anatomical sites</u>:

dorsal region vs. ear

[96,4,0] vs. [3,0,97]

Closure diagram showing values of C, S and R at various stages of development

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See Figure 8.3 in [Yannas].

Ear cartilage regene-ration. 1-cm full-thickness hole in rabbit ear

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See Figure 8.4 a, b in [Yannas].

1 d post-injury

2 wk

(cont.)
Ear cartilage regene-ration.
1-cm full-thickness hole in rabbit ear

4 wk

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See Figure 8.4 c, d in [Yannas].

6 wk

Scar was abolished when contraction was inhibited.

See data in Table 8.1 above.

Suppression of contraction did not suffice to induce regeneration.

- See data in Table 8.2 above.
- Addition of cortisone acetate (anti-inflammatory steroid), aspirin or prostaglandin inhibitor in the healthy rat wound delayed contraction; however, regeneration was not observed.
- Delayed contraction, but not regeneration, observed with impaired wounds (diabetic, or obese rats; infected wounds).

Specificity of contraction blocking by ECM analogs.

Contraction was blocked only when each of the following structural features of ECM analogs was maintained within a narrow range (selective blocking):

- **average pore diameter**
- **degradation rate**
- **chemical composition**

Structural Features of ECM analogs

1. pore structure (ligand density)

2. macromolecular structure (ligand duration)

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3. chemical composition (ligand identity)

Table 8.3

1. Ligand identity

High specificity of contraction blocking (contraction delay) by ECM analogs

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See Table 8.3 in [Yannas].

2. Ligand density

3. Ligand duration

4. Cell-seeding

Effect of pore diameter of ECM analog on contraction delay

Effect of degradation rate of ECM analog on contraction delay

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See Figure 8.5 in [Yannas].

Peripheral nerve regeneration. Regenerated activity of several tubulated configura-tions

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See Table 6.1 in [Yannas].

the length shift, ΔL, measures the regenerative advantage of a device relative to the silicone tube standard. e.g., $\Delta L > 0$ is better than standard.

Conclusion

- **The data support the hypothesis that regeneration in adults is induced by selective blocking of contraction.**
- **Although blocking of contraction appears to be required, it is not sufficient to induce regeneration.**