Gene Regulation and
Cell Differentiation
(and stem cells and cancer)
Cell Differentiation

terminally differentiated cells

some need to be replenished often
• blood cells
• surface epidermal cells
• intestinal lining cells
Differentiated cells are continuously supplied by a stem cell population

- No limit to number of cell divisions
- One daughter is always a stem cell
- Other daughter begins process of differentiation into precursor cell

Precursor cells can divide a limited number of times
Hematopoietic cell lineage

• **Signals** make it happen (inter-cellular and extracellular)
• **Regulatory Proteins** achieve sequential differentiation

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**Figure 23-42 Molecular Biology of the Cell 5/e (© Garland Science)**
• drop in $O_2$ levels in any tissue (ex. high altitude) = hypoxia
• $\rightarrow$ activation of HIF1 Transcription Regulator
  • (hypoxia-inducible factor 1)
  • HIF1 = $\alpha$ and $\beta$ subunits, both transcribed and translated "constitutively"
  • HIF$\beta$ is constitutively active but HIF$\alpha$ is regulated by $O_2$ levels in tissues

Normal $O_2$

HIF$\alpha$

HIF$\alpha$

HIF$\alpha$

dioxygenase enzymes

HIF$\alpha$

degradation enzymes

Hypoxia (Low $O_2$)

HIF$\beta$

HIF$\alpha$

HIF$\alpha$

HIF$\alpha$

HIF$\beta$

Target gene

HRE
## HIF1 Target Genes (only those that are known)

<table>
<thead>
<tr>
<th>Function</th>
<th>Gene (abbreviation)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoiesis/iron metabolism</td>
<td>Erythropoietin (EPO)</td>
<td>Semenza et al., 1991</td>
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<tr>
<td></td>
<td>Transferrin (Tf)</td>
<td>Rolfs et al., 1997</td>
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<td></td>
<td>Transferrin receptor (Tfr)</td>
<td>Bianchi et al., 1999</td>
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<td></td>
<td>Ceruloplasmin</td>
<td>Lok and Ponka, 1999</td>
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<tr>
<td>Angiogenesis</td>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>Levy et al., 1995</td>
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<td></td>
<td>Endocrine-gland-derived VEGF (EG-VEGF)</td>
<td>LeCouter et al., 2001</td>
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<td></td>
<td>Leptin (LEP)</td>
<td>Grosfeld et al., 2002</td>
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<td></td>
<td>Transforming growth factor-β3 (TGF-β3)</td>
<td>Scheid et al., 2002</td>
</tr>
<tr>
<td>Vascular tone</td>
<td>Nitric oxide synthase (NOS2)</td>
<td>Melillo et al., 1995</td>
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<tr>
<td></td>
<td>Heme oxygenase 1</td>
<td>Lee et al., 1997</td>
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<tr>
<td></td>
<td>Endothelin 1 (ET1)</td>
<td>Hu et al., 1998</td>
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<tr>
<td></td>
<td>Adrenomedulin (ADM)</td>
<td>Nguyen and Claycomb, 1999</td>
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<td></td>
<td>α1B-Adrenergic receptor</td>
<td>Eckhart et al., 1997</td>
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<td>Matrix metabolism</td>
<td>Matrix metalloproteinases (MMPs)</td>
<td>Ben-Yosef et al., 2002</td>
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<tr>
<td></td>
<td>Plasminogen activator receptors and inhibitors (PAIs)</td>
<td>Kietzmann et al., 1999</td>
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<td></td>
<td>Collagen prolyl hydroxylase</td>
<td>Takahashi et al., 2000</td>
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<tr>
<td>Glucose metabolism</td>
<td>Adenylate kinase-3</td>
<td>O’Rourke et al., 1996</td>
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<tr>
<td></td>
<td>Aldolase-A.C (ALDA,C)</td>
<td>Semenza et al., 1996</td>
</tr>
<tr>
<td></td>
<td>Carbonic anhydrase-9</td>
<td>Wykoff et al., 2000</td>
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<tr>
<td></td>
<td>Enolase-1 (ENO1)</td>
<td>Semenza et al., 1996</td>
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<tr>
<td></td>
<td>Glucose transporter-1,3 (GLU1,3)</td>
<td>Chen et al., 2001</td>
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<tr>
<td></td>
<td>Glyceraldehyde phosphate dehydrogenase (GAPDH)</td>
<td>Graven et al., 1999</td>
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<tr>
<td></td>
<td>Hexokinase 1,2 (HK1,2)</td>
<td>Mathupala et al., 2001</td>
</tr>
</tbody>
</table>

### Increase glycolysis (O\textsubscript{2}-independent energy production)

- Lactate dehydrogenase-A (LDHA)
- Pyruvate kinase M (PKM)
- Phosphofructokinase L (PFKL)
- Phosphoglycerate kinase 1 (PGK1)
- 6-phosphofructo-2-kinase/glucone-2,6-bisphosphate-3 (PFKFB3)
- Cell proliferation/survival
  - Insulin-like growth factor-2 (IGF2)
  - Transforming growth factor-α (TGF-α)
  - Adrenomedullin (ADM)
  - Bcl-2/adenovirus EIB 19kD-interacting protein 3 (BNip3)
  - Nip3-like protein X (NIX)

### RBC production

- Semenza et al., 1991
- Semenza et al., 1996
- Semenza et al., 1999
- Minchen et al.
- Feldser et al., 2003
- Krishnan et al., 1998
- Cormier et al.
- Carrero et al.
- Bruick et al.
• EPO (erythropoietin) gene is now transcribed under influence of HIF1
  • 165 a.a. protein hormone that travels through bloodstream

in bone marrow some cells have EPO Receptor Protein on their cell surface allowing them to be stimulated by EPO...
ergythropoiesis yields new RBCs within ~ 4 days

(what genes are activated?)
**Signals** make it happen (inter-cellular and extracellular)
**Regulatory Proteins** achieve sequential differentiation
EPO hormone is recognized and bound by a cell-surface receptor protein (EPO receptor)

erythocyte progenitor cells are induced to proliferate
SFFV (spleen focus-forming virus) hijacks the system: viral gp55 envelope protein tricks the EPO receptor. Erythrocyte progenitor cells are induced to proliferate even though there is no EPO.
Misbehaving cells: cancer
(when normal controls are absent or ignored)
misbehaving cells: cancer

1) uncontrolled proliferation
2) invasion of other territories

benign tumor = (1) alone
malignant tumor = (1) + (2)
1) consequence of mutations
2) somatic cells

cancer = genetic disease

Figure 9-4 Essential Cell Biology 3/e (© Garland Science 2010)
cancer = genetic disease

1) consequence of mutations
2) somatic cells
3) cumulative mutations (~5-7)
human lifetime = $10^{16}$ cell divisions

spontaneous mutation rate = between $10^{-6}$ and $10^{-7}$ mutations per gene per cell

in one lifetime: a given gene could mutate $10^9$ times!!

why will most of these not matter?

Figure 20-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)
Two classes of mutations can cause cancer:

1) Those that inactivate gene function of a protein that **halts** cell proliferation (or other cancerous bad behavior) = Tumor Suppressor Genes
   - ex. p53, APC (\(\frac{1}{2}\) of all cancers have mutant p53)

2) Those that hyperactivate gene function of a protein that **promotes** cell proliferation (or other cancerous bad behavior) = Oncogene
   - ex. Ras

![Diagram of cancer progression](image-url)