Cancer stem cells in colorectal cancer

Denis Bulanin, CLS, NU 2015
Outline

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Colorectal cancer (CRC) is the third leading type of cancer with 1,361,000 newly recorded cases in 2012, accounting for more than 694,000 deaths worldwide and the fifth in Kazakhstan 2500-3000 cases a year.
Stages of colorectal cancer

- **Stage 0**: Early detection, no spread.
- **Stage I**: Cancer has spread to nearby lymph nodes.
- **Stage II**: Cancer has spread to nearby lymph nodes and parts of the bowel wall.
- **Stage III**: Cancer has spread to nearby lymph nodes and other areas of the abdomen.
- **Stage IV**: Cancer has spread to other parts of the body.
Anatomy of the intestine

Cell division takes place at the bottom of the crypt. Cells move up the vilus and shed to the lumen.
Intestinal crypt organization

1. Enterocytes - absorption of nutrients, contain microvilli increasing the surface area
2. Goblet cells – secretion of mucus
3. Enteroendocrine cells secret various hormones influencing gastrointestinal secretion or motility
4. Panneth cells – secrete anti-bacterial proteins into crypt lumen to protect the stem cells

Stem cells located at +1 and +4 positions
At +1 CS are actively cycling
At +4 SC slow cycling
Current models for development of a tumor

Stem cell vs. Cancer stem cell

**Stem cells features**
- Self renewal
- Multilineage differentiation
- Controlled division rate
- Niche dependent

**Cancer stem cell features**
- Self renewal
- Multilineage differentiation
- Tumorigenic potential
- Uncontrolled/Unlimited cell division rate
- Niche independent (often)
- High invasiveness capability
- Drug resistance
- Metastatic potential
- Genomic instability
- Existence of different pulls in one tumor
- Evolution
The cancer stem cell theory suggests that tumors grow like normal tissues of the body, with stem cells at the starting point of an organized system that produces new cells to make a tissue grow. According to this idea, tumors contain:
Cancer stem cells that divide and feed tumour growth. These cells can self-renew (copy themselves) extensively, and also produce more mature cells called transit amplifying cells.

Transit amplifying cells that divide a certain number of times then differentiate (or 'mature') into specialized tumor cells.
Specialized tumor cells that do not divide and so do not contribute to tumor growth. According to this idea, the cells in a tumor are in a strictly organized system with cancer stem cells at the top of the tree, giving rise to all other cancer cells.

The stochastic model of cancer growth gives a different possible explanation of tumour growth. This theory argues that all cancer cells have the same potential to grow and divide, but each cell chooses at random between self-renewal and differentiation. The cells in a tumor are not in an organized system – any cell has the same intrinsic potential to contribute to tumor growth.
Alternative strategies for cancer treatment

Chemotherapeutic drugs as a DNA damaging agents

Nitrogen mustards
Nitrosoureas:  
Alkyl sulfonates  
Triazines  
temozolomide  
Ethylениmines

P53 is necessary for DNA repair at G1
P53 is mutated in 50% of all cancers
Current and potential future research directions

1. We aimed to evaluate the resistance development of CSC to chemotherapeutic drugs
   a. CRCSC are grown in elevating concentrations of 5FU until they develop the resistance
   Resistance can be developed through a wide spectrum of protective mechanisms including DNA damage repair, altered cell-cycle checkpoint control, malfunction of apoptosis, drug transporters, and detoxifying enzymes

   b. Genomic approach using RNA sequencing of the cells that developed resistance to evaluate the potential mechanism of the resistance development in CRCSC

2. Using P38/MK2 cascade blockers in P53 mutants.
Thank you