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Streaming Organism

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Abstract — The cell kinetic characteristic of all epithelia is the same. All are analogs of the crypt-villus unit of the gastrointestinal mucosa. Each unit is nourished by at least one determined uncommitted stem cell (DS). When the DS divides, one of its progeny replaces the parent and remains a DS, while the other starts streaming outward. When entering a differentiation pathway it is called a committed stem cell (CS). Cells in the unit differentiate while streaming. Initially they continue multiplying and are called amplifying progenitors (P-cells), then they lose the capacity to synthesize DNA and become non-dividing (quiescent) end cells (Q-cells). All cells except the DS are transitional and short lived (in the crypt they live several days): only the DS is permanent. Since epithelial tissues are cell kinetic analogs of the crypt, it is assumed here that their neoplastic progression is analogous with the adenoma-carcinoma sequence of the crypt. Neoplasia starts when a normal cell is transformed into a neoplastic. If a transitional cell is hit by a carcinogen and transformed into a neoplastic, it soon will be washed out from the system. Only a transformed DS can maintain the neoplastic trait since it never leaves the crypt. Neoplasia is thus a pathology of the DS. There are two differentiation scales in the embryo: global and local. The first starts with the fertilized ovum that divides into stem cells that become more and more determined. Following gastrulation each determined stem cell generates its local progeny of transitional cells that make the tissue units. Determined stem cells are direct descendants of the fertilized ovum, while their transitional progenitors are direct descendants of determined stem cells.

Changing representation of the organism

Until the beginning of the twentieth century the human organism was conceived as an engine immersed in its own liquid environment. It was assumed that all engine constituents exist as long as the organism does. Only the watery envelope turns over, maintaining a steady state that is called homeostasis.

The first experiments with radioactive isotopes that were introduced in the 1930s revealed that all molecules of the organism continuously turn over and are randomly replaced with new ones. In spite of this, microscopic constituents, e.g. cells and tissues, were assumed to be permanent and replaced only when damaged. The 1950s revealed that molecular turnover is not at all random. Molecules are replaced according to the fi-fo rule (first in, first out). The first that are incorporated are also the first to leave, which was first demonstrated in protein synthesis. The protein starts its existence when its DNA code is translated into RNA that serves as template for the assembly of amino acids into short protein chains that grow with

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time and stream away from the nucleus. They stream through sub-microscopic cavities of the endoplasmic reticulum toward the cell periphery where they are secreted. The protein is born near the nucleus and ages while streaming. Its age may be read off by its position in the cytoplasm, the more distant it is from the nucleus the older it gets.

Streaming tissues

Experiments with tritiated thymidine revealed that cells turn over in an orderly fashion. Thymidine is a building block of DNA. When a cell decides to divide, it synthesizes a new DNA strand and so doubles its DNA content. If at the same time tritiated thymidine is injected into the body it is incorporated into the DNA. Cells that do not intend to divide do not synthesize DNA and remain unlabeled.

Using this tool, Leblond divided cells into three groups (1): renewing populations, e.g. skin or the inner lining of the gut; static populations, e.g. liver; and non-dividing cells, e.g. nerve cells that in the adult do not divide. Initially he assumed that turnover in dividing cells proceeds in a random fashion. Soon it was discovered that in renewing populations turnover is oriented. Dividing cells occupy the unit interior. Following cell division one cell replaces the parent while the other advances outward. Together with other newly formed cells it participates in a cell stream that is directed from tissue interior outward. Cells are neither pushed nor pulled in a mechanical sense, they simply stream, in the same way as water molecules do in the river. By this analogy the cells are carried on a 'metabolic' stream.

Recently we have demonstrated that static populations, e.g. adrenal cortex (2), salivary glands (3), pancreas (4) and liver (5), also stream. Thus, all cells except nerve cells continuously stream from tissue interior outward. In spite of this, the organism maintains an invariant appearance, a property that is called homeorrhesis. These experiments demonstrated that all epithelial tissues have the same cell kinetic make up, and are analogs of the crypt-villus unit of the intestinal mucosa.

The streaming tissue theory to be presented herewith provides one cell-kinetic frame work for describing neoplastic progression. Since all epithelial tissues behave cell-kinetically as the crypt-villus unit, we shall first describe its kinetic features. Next, the cell kinetic properties of the 'adenoma-carcinoma' sequence in the crypt will be described (6). Since epithelial tissues are cell kinetic analogs of the crypt, it is assumed here that their neoplastic progression is analogous with the adenoma-carcinoma sequence of the crypt. The following section illustrates a prototype of the streaming tissue, the crypt-villus unit.

The crypt-villus unit

All cells in the unit are descendants of one cell, called a determined stem cell (DS) (Fig. 1). When the DS divides, one of its progeny replaces the parent and remains a DS, while the other starts streaming outward. It may differentiate along four cell lines; absorptive,

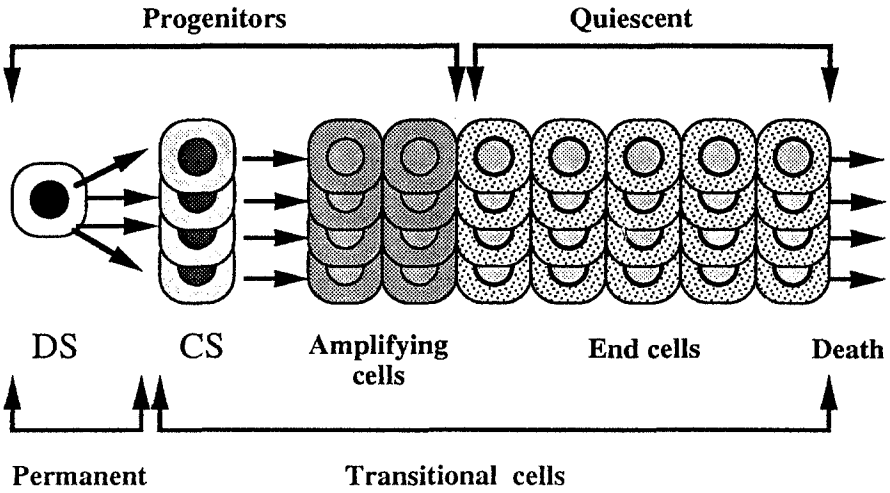

Fig. 1 The tissue unit. The only permanent cell in the unit is called determined stem cell (DS). It differentiates into four committed stem cells (CS), each maturing along a distinct pathway.

goblet, endocrine and Paneth. When entering a differentiation pathway it turns into a committed stem cell (CS). The CS differentiates while streaming, gradually maturing until reaching the unit periphery where it dies. If for example the DS is scheduled to generate a mucus-producing cell line, one of its progeny becomes a mucus-CS with a big nucleus and scanty cytoplasm. At this stage nothing reveals that it will turn into a secretory cell since it still lacks the typical organelles. As the cell advances through the unit the organelles appear and the cell starts secreting its product. This process is called differentiation. Differentiation is time dependent. The older the cell the more differentiated it becomes. In the crypt-villus unit the entire differentiation process lasts several days.

Cells in the unit differentiate while streaming. Initially they continue multiplying and are called amplifying progenitors (P-cells), then they lose the capacity to synthesize DNA and become non-dividing (quiescent) end cells (Q-cells). When reaching the unit periphery they die. Cell death in the healthy tissue unit is a differentiation state. In the crypt-villus, cells are sloughed off at the villus tip. In parenchymatous organs, like liver, cells die by apoptosis. This differentiation dependent cell death has to be distinguished from random cell death, necrosis, that occurs only in disease.

When the DS divides, one of its progeny replaces the parent and remains a DS and the other turns into a streaming transitional cell. A DS division generally results in two different cells, a stem and a transitional. It is therefore called an asymmetric division. A transitional cell may divide several times (if it is an amplifying cell). Both its descendants are always transitional. A cell division that generates two equal cells is called symmetric. Since all transitional cells are descendants of one DS, they belong to one cell clone and the entire unit is monoclonal.

All cells except the DS are transitional and short lived (they live several days): only the DS is permanent. It is the source of a cell stream from tissue interior and outward. After destroying transitional cells, the tissue unit is repopulated with new cells that are formed by the DS. Yet when the DS dies transitional cells continue streaming and since not being replaced by newcomers, soon the entire unit disappears.

Adenoma-cancer sequence in the colon

Progenitors generally occupy the lower two-thirds of the healthy crypt. Non-dividing Q-cells occupy the upper third. The healthy crypt is divided into two compartments, P and Q. Following dimethylhydrazine injection P-cells enter the upper third, the P-compartment elongates, and the Q-compartment shrinks, while crypt length does not change. This change was called by Lipkin a Phase-1 lesion (7,8) (Fig. 2). Q-compartment shrinkage is known also as maturation arrest. As carcinogen treatment continues, the crypt starts elongating, the P-compartment elongates proportionally, and Q-compartment shrinks (Phase-2 lesion). Finally the crypt grows additional branches (Phase-3 lesion) (9). Apparently each new branch is inhabited by a distinct DS. Phase-3 lesions are marked by a rising number of DS. Subsequent changes, e.g. dysplasias, carcinoma in situ and carcinoma, exhibit the same cell kinetic changes, only much more pronounced. All epithelial cancers exhibit the same cell kinetic changes.

Neoplasia is a stem cell pathology

Neoplasia starts when a normal cell is transformed into a neoplastic one. If a transitional cell is hit by a carcinogen and transformed into a neoplastic one, it soon will be washed out from the system. Only a transformed DS can maintain the neoplastic trait since it never leaves the crypt. The genetic change is then inherited by the stem cell progeny that forms a neoplastic clone. The three phases described above are phenotypic manifestations of the stem cell change. Neoplasia is thus a stem cell pathology. We have distinguished above between determined uncommitted (DS) and committed stem (CS) cells. Since the latter are transitional, neoplasia is a pathology of the determined uncommitted stem cell (10–12).

Global and local differentiation

We may distinguish now between two differentiation scales: global and local. The first starts with the fertilized ovum that divides into stem cells that become more and more determined (Fig. 3). Following gastrulation each determined stem cell generates its local progeny of transitional cells that make the tissue units. Determined stem cells are direct descendants of the fertilized ovum, while their transitional progenitors are direct descendants of determined stem cells in their units. Global differentiation is equivalent to the notion of increasing determination. Globally differentiating stem cells carry the somatic genotype and distribute it among tissue units. Transitional cells make up the adult phenotype. Roughly 0.2% of crypt-villus cells are determined stem cells. Extrapolated to other tissue units, this means that 99.8% of all cells are transitional. Only the determined stem cell popu-

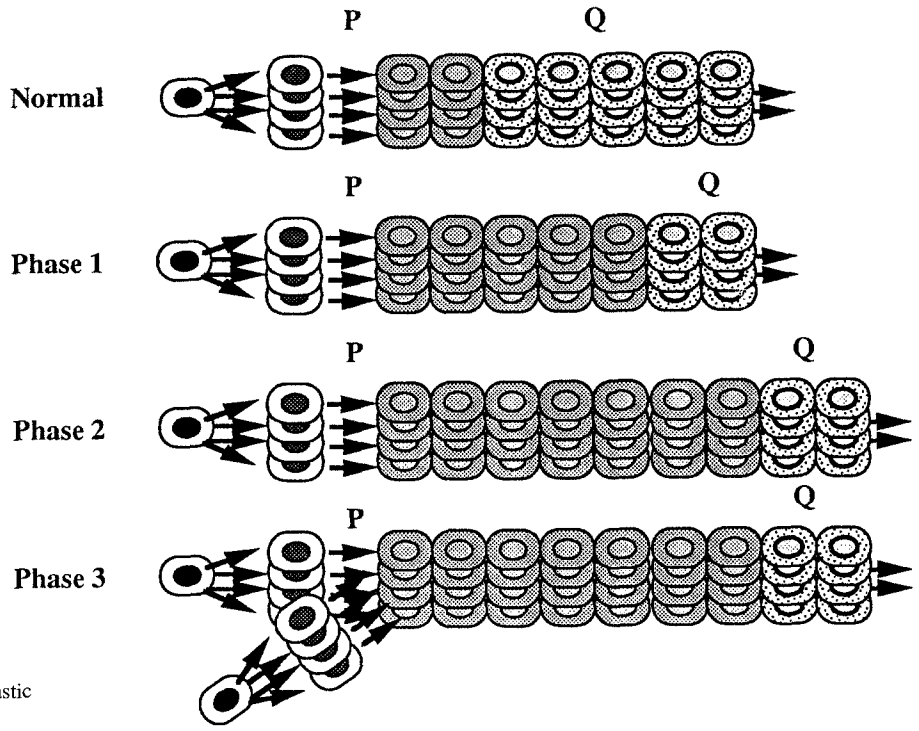

Fig. 2 First phases of neoplastic progression.

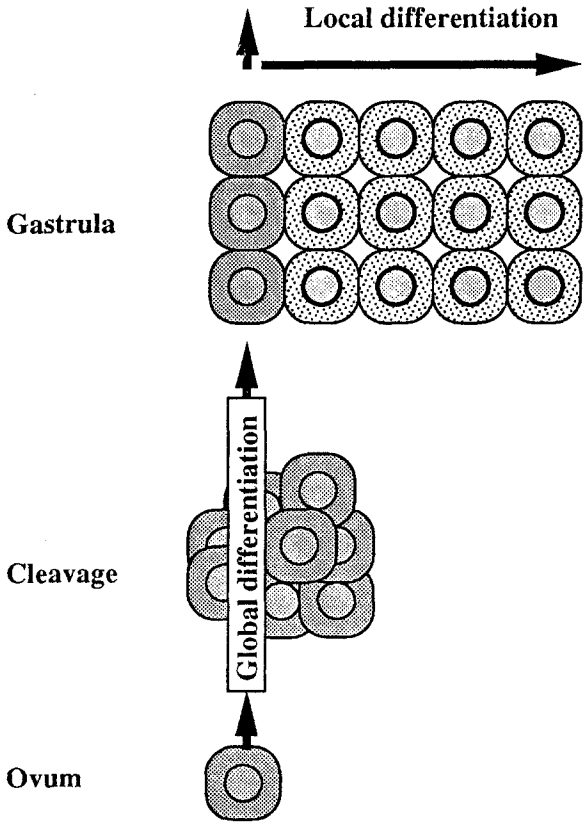

Fig. 3 Global and local differentiation.

lation lives as long as the organism does, all other cells are short lived.

Neoplastic resistance to chemotherapy

Most chemotherapy agents are either mitotic poisons (M-poisons), or they inhibit DNA synthesis (S-poisons). Amplifying cells respond first to chemotherapy, since they multiply relatively fast. Neoplastic DS are less sensitive, since they are dividing much more slowly. These stem cells are known as clonogenic since when treatment ends, they generate new progeny of transitional neoplastic cells that repopulate the tumor or its metastases. Since each treatment eliminates sensitive transitional cells, leaving behind slow cycling clonogenic stem cells, it appears as if chemotherapy gradually fails, while in reality chemotherapy fails from the beginning. It eliminates the less significant transitional neoplastic cells, leaving behind the clonogenic.

The idea that everything streams, or Panta Rhei, dates back to the Greek philosopher Heraclitus, who lived in the fifth century B.C. He said: 'You never enter the same river twice' since it continuously changes. To which we may now add: 'You never meet the same individual twice' since all its constituents change (13,14).

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