Medical Hypotheses 7: 1241-1251, 1981

THE HISTOGENESIS OF GLANDULAR NEOPLASIA

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ABSTRACT

Tissues in the organism may be divided according to their proliferative capacities into three categories: 1. Fast replicators (FR) e.g., epidermis; 2. Slow replicators (SR) e.g., liver and 3. Non replicators (NR) e.g., nerve cells. Evidence is presented that FR as well as SR tissues continuously proliferate exhibiting two distinct histomorphological structures; a progenitor region in which cells are formed and a functional region into which they enter Throughout their displacement, the cells cover a typical path denominated as tissue radius. The SR tissues e.g., parotid gland, mammary gland, liver and prostate, exhibit similar ontogenies, and proceed during regeneration and neoplasia through similar stages. All are compound glands with two distinct stem cell types, one residing in the excretory duct epithelium and the second in the intercalated duct. Each stem cell gives rise to its typical neoplasm. Excretory duct originating neoplasms consist of papillomas, epidermal and adenocarcinomas, while intercalated stem cell bound neoplasms embrace the canalicular adenoma, oncocytoma acinic cell and lobular carcinomata. All tissues continuously stream along the tissue radius. Evidence is presented that even the liver cords are continuously displaced from the limiting lamina toward the terminal hepatic (or central) vein. The histological image of these tissues actually reflects an instantaneous picture of cells in a continuous flux.

Cancer, Neoplasia

INTRODUCTION

Tissues in the organism may be divided according to their proliferative capacity into three categories: 1. Fast replicators (FR) e.g., the gastrointestinal (GI) mucosa, epidermis or bone marrow; 2. Slow replicators (SR) e.g., liver and kidney and 3. Non replicators (NR) e.g., nerve cells which after birth cease to proliferate. The first two categories are known respectively also as "continuous" and "discontinuous" replicators. These terms originate in the assumption that organs like liver or exocrine glands remain essentially static, proliferating only occasionally e.g., during regeneration. Recent studies to be described herewith have revealed that even these tissues

continuously proliferate, yet do so much more slowly than the first group so that the application of the adjectives "Fast" and "Slow" for their description seems more appropriate.

Cell proliferation in the FR is generally associated with a typical histomorphological pattern (1). Each FR tissue is composed of two cell subpopulations, progenitors and functional cells, occupying two distinct tissue regions. Cell proliferation in the progenitor region is associated with cell displacement into the functional. In the GI mucosa for instance, the crypt represents the progenitor region while the villus harbours the functional cells. Cells formed in the crypt are continuously displaced into the villus. Such an arrangement common to all FR tissues, is expressed also by a typical tissue orientation according to which cells are formed at tissue origin, the progenitor region site, and are displaced outward toward the tissue periphery. The typical displacement trajectory has been denominated as tissue radius (1). Radius origin is occupied by the tissue stem cell. It is the only cell maintaining its location in the tissue while all its descendants continuously flow outward. Each stem cell divides asymmetrically into two daughter cells. One replaces its parent to remain a stem cell, while its kin, which already had been slightly displaced outward, starts its voyage toward the tissue periphery, differentiating as it goes. It may continue to divide several times, generating a cell clone known as transit cells (2). Upon crossing the progenitor region outer boundary, it ceases to proliferate, maturing into a functional cell. The FR tissue may thus be viewed as a cell stream nourished by its stem cell. Its histological image reflects an instantaneous picture of this flux at a given moment. However the tissue is oriented, this flux may easily be reconstructed from the tissue's histomorphological structure. Suppose the tissue exists in a steady state and all its cells are eliminated at its periphery, since the tissue always maintains a constant cell count, the loss of a cell has to be replenished by the formation of a new one at tissue origin so that the overall structure is preserved. The tissue radius actually summarizes the life history of a typical cell. Once the radius and its orientation have been determined, the various cell locations on the radius are related to the differentiation states of the cells occupying it, so that a cell at location i+1 is generally older or more differentiated than its proximal neighbour at location i. The displaced tissue cell along the radius may be viewed as a point advancing in a rectlinear motion and studied in the realm of the Galilean Geometry in which the comparison between two FR tissues e.g., epidermis and GI mucosa reduces to the study of trajectories outlined by the advancing keratinocyte and enterocyte (3). All FR tissues respond to external noxae affecting cell turnover in a similar fashion (4). One response,neoplastic progression, is shared by them all so that neoplasias originating in the FR tissue evolve through similar stages outlined previously in form of the "ideal human neoplasm" theory (5). Neoplastic progression is marked by two processes proceeding hand in hand; a gradual and continuous progenitor region expansion accompanied by its dedifferentiation. Since all FR tissues are regarded here as cell streams nourished by their stem cells generating a typical trajectory of their displaced descendants, each neoplastic state is marked by its trajectory changing throughout neoplastic progression (3-5). These changes are expressed in relation to the tissue radius, so that its proper outlining is essential for the successful application of the method.

Similar reasoning will be applied herewith for the description of neoplastic progression in SR tissues. It is intended here to proide the evidence that excretory glands representing in this study SR tissues, do exhibit a typical tissue radius along which cells are continuously displaced. Other SR tissue e.g., endocrine glands and the kidney will be dealt with separately. The outline of a SR tissue radius is not at all simple. In the FR, the radius may be visualized by labelling epithelia once with tritiated thymidine (^{3}HTdR) and following their displacement in autoradiograms of histological sections examined at various time intervals afterwards (1). In the GI mucosa for instance, 0.5 h after ^{3}HTdR instillation, all labelled cells are confined to the crypt. These are the progenitors which at time of injection were synthesizing DNA. The site of the most distant labelled cell, the "leading edge", marks the outer progenitor region boundary. During the subsequent days, labelled cells advance along the villus until reaching its tip whereupon they slough off into the intestinal lumen. The advancing cells are functional cells which have been labelled during their progenitor state and ceased to proliferate since, retaining their labelled DNA. Their cruising velocity may be determined by following the displacement of their leading edge (1). In order to outline the tortuous radius of a SR tissue, such an experiment would require a three dimensional tissue reconstruction from sequential histological sections. Fortunately, important deductions may be made even from a simple outline of the progenitor and functional regions and their relative changes during neoplastic progression. Since all exocrine glands to be described herewith exhibit similar ontogenies, regeneration response and neoplastic progression, they all will be regarded as variants of an "ideal exocrine gland", so that a manifestation observed in one gland will be assumed to exist in them all. First it is intended to explore these manifestations separately in each gland.

SALIVARY GLANDS

The first identifiable evidence of a salivary gland origin is manifested by a double row of cuboidal progenitor cells arising from the surface epithelium as an invagination into the subjacent mesenchyme. The more proximal cells of this cord begin to stratify in two double layers (6) forming the future excretory duct. This structure is appended by a single cell cord, the "terminal bulb", an anlage for the intralobular salivary parenchyma, differentiating in the adult into the intercalated duct (7). Both duct types represent different stem cell determination states. In the adult the excretory duct stem cell gives rise only to excretory duct stratified or columnar epithelia, while the intercalated duct yields the salivary gland acinus and its adjacent striated duct (7).

The adult intercalated duct cells may be induced to proliferate by various stimuli. Following isoproterenol injection, centroacinar cells exhibit an increased mitotic activity (8). Partial submandibular gland extirpation in the rat induces intercalated duct proliferation followed by the formation of new acini (9), while parotid extirpation in the mouse induces a similar response in the remaining contralateral gland (10). Each progenitor region generates its typical neoplasms. The excretory duct with its "epidermal configuration" may form an intraductal papilloma or epidermoid carcinoma, while

the intercalated duct neoplasms include the canalicular adenoma, oncocytoma and acinic cell carcinoma (6). Since the excretory duct epithelium resembles the epidermis it is assumed to belong to the FR tissue group and its neoplasms to progress through the "ideal human neoplasm" stages (5). Only the pleiomorphic adenoma known also as mixed tumor of the parotid, marked by a neoplastic involvement of its parenchyma as well as stroma, fails to fit into this scheme. It is assumed here to belong to a separate neoplastic entity, congenital aberrations. Neoplasms may be broadly classified into three groups. The first two originate in the FR and, respectively, SR tissues, while the third includes "congenital tumors"e.g., neuroblastoma or Wilms tumor. Pleiomorphic adenoma is believed to belong to the third originating in congenital aberrations or cell malformations (5).

The intercalated duct progenitor cell serves as origin for two radii pointing in opposite directions (Fig. 1). Proximally, the intercalated cells differentiate into the striated duct epithelium, while distally into acinus components e.g., serous, mucous and myoepithelial cells. Intercalated stem cell proliferation is assumed here to generate a slow yet continuous cell displacement in both directions which during regeneration markedly accelerates. The inwardly displaced cells mature into the acinus component and then gradually disintegrate, while the outwardly displaced cells make up the striated duct.

MAMMARY GLANDS

The development of mammary glands starts in the form of an ectodermal thickening running from the axilla to the groin. At the future mammary gland site, the primordium continues to thicken, growing into underlying dermis, giving origin to about 20 secondary sprouts (11). Each of these cords develops later into a compound exocrine gland. They are surrounded by a special connective tissue originating in the epidermal papillary layer, a mammary epithelium lamina propria, intimately surrounding the branching duct system (12). At birth they exist only as rudiments. During puberty they branch further, while the true secretory units develop only during pregnancy differentiating into alveoli. Following the discontinuation of breast feeding most alveoli and terminal ducts disappear. Each main excretory or lactiferous duct drains a separate mammary lobe branching into many intralobar ducts. Mammary and salivary glands obviously exhibit similar ontogenies, starting in the form of a simple gland appended by a "terminal bulb" differentiating at a later stage into the intercalated duct system which in the mamma received the name "terminal ductular lobular unit" (TDLU) (13) and its acinus analog is called an alveolus. Both the TDLU as well as its accompanying lamina propria participate in the mammary changes during lactation and neoplasia. Adult normal resting mammary gland pieces were grown in organ cultures and labelled with ^{3}HTdR (14). Autoradiograms of the sectioned pieces revealed labelling in epithelia as well as their accompanying lamina propria fibroblasts. A similar response was observed in Sprague Dawley virgin rats injected with ^{3}HTdR (15). Twenty percent of all examined terminal and bud epithelia were labelled. Both experiments indicate the TDLU to be continuously proliferating even in quiescent states.

The mamma, like the salivary gland exhibits two stem cell types: the lactiferous wall epithelium and the terminal duct. Both serve as a source for two neoplastic lines. Duct papilloma, sqamous cell carcinomas arising in the first, while ductal and lobular carcinomas in the second. It seems striking that in most mammary neoplasias, lamina propria constituents actively proliferate (16), accompanying the invading lobular carcinoma in situ and are assumed here to contribute the fibrous element of the scirrhous carcinoma. Stromal proliferation is assumed here to reflect a parenchymal-stromal interaction in the adult similar to that observed in the embryo, where it is believed that the mesenchyme actually determines or governs epithelial differentiation. Only when cultured with its mesenchyme, mammary epithelium undergoes its typical morphogenesis (17). If however salivary gland is used as mesenchyme donor, the subsequent morphogenesis of the mammary epithelium follows the salivary pattern keeping only a mammary type of biochemical activity (18). It seems as if this interaction between the two tissues continues also during neoplasia. A similar dedicated lamina propria is postulated here to accompany the salivary gland epithelium during its morphogenesis, regeneration and neoplastic progression.

The pancreas, the "abdominal salivary gland" apparently behaves accordinly. Its ontogeny (19)follows the course described above. It still serves as an elegant model for the study of tissue interactions and morphogenesis (20), and is assumed to have a dedicated lamina propria.

THE STREAMING LIVER

The liver starts its existence in the form of a small bud arising from a thickened area of the duodenal endoderm, penetrating the transverse septum. It soon splits into a cranial or hepatic and a caudal or cystic portion. The latter becomes closely associated with the ventral pancreatic bud, giving rise to the gall bladder and cystic duct (21). Both portions exhibit a salivary gland ontogeny, generating a compound gland with acini in the form of liver cell cords. We should thus expect to find in the liver two distinct stem cell types residing respectively in the excretory and intercalated ducts. The first clearly resembles the FR tissue pattern. Its progenitor cells are scattered along the epithelium-lamina propria junction (22) breeding stratified squamous or columnar cells and their typical neoplasms e.g., papilloma, sqamous oradenocarcinoma. The intercalated duct site seems less obvious. It should be located in the Hering ducts (23) connecting the terminal bile ducts and liver cords, believed to generate the oval cells. In the normal liver they exhibit only scanty mitotic activity. Most of the labelled cells following ^{3}HTdR injection to rats or mice, occupy the periportal limiting lamina (24). This does not yet exclude the possibility that the stem cells reside in the terminal Hering duct portion.

The liver acinus extends from the portal space toward the central vein known also as the terminal hepatic vein (THV) (25, 26). Its liver cords are arranged along an axis consisting of a terminal hepatic arteriole, portal vein, bile ductules, lymph vessels and nerves. The cords, extending up to the terminal hepatic vein may be divided into three zones, I-III, each marked by a distinct metabolic function performed by its cell elements. The first labelled cells following ^{3}HTdR injection appear along the limiting lamina of zone I gradually moving toward the terminal hepatic vein, a voyage lasting for 150 days (24). Following partial hepatectomy, liver cytogenesis and displacement accelerate (26-28). Blikkendaal et al. studied liver cell displacement along liver cell cords connecting the portal space and the terminal hepatic veins.

This "standard plate" of liver cells consisted on the average of 16 cells which were numbered according to their distance from the limiting lamina. Position numbers 1-6 corresponded to zone I, 7-11 to zone II, and 12-16 to zone III of Rappaport's simple liver acinus (24). Three hours after ^{3}HTdR injection, cells occupied position 1-11. In livers observed after 1, 7, 30 and 90 days, the labelled cells were gradually displaced toward the terminal hepatic vein. The "standard plate" fulfills the above defined tissue radius requirements, extending from acinus origin at the terminal Hering duct portion, toward acinus periphery at the terminal hepatic vein (Fig. 1). The progenitor region extending up to location 11 while the periphery rests at location 16 adjacent to the terminal hepatic vein. This experiment clearly indicates liver cells to be continuously displaced along the tissue radius outward exactly as in the colonic crypt, yet much more slowly. Since throughout this voyage liver cells cross zones I to III, these zones actually represent the consecutive differentiation states a liver cell assumes.Following partial hepatectomy this displacement is markedly accelerated (29-31). Within 24 hours most progenitors divide, so accelerating the hepatocyte displacement.

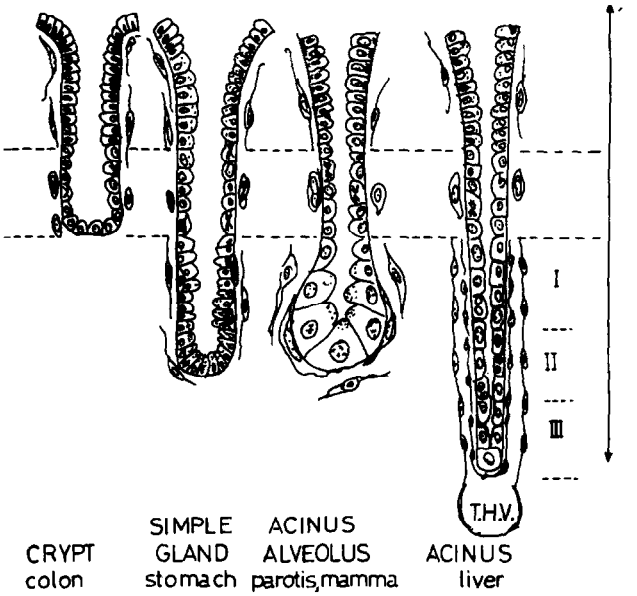

Fig. 1. Intercalated duct analogs
THV (terminal hepatic vein)

The acinus analogy between liver and salivary gland may be stretched even further so as to expect also an opposite cell displacement from the terminal Hering duct portions outward, accompanied by a differentiation into the terminal bile ductules. It is proposed herewith that the Hering duct stem cell actually forms the origin of two oppositely directed radii, each generating its own cell genealogy as well as neoplasm. Accordingly, the acinus facing stem cell generates the hepatocellular carcinoma while its oppositely directed kin, the cholangiocarcinoma.

THE PROSTATE

Series of solid buds arise in the endodermal part of the primitive embryonal urethra penetrating the surrounding mesenchyme (32). The buds are arranged into five groups: an anterior, a middle, two lateral and a posterior. In the adult they differentiate into mucosal, submucosal and main glands. The first groups harbour short and simple glands, while the other two are compound glands (33). The first two groups are the site of benign prostatic hypertrophy while the main glands originating in the embryonal posterior buds may progress toward neoplasia. Since these are compound glands drained by excretory ducts, one may expect them to breed two neoplastic lines: tubular-scirrhous and alveolar medullary (34). Other neoplasms known as paraprostatic arise in the mucosal and submucosal glands(35).

THE HISTOKINETIC STRUCTURE OF THE EXOCRINE GLAND

The foregoing sections should convince the reader that the five major exocrine glands have much in common. They share similar ontogenies, exhibit two distinct progenitor types and respectively two neoplastic groups: excretory and intercalated duct originating neoplasms. Their analogy will serve here for the definition of the "ideal excretory gland" representing them all. This theoretical gland exhibits all the features described above and more. Features more distinct in some glands are assumed to exist in the whole group. We shall distinguish between simple and compound glands (36). The first consist of a duct draining one or more secretory units, while the compound gland has a branching duct system conveying secretions from many secretory units. The secretory units may be tubular, alveolar or acinar in shape. All will be referred here as "acinus". The best studied simple excretory gland resides in the gastric body wall, exhibiting a neck, the site of the epithelial progenitors (37). Cells nascent there are displaced in opposite directions along two radii. Outward, the cells mature into gastric pit epithelia, while the inward displaced cells differentiate into zymogenic, parietal, argentaffine and sometimes also Paneth cells. The terminal secretory unit of the compound gland is regarded here as a simple gland analog. It has received various names:"acinus", "terminal and bud" (15), "terminal ductal lobular unit" (13). In all these unit cells are being continuously displaced along tissue radii pointing in two opposite directions (Fig. 1). The excretory ducts belong to the FR tissue group and obey the rules outlined in the "ideal human neoplasm" theory (5). They exhibit only one tissue radius pointing inward, into the excretory duct lumen.

PROLIFERON

During its ontogenic development the exocrine gland epithelium penetrates its underlying mesenchyme differentiating into intra- and extralobular connective tissue. The first is regarded here as the gland's lamina propria participating in its metabolic and proliferative activities. In the mammary gland it is most pronounced, resembling the dermal papillary layer, responding to all hormonal stimuli affecting the mammary gland during puberty, pregnancy and lactation. Its morphological changes involve also the lamina

propria blood and lymphatic vessels as well as its nerve supply. The lamina propria participates also in salivary gland regeneration. Even in the regenerating liver littoral cells proliferate along with liver cells (29) so that the regenerating organ restores not only the liver cords' continuity but the vascular supply e.g., sinusoids, as well. It is proposed further that the lamina propria participates also in the streaming exocrine gland. The liver cell nascent at the terminal lamina encounters a nascent endothelial cell, to accompany it during its journey toward the terminal hepatic vein whereupon both disintegrate. Such a joint displacement is observable in the colonic crypt where the epithelial progenitor region is apparently surrounded by lamina propria progenitors. Each epithelial cell nascent there is accompanied by a newly formed fibroblast, a capillary bud and a special nerve fibre sprout. All are assembled into a tissue unit "the proliferon" (38, 39). The newly assembled proliferon is gradually displaced outward. Epithelial maturation into a goblet cell is responded by a fibroblast differentiation into collagen secreting fibrocytes, and when the first reaches the crypt outlet to be shed off into the colonic lumen, the dying connective tissue cell disintegrates. Each intercalated duct is assumed herewith to be surrounded by lamina propria progenitors accompanying the displaced parenchyma in the form of proliferon units.

NEOPLASTIC PROGRESSION

Since all exocrine glands exhibit tissue radii, the FR states of neoplastic progression are assumed to have their counterpart in the SR as well and the "ideal human neoplasm" theory is assumed to embrace also the exocrine gland neoplasms. Neoplastic progression starts in the colon with a progenitor region expansion accompanied by maturation arrest (Phase 1 lesion (5)). Similar changes are assumed to occur in the intercalated duct. Crypt branching, known in the colon as a Phase 2 lesion is believed here to be manifested by a branching of the intercalated duct. The hyperplastic terminal duct (13) is regarded here as a villous adenoma analog and so on, so that exocrine neoplasia proceeds through the same stages as described for FR derived neoplasms(3-5).

PANTA RHEI

"Everything exists in a state of flux", the essence of Heraclitus' philosophy (500 B.C.) (40), serves as motto of the presented study. All tissues in the organism except the neurons continuously renew and "flow", yet the organism preserves its appearance. "You cannot step twice into the same river" assumes in the present context "You never meet the same human being twice". The modern era of Heraclitus' philosophy started with the introduction of isotopes into medical research, highlighted by the concept of "turnover". Modern histokinetic and histochemical techniques revealed that turnover actually proceeds in an oriented fashion, manifested in the organism by flowing matter, so that both, turnover and flux, are associated phenomena.

Throughout its lifetime each cell traces a definite trajectory, the outline of which forms the cornerstone for a quantitative histopathology.

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