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Introduction: A Tribute to Cell-to-Cell Channels

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Introduction

Pascal's saying "The heart has its reasons which reason knows not" is well known. According to him, the mind thinks in two ways, the mathematical way (*l'esprit geometrique*) and the finer, subtler way (*l'esprit de finesse*). In the latter case we see and feel the truth. The truth or the idea — that a homeostatic mechanism mediated by communication through cell-to-cell channels governs the growth and differentiation of cells and that this mechanism is gradually weakened and eventually breached during the pathogenesis of several diseases, including cancer — was proposed by Professor Werner Loewenstein several decades ago, to whom this volume is dedicated. From time immemorial, a theory or hypothesis has inspired human intellect by prescribing to it the goal to which experimental evidence must approximate, if it is true to itself. Upon discovering a pathway that directly interconnected the cytoplasmic interiors of contiguous epithelial cells (Kanno & Loewenstein 1964b, 1966; Loewenstein & Kanno, 1964), Werner realized that our faculty of knowledge felt a much higher need of a hypothesis. I will not dwell on all aspects of the rich scientific life of Werner, for during his active, hands-on scientific career spanning from 1950 till 1993, he published nearly 100 research papers, 33 of which were in either *Nature* or *Science*, a fact that highlights his passion for and innovative contributions to science. Since the discovery of cell-to-cell channels, the past two decades have seen a considerable increase in our knowledge about the molecular architecture of these channels, their assembly into ensembles called "gap junctions," the signaling molecules transmitted through them and the myriad roles played through this form of signaling in maintaining homeostatic controls at the organismic, systemic, tissue and cellular levels. Thanks to the work of a number of laboratories (Goodenough, Goliger & Paul, 1996; Kumar & Gilula, 1996; Harris, 2001; Saez et al., 2003; Segretain & Falk, 2004; Wei, Xu & Lo, 2004; Sosinsky & Nicholson, 2005; Sohl, Maxeiner & Willecke, 2005), tremendous strides have been made in research related to cell-cell communication mediated by gap junctional channels, and new insights have been provided to several important questions, both familiar and intriguing, raised by Werner in several of his thought-provoking articles (Loewenstein, 1967, 1968a, 1968b, 1974, 1979, 1981, 1989).

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Molecular Anatomy of a Cell-to-Cell Channel and Gap Junction Assembly

Based on a series of experiments performed in the early 1960s (Kanno & Loewenstein 1964a, 1964b, 1966; Loewenstein & Kanno, 1964), Werner sketched out the direct pathway of communication, which he represented as a composite of unitary membrane conduits; teased it out in abstract terms as a special cell-to-cell channel formed of two symmetrical halves made by the collaborative efforts of two neighboring cells; and envisioned it as a pair of tightly joined proteinaceous hemichannels spanning the intercellular gap, with the channel core lined by the hydrophilic amino acids that allow it to act as a molecular sieve (Fig. 1). The channel has endured the test of time and has now been shown to be formed by the members of a family of about 20 proteins called "connexins" that first

oligomerize as hexamers to form hemichannels or connexons, which are then transported to the cell surface and dock with their counterparts on adjacent cells in the extracellular space. Conglomeration of several cell-to-cell channels at particular spots between adjacent cells leads to the formation of large macromolecular structures called "gap junctions" (Fig. 2). Our view of the channel pore has to date remained unchanged with respect to its permeant selectivity to hydrophilic molecules; however, based on the mutagenic studies of connexins, the structural analysis of channels at atomic resolution and the existence of inherited disease-linked mutations, a clearer image of the pore architecture, its mode of regulation and its molecular sieving properties has begun to unfold (Goodenough et al., 1996; Harris, 2001; Saez et al., 2003; Sosinsky & Nicholson, 2005) (Fig. 3).

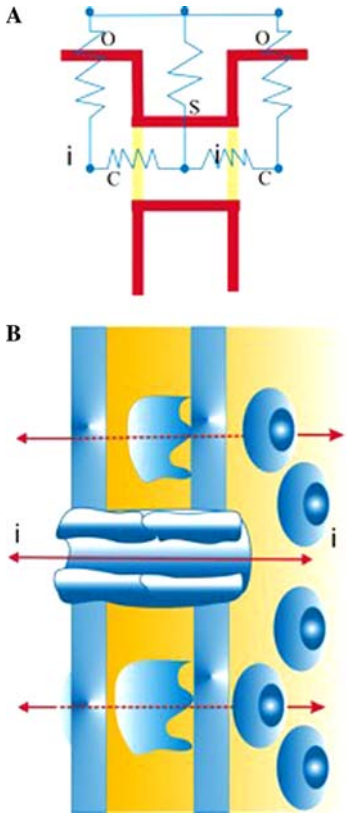

Fig. 1 Loewenstein's cell-to-cell channel. **a** Unit as originally inferred from biophysical measurements. Junctional aqueous membrane channels (*C-C*), one from each apposing cell membrane (*O*), and insulation (*S*) of those elements from the exterior. *i*, Interiors of the two cells. A permeable junction is composed of many such units (Loewenstein, 1966). **b** Unit represented as a protein channel. These features are vested in a pair of matching protochannnels, made of protein, traversing the membranes. A protochannel pair has a continuous aqueous bore (*C-C* element in **a**) and interlocking wall with hydrophobic exteriors providing continuous insulation (*S* element in **a**). (From Loewenstein, 1974; redrawn in color)

Earlier studies by Werner and others showed that cell-to-cell channels were formed randomly and perhaps stochastically at the areas of cell-to-cell contact (Loewenstein, 1967, 1975; Johnson et al., 1974). Because of the short half-life of connexins in the range of 2-5 h, the recruitment of channels or connexons to the preformed gap junctional plaque and their subsequent incorporation is considered to be a random process and the plaque, a highly dynamic structure that incessantly models and remodels itself, collapsing with unpredictable kinetics into annular junctions, which are degraded (Evans & Martin, 2002; Laird, 2006; Saez et al., 2003; Berthoud et al., 2004; Segretain & Falk 2004) (Fig. 4). These genuine advances and others have set the stage for new investigations on the regulatory mechanisms that govern this modeling and remodeling, such as the trafficking of connexons to the cell surface and their subsequent recruitment and assembly into gap junctions, followed by their disassembly and degradation.

If the transfer of information between and among cells were to fulfill a homeostatic role, the biogenesis of gap junctions has to be precisely regulated spatiotemporally in response to physiological stimuli, be they intrinsic (hormonal) or extrinsic (environmental). Our knowledge of the molecular events leading to the formation of a primordial gap junction plaque, the identity of molecular players involved in the trafficking of connexins along the secretory pathway and their assembly into gap junctions, the degradation of gap junctions along the endocytic pathway as well as the physiological stimuli that orchestrate these events has remained scant (Berthoud et al., 2004; Laird, 2006; Segretain & Falk, 2004). These intriguing regulatory aspects of the biogenesis of gap junctions are discussed in the articles in this issue from the laboratories of Hiroshi Yamasaki, Dale Laird, Paul Lampe, David P. Kelsell, Herve Jean-Claude, Klaus Willecke and Edgar Rivedal. These studies have shown that the assembly and disassembly of gap junctions are complex processes governed through the phosphorylation and dephosphorylation of the carboxyl termini of connexins by protein kinases and phosphatases, through proteins that interact with connexins and through a variety of other adhesion molecules, e.g., cadherins and semaphorins, that likely control trafficking and recruitment of connexons to the cell surface and their subsequent incorporation into a gap junction plaque. These articles, along with other studies (Berthoud et al., 2004; Laird, 2006; Lampe & Lau, 2000; Segretain & Falk, 2004; Warn-Cramer & Lau, 2004; Wei et al., 2004), suggest a cross-talk among the components of various junctional complexes in facilitating one another's assembly; moreover, they also provide a rational explanation for why the loss of one junctional complex paves the way for the loss of other complexes, or vice versa, during several disease processes, including the pathogenesis of cancer.

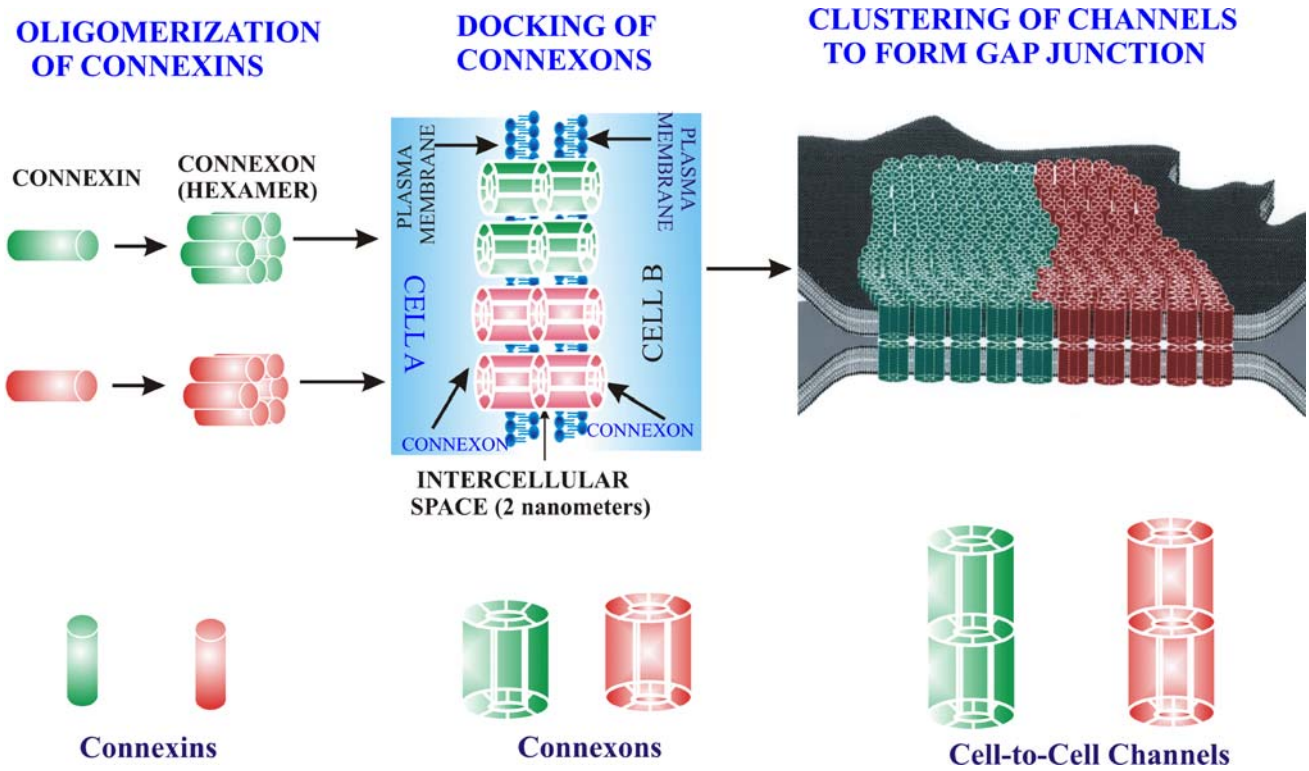

Fig. 2 A cell-to-cell channel is formed by connexins, which first oligomerize as hexamers (now called "connexons" or "hemichannels"), transported to the cell surface and dock with connexons in the adjacent cells. A gap junction is formed when several channels cluster at one particular spot. A gap junction may be composed of channels formed of more than one type of connexin. Thus, the basic structure of the channel has remained unchanged since its earlier inception

Gap Junctions and the Polarized and Differentiated State of Epithelial Cells

The polarized state of epithelial cells is maintained by cell-cell and cell-matrix adhesion molecules and their associated proteins, which assemble into junctional complexes (Braga, 2002; Matter & Balda, 2003; Wheelock & Johnsson, 2003a, 2003b; Balda & Matter, 2004; Gumbiner 2000, 2005). The architecture of the epithelium is maintained by adherens junctions and desmosomes, whereas the apical and the basolateral plasma membrane domains are delineated by tight junctions and hemidesmosomes, respectively (Fig. 5). Despite the widespread occurrence of gap junctions in polarized epithelial cells, the role of gap junctions, and, hence, of junctional communication, was thought to be limited to the maintenance of ionic continuity of cells within an epithelium and had escaped the attention of epithelial biologists, not being experimentally elaborated. Gap junctions are different from other junctional complexes not only in terms of function but also in terms of structure because, unlike other junctional complexes, the apposing junctional plasma membranes are not linked to any cytoskeletal elements and yet have undergone a high degree of differentiation (Fig. 5, *see also* Fig. 2). Since the earlier

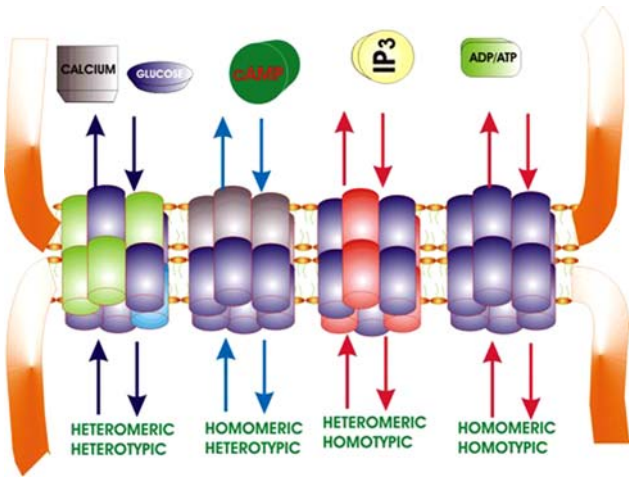

Fig. 3 The channel pore has to date remained unchanged with respect to its permeant selectivity to hydrophilic molecules. The channels act as molecular sieves due to different combinatorial oligomerization of connexins to form connexons, which may be homomeric or heteromeric, and due to combinatorial docking of connexons to form cell-to-cell channels, which may be homotypic or heterotypic

findings reported by Werner, that the formation of cell-to-cell channels was contingent upon calcium-dependent cell-cell adhesion (Loewenstein, 1967, 1975, 1981), it has

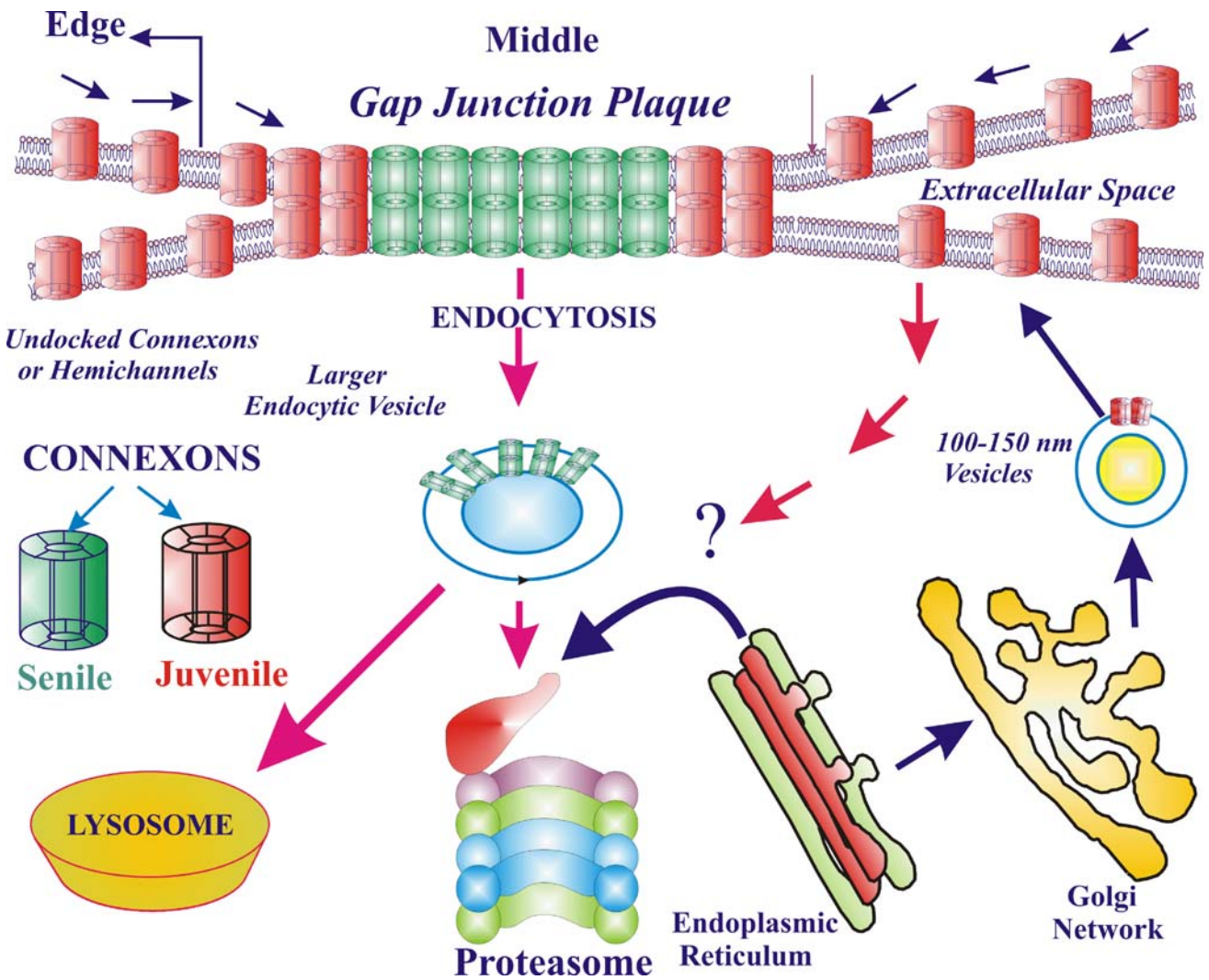

Fig. 4 The molecular mechanisms involved in the assembly and disassembly of connexins into gap junctions and the physiological stimuli that orchestrate these processes are not understood. Based on our current understanding, juvenile (*red*) connexons are carried to the plasma membrane as 100-150 nm particles and diffuse laterally to the preexisting gap junctional plaque, where they dock with their counterparts in the plasma membrane of apposed cells. Senile connexons (*green*) are endocytosed from the middle. Connexins and gap junctions have been shown to be degraded in the proteasome and in the lysosome

generally been assumed that their formation and assembly into gap junctions followed assembly of other junctional complexes, the so-called junctional complexes of epithelia, thus underlining the role of the junctional pathway in maintaining the polarized and differentiated state of epithelial cells. It turns out that among diverse cellular and molecular mechanisms, signaling through gap junctions, and, hence, their formation and degradation, has emerged as an important factor not only for the maintenance of the differentiated state of an epithelium but also for its barrier and transport functions (Kojima et al., 2002).

Along these lines, Yao et al. (this issue) discuss the pathophysiological role of gap junctions in regulating the growth, differentiation and survival of glomerular mesangial cells, while Man et al. (this issue) and Thomas et al. (this issue), using organotypic cultures, shed light on the intriguing role of communication mediated by gap junctions composed of connexin26 in regulating the skin barrier function and differentiation of epithelial cells and in controlling migration and motility. Work reported from the laboratories of Kojima and Spray further supports an important role played by gap junctions composed of connexin32 and connexin43 in the assembly of tight junctions in hepatocytes and human nasal epithelial cells, respectively, and in maintaining the barrier function of these epithelia. These studies are a logical sequel to the earlier studies published by Kojima and Spray's laboratories (Kojima et al., 2001, 2002).

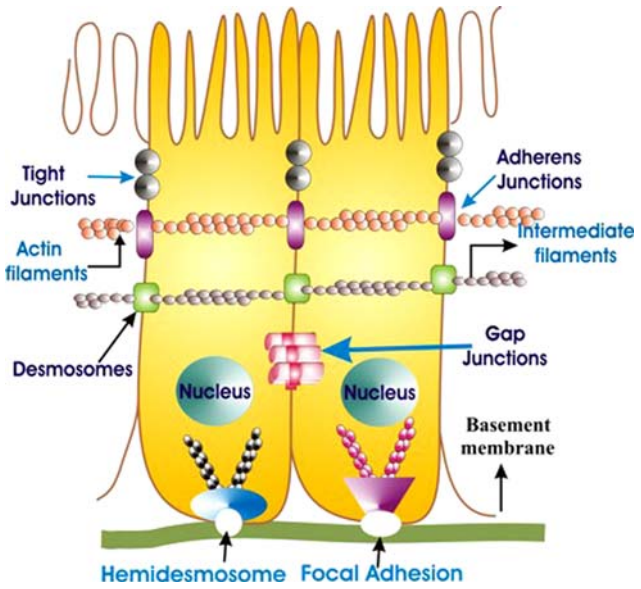

Fig. 5 The polarized state of epithelial cells is maintained by cell-cell and cell-matrix adhesion molecules and their associated proteins, which assemble into cell junctions and are linked to cytoskeletal elements. The architecture of the epithelium is maintained by adherens junctions and desmosomes, whereas the apical and the basolateral plasma membrane domains are delineated by tight junctions and hemidesmosomes, respectively. Unlike other junctional complexes, gap junctions are not robustly linked to actin and intermediate filaments

Gap Junctional Communication and Cancer

A hallmark of tumor cells is the loss of homeostatic control mechanisms, which govern the balance between cellular autonomy and interdependence essential for normal growth and development (Hunter, 2000; Weinberg, 2007). The initial observations, showing loss of communication mediated by cell-to-cell channels in cancer cells (Loewenstien & Kanno, 1966; Loewenstein, 1968a, 1979), provided the first evidence not only for the early gross pathological consequences that ensued upon the disruption of this form of communication but also led to the hypothesis that this loss may relieve incipient cancer cells from the growth control imposed upon them by normal cells, resulting in their clonal expansion and autonomous and malignant status (Fig. 6). This hypothesis advanced by Werner not only has endured the test of time but also has laid the foundation for several other studies that uncovered the multifaceted role of cell-to-cell communication (*reviewed in* Yamasaki & Naus, 1996; Trosko & Ruch, 1998; Saez et al., 2003; Wei et al., 2004; Mesnil et al., 2005; Laird, 2006). Moreover, Werner's hypothesis has become folkloric among gap junction biologists, who firmly believed in the homeostatic function of gap junctional communication and its pivotal role in regulating cell growth, differentiation and tumor progression from its inception (Mehta, Bertram & Loewenstein, 1986; Trosko, Chang & Madhukar, 1994; Yamasaki & Naus, 1996; Trosko & Ruch, 1998; Warn-Cramer & Lau, 2004; Mesnil et al., 2005). This hypothesis has now been tested through studies involving overexpression of connexin genes in connexin-deficient tumor cell lines, which attenuated their malignant phenotype both in vivo and in vitro; through studies with knockout mice that identified connexins as legitimate tumor suppressors; and through studies showing association of specific connexin mutations with human genetic diseases associated with aberrant proliferation and differentiation (Yamasaki & Naus, 1996; Temme et al., 1997; Trosko & Ruch, 1998; King & Lampe, 2004a, 2004b; King et al., 2005; Mesnil

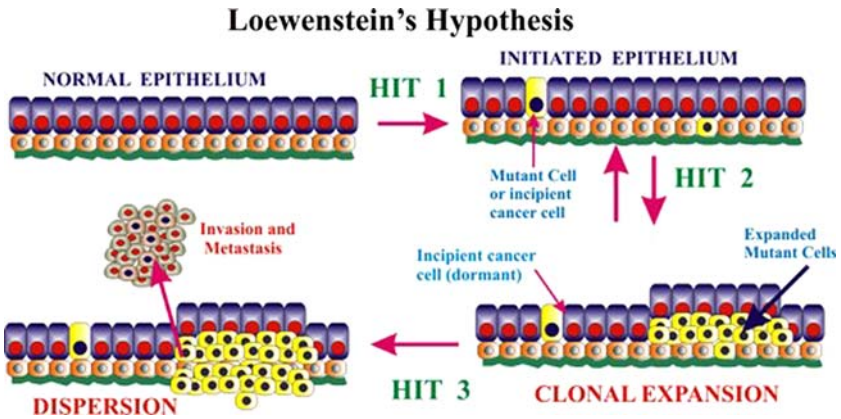

Fig. 6 Multiple mutations are required to convert a normal cell into a malignant cell. Each successive mutation confers a growth advantage on mutant (incipient cancer) cells. There is a long latency period between the occurrence of mutations and the clinical manifestation of cancer (invasion and metastasis). The hypothesis had three postulates: (1) gap junctional communication permits the dissemination of putative growth regulatory signals in a cell population, (2) cells that lose the ability to communicate among themselves or with the surrounding cell population become cancerous and (3) cancer-promoting agents, be they extrinsic (environmental) or intrinsic (hormones), disrupt gap junctional communication. The discovery of multiple mutations in connexin genes in diseases associated with proliferation and aberrant differentiation, along with gene knockout studies, has attested to the hypothesis

et al., 2005). The elegant studies by McLachlan et al. reported in this special issue highlight the role of connexin26 and connexin43 in the development and function of normal mammary gland and in the development and progression of breast cancer. Their studies show that connexins generally act as tumor suppressors as long as the tumor cells remain confined to the primary organ; however, during invasion and metastasis, they appear to act as both context-dependent tumor suppressors and facilitators of disease progression. Hokaiwado et al. (this issue), using a mutant transgenic rat, show an important role of disrupted gap junctional intercellular communication in suppressing the early and late stages of hepatocarcinogenesis, substantiating earlier studies that demonstrated a tumor-suppressor role of connexins (Loewenstein, 1979; Yamasaki & Naus, 1996; Temme et al., 1997; Trosko & Ruch, 1998; King & Lampe, 2004a, 2004b; King et al., 2005; Mesnil et al., 2005). Also, a review by Dagli et al. (this issue) raises several issues with regard to the role of junctional communication in nonneoplastic pathological processes in which cell proliferation is involved.

Gap Junctions and the Pathobiology of Diseases

Gap junctions are ubiquitous in most vertebrate tissues and are subject to regulation by a variety of physiological stimuli. If junctional communication, or formation of gap junctions per se, is vital for homeostatic control, impairment in this control should manifest during the pathogenesis of a disease — whether genetic or acquired — and should bear phenotypic and functional consequences. Because biogenesis of gap junctions is a multistep process, diminished gap junction function could result from impaired trafficking of connexins and/or their enhanced degradation, aberrant assembly and disassembly of gap junctions and alterations in the permeant selectivity of the channels themselves. Not surprisingly, these pathophysiological consequences of signaling mediated via gap junctions are manifested as loss of retinal rod signaling and cortical asynchrony, cardiac arrythmias, hereditary deafness, aberrant glucose homeostasis in the liver, aberrant neural crest migration and heart development, female sterility and aberrant differentiation (White & Paul, 1999; Krutovskikh & Yamasaki, 2000; Kelsell, Di & Houseman, 2001; Saez et al., 2003; Wei et al., 2004). The molecular basis of the pathobiology of acquired and genetic diseases with respect to specific mutations in the connexins and their assembly into gap junctions as well as with respect to alterations in gap junction function remains to be explored and is an intense area of research.

Substantiating the earlier experimental evidence regarding the role of communication compartments in regulating growth and development (Lo, 1989; Lo & Gilula 1979; Wei et al., 2004), Hibayashi et al. (this issue) further implicate an important role of communication mediated by gap junctions composed of connexin32 in maintaining hematopoietic progenitor cell compartments. Also, findings reported from Gong's laboratory provide a molecular insight into the specific role played by two connexins, connexin46 and connexin50, in controlling the growth, transparency and development of the lens. Both acute and chronic forms of heart disease caused by diverse etiologies are associated with changes in the expression of connexins and remodeling of gap junctions. In this issue, Saffitz's laboratory has reviewed the mechanistic aspects of regulating cell-cell electrical coupling in the heart under physiological and pathophysiological conditions, pertaining to changes in coupling in response to acute and chronic ischemic heart disease and in familial cardiomyopathies caused by mutations in genes encoding desmosomal proteins. Work reported from the laboratories of Willecke, Laird, Yamasaki and Kelsell has explored the molecular basis of connexin trafficking and assembly and their functional regulation. These studies shed important light on the intricacies involved in providing a molecular explanation for the diseases associated with connexin mutations.

Signaling Through Gap Junctions

As elegantly discussed by Werner, the most basic physiological role of junctional communication is homeostatic — buffering of individual variations in permeant molecules in a cell population — and from the evolutionary perspective probably the most primitive function and one that pervades all others added later, such as regulation of cellular growth and differentiation (Loewenstein, 1967, 1968a, 1968b, 1979, 1981). What are the molecular mechanisms by which signaling through gap junctions regulates tissue growth and differentiation? Are somatic and genetic regulatory signals disseminated throughout the cell population via junctional channels? If so, how does the transmission of such signals orchestrate cellular growth and differentiation? Because junctional channels are large enough to admit a wide range of cellular molecules – e.g., the inorganic ions; virtually all metabolites; second messengers such as cAMP, Ca^{2+} and IP_3; as well as vitamins – identification of the genes or signaling pathway(s) regulated through the transmission of these molecules is currently an intense area of research.

The adherens and tight junctions are beset with a plethora of associated proteins that have been shown to disseminate signals in a cell population by two major pathways: (1) activating a signaling cascade at the site of cell-cell contact through recruitment of signaling proteins and activation of kinases and (2) altering gene expression through the

nucleocytoplasmic shuttling of the associated junctional proteins (Braga, 2002; Gumbiner, 2000, 2005; Balda & Matter, 2004; Matter & Balda, 2003; Wheelock & Johnson, 2003a, 2003b). It is possible that signaling through gap junctions, or the formation of gap junctions per se, allows cells to employ similar mechanistic strategies in disseminating signals. Recent identification of several proteins that interact with connexins on the cytoplasmic side raises the possibility that gap junctions may be at least transiently linked to the cytoskeletal elements and their formation and dissolution might initiate or interrupt a signaling cascade, permitting signals to be dissipated and transduced to the nucleus. Alternatively, formation of gap junctions may permit the assembly of other junctional complexes, as alluded to above, and thus alter signaling in an epithelium.

In this issue, Spray & Iacobas show that deletion of genes encoding connexin32 and connexin43 or connexin36 modulates the expression level of several genes in mouse brain. Moreover, their work suggests several principles regarding regulatory transcriptomic networks involving gap junction genes and how these networks may be involved in the manifestation of connexin null phenotypes and, by inference, in disease states. The work reported from the laboratories of Scemes & Spray shows that deletion of connexin43 not only alters the expression level of P2 receptors involved in the transmission of calcium signals but also changes the expression level of numerous genes; moreover, these studies point out that genes synergistically or antagonistically expressed in wild-type tissues are more prone to be similarly or oppositely regulated. Also, studies reported by Geneau show that communication mediated by gap junctions composed of connexin43 plays an important role in osteoblastic differentiation and mineralization of bone by modulating the intracellular levels of Ca^{2+}.

Summary

Hypothesis is the principle of growth in knowledge. In framing a hypothesis, one seems to contemplate the nonexistent and ponder over a number of alternatives, which do not necessarily exist. It is not put forward merely on a supposition, which is the work of imagination, but through integral knowing or intuition. Similarly, a creative work is not blind imitation or mechanical repetition. It is synthetic insight which advances by leaps. A new truth altogether unknown, startling in its strangeness, comes into being suddenly and spontaneously owing to the intense and concentrated interest in the problem (Radhakrishnan, 1937). Truth is not factitious; it is a thing which cannot be arbitrarily *made* but *is* (Radhakrishnan, 1937). One such truth was revealed four decades ago upon discovery of cell-to-cell channels that interconnected the cytoplasmic interiors of cells which were not electrically excitable (Kanno & Loewenstein, 1964a, 1966; Loewenstein & Kanno, 1964b, 1966). Startling in its strangeness was this truth, then as it is now — that the channels transmit somatic-genetic growth regulatory signals; Werner's intense and concentrated efforts aroused curiosity in the minds of many young investigators. This laid a solid foundation on which several glorious edifices that portray the many panoramic views of the functional role of cell-to-cell channels and the mysterious ways in which they conglomerate into gap junctions and then disassemble are continuing to be raised. The diversity of the connexin gene family and the many ways in which various connexins can oligomerize, form channels, assemble into gap junctions and transmit signals are constantly raising a vow among gap junction biologists: when the fire lights up, the smoke disappears. Werner Lowenstein both created the initial sparks and stoked them into the radiant flames that embody our current knowledge of gap junctions. Various articles authored by some of the foremost scientists in this special issue are living testament to Professor Werner Lowenstein's legacy in the field of gap junctions and cell-to-cell communication in health and disease. It is my sincere hope and ardent belief that these articles will inspire the future generation of biologists, as Werner's work inspired my generation of gap junction biologists.

Acknowledgement I thank Werner for introducing me to cell-to-cell channels and giving me a chance to work and explore them. I thank Birgit Rose for her friendship and Kamlesh Asotra for critical reading of the manuscript on short notice and for his friendship. I also thank Richard G. MacDonald for his instructive comments on the manuscript. I apologize for not citing, due to space limitation, important work of many investigators who have also made contributions to this field. Current research in my laboratory is supported by the National Institutes of Health (CA 113903) and the Nebraska Health and Human Service System (LB 506).

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