The role of gap junctions in inflammatory and neoplastic disorders (Review)

PUI WONG[1], VICTORIA LAXTON[2], SAURABH SRIVASTAVA[3], YIN WAH FIONA CHAN[4] and GARY TSE[5,6]

[1]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, SAR, P.R. China; [2]Intensive Care Department, Royal Brompton and Harefield NHS Foundation Trust, London SW3 6NP; [3]Faculty of Medicine, Imperial College London, London SW7 2AZ; [4]School of Biological Sciences, University of Cambridge, Cambridge CB2 1AG, UK; [5]Department of Medicine and Therapeutics and [6]Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China

Received September 9, 2016; Accepted December 23, 2016

DOI: 10.3892/ijmm.2017.2859

Abstract. Gap junctions are intercellular channels made of connexin proteins, mediating both electrical and biochemical signals between cells. The ability of gap junction proteins to regulate immune responses, cell proliferation, migration, apoptosis and carcinogenesis makes them attractive therapeutic targets for treating inflammatory and neoplastic disorders in different organ systems. Alterations in gap junction profile and expression levels are observed in hyperproliferative skin disorders, lymphatic vessel diseases, inflammatory lung diseases, liver injury and neoplastic disorders. It is now recognized that the therapeutic effects mediated by traditional pharmacological agents are dependent upon gap junction communication and may even act by influencing gap junction expression or function. Novel strategies for modulating the function or expression of connexins, such as the use of synthetic mimetic peptides and siRNA technology are considered.

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Correspondence to: Dr Gary Tse, Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, 30-32 Ngan Shing Street, Hong Kong, SAR, P.R. China
E-mail: tseg@cuhk.edu.hk

Key words: cancer, gap junctions, connexins, mimetic peptides, inflammation

1. Introduction

Gap junctions are intercellular channels that mediate both electrical and biochemical coupling through the exchange of ions, second messengers and small metabolites (1,2). Gap junction intercellular communication (GJIC) is essential for regulating cellular differentiation and apoptosis, movement of cells within tissues, and intracellular signalling (3). In excitable tissues, GJIC also governs conduction of electrical signals between successive cells (4-8). Each gap junction is formed by two connexons (hexamers of connexins, Cx) that align in the extracellular space (9). Currently 21 members of the human connexin gene family have been identified (10). Some connexin isoforms are cell-type specific, and their expression varies during different metabolic states, such as pluripotent stem cell induction (11), epidermal wound healing (12), epithelial-to-mesenchymal transition (EMT) (3) and pathological states such as hepatitis (13).

Connexin can be found in both excitable and non-excitable tissues. An example of excitable tissue, the cardiac myocardium, has abundant expression of the isoforms Cx30.2, Cx40, Cx43 and Cx45 (14). Their expression levels vary with the region concerned. Thus, Cx40 is only expressed in the atria, whereas the ventricles show extensive expression of Cx43 and Cx45 but not Cx40. Other connexin isoforms have been detected in many non-excitable tissues (15). Cx43 can be found in breasts, kidneys, skin and lungs. Cx26 is expressed in liver, kidneys and oesophageal epithelium, and Cx32 is found in liver and kidneys (16).

Gap junctions function through two distinct gating mechanisms: membrane voltage-dependent and transjunctional voltage-dependent gating (also known as fast and slow gating) (17). Besides voltage sensitivity, both mechanosensitivity and chemosensitivity have been reported (17,18). For example, connexin activity is influenced by intracellular Ca^{2+}, pH, chemical uncouplers (19), phosphorylation events (20,21), and lipid availability in the immediate environment, including LDL, apo-B (22) and cholesterol (23).

In recent years, there has been a growing interest in the role of connexins in different physiological and pathological

states, and the use of gap junction modulators in different clinical conditions (24). Apart from modifying gap junction function, interventions can be applied through modulating synthesis, transport, assembly, phosphorylation, and degradation of gap junction proteins (25). It has been shown that gene therapy restores or increases GJIC in transfected cells or 'knock-in' animals (25,26). This review focuses on reviewing the therapeutic applications of gap junction modulators in inflammatory and neoplastic disorders. Potential directions for further investigation and treatment development are also discussed.

2. Hyperproliferative skin disorders

Several autosomal dominant hereditary epidermal diseases are attributed to mutations in genes encoding for connexins. These diseases include Vohwinkel syndrome, Bart-Pumphrey syndrome, hystrix-like ichthyosis with deafness syndrome, keratitis-ichthyosis-deafness (KID) syndrome, erythrokeratoderma variabilis, hidrotic ectodermal dysplasia and oculodentodigital dysplasia (27,28).

Cx26 is known to be a significantly upregulated gene in psoriatic patients. In contrast to normal skin, it is detected intensely in keratinocytes in psoriatic plaques (29,30). It has been proposed that Cx26 regulates epidermal differentiation, more specifically epidermal barrier acquisition. There is therapeutic potential in the reestablishment of skin barrier and inflammatory response regulation, particularly in hyperproliferative skin conditions (31).

Currently, 10 missense substitution mutations in the Cx26 gene are known to cause KID syndrome (32). It has been hypothesized that the abnormally high activity of defective Cx26 hemi-channels allows leakage of cytoplasmic contents, and is therefore detrimental to cell survival and tissue integrity (33). Due to repeated skin fissuring and micro-wounding, bacterial and fungal infections are common, thus requiring a combination of drugs such as emollients, barrier creams, topical keratolytics and anti-microbial agents (33). Retinoic acid is a prospect for novel treatment in hyperkeratotic skin. It unexpectedly causes: i) significant Cx26 upregulation; ii) Cx43 upregulation; and iii) increased epidermal thickness (34). Yet, the mechanisms by which elevated Cx26 expression results in beneficial therapeutic effects in KID syndrome without exacerbating this condition remain unknown. The precise underlying mechanism of action will need to be understood before further testing.

3. Lymphatic vessel diseases

Lymphatic vessels collect lymph from excess tissue fluid, return it to the blood circulation and mediate the uptake of lipids, including lipid-soluble vitamins. Previous studies have demonstrated the variable expression of Cx37, Cx43 and Cx47 during development of the lymphatic system, with the first two segregated at the downstream and upstream sides of valves respectively, while Cx47 was found in a subset of endothelial cells on the upstream of adult valves (35). It is known that differential expression is involved in initiating the formation and determining the cell polarity of the valve (36); whereas Cx37 and Cx43-knockout mouse models developed defective valves and abnormal thoracic duct formation (35). Several connexin gene mutations have been identified to cause both primary (37) and secondary lymphedema (38,39). Underlying mechanisms and the importance in physiological functioning of the lymphatic system remain unclear; however, future studies may provide answers to developing potential regimens for lymphatic diseases.

4. Inflammatory lung diseases

In the respiratory tract, connexins are found in the epithelium, from the airways to alveoli, with regional specific expression patterns (40). At the upper respiratory tract Cx26, Cx30, Cx31, Cx32, Cx37, Cx43 and Cx46 are found, and Cx26, Cx32, Cx37, Cx40, Cx43 and Cx46 are present at lower levels (41). Cx43 is also found extensively throughout the rest of the lung tissue, including smooth muscles, both alveolar epithelial cell types and even alveolar macrophages (41). Cx32 and Cx43 are both found in cultured human pulmonary artery endothelial cells (42). Gap junctions contribute to mucociliary clearance, surfactant secretion and synchronization of pulmonary vascular smooth muscle contraction (41).

Carbenoxolone, a gap junction uncoupler, was tested in a mouse model of asthma, where it was found to reduce infiltration of inflammatory cells and interleukin production, thereby decreasing lung inflammation (43). It acted by preventing the increase in interleukins 4 and 5 and eosinophils (43,44). These findings suggest that use of gap junction uncouplers can be used in nebulized form for the treatment of asthma.

In a mouse model of allergen-induced airway inflammation, Cx37 expression levels were found to be negatively correlated with airway inflammation, airway responsiveness, and levels of Th2 cytokines (45). Cx37, Cx40 and Cx43 are thought to play a role in regulating vascular resistance and right ventricular function (46). Decreased expression of these connexins are implicated in the pathogenesis of pulmonary arterial hypertension (PAH) by increasing airway inflammation and sensitivity (41,47).

The role of Cx40 in pulmonary vascular function was explored in an animal model of acute lung injury (48). During the course of lung injury, Cx40 expression was decreased in a time-dependent manner with increased vascular permeability. The latter was aggravated by the gap junction uncoupler heptanol, which produced abnormal Ca^{2+} handling in smooth muscle cells. In Cx40-knockout mice, increased inflammation with induced leukocyte infiltration was observed (49). Cx40 was found to mediate anti-inflammatory effects by activating CD73, which reduced adhesion by adenosine production. Another study tested the hypothesis that a reduction in Cx40 expression may limit acute lung inflammation (50). However, these authors found that the development of acute lung inflammation did not differ between wild-type and Cx40-knockout mice.

Cx43 expression is upregulated in lung epithelium and vascular endothelium (51), and was found to be positively correlated with increased pulmonary vascular permeability in many disease states (41), such as acute inflammation induced by radiation (52) and bacterial sepsis (53,54). In contrast, decreased Cx43 expression in chronic pulmonary diseases such as cystic fibrosis and idiopathic pulmonary fibrosis,

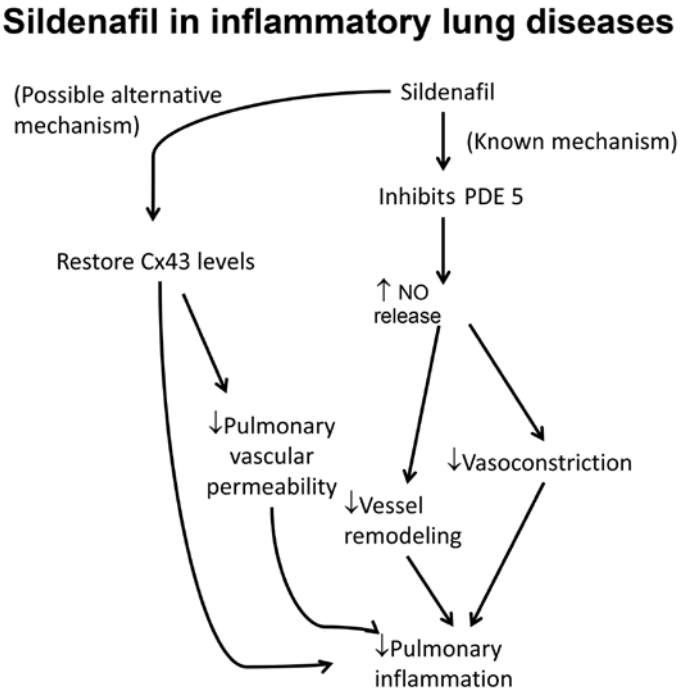

Figure 1. The mechanisms of action of sildenafil in the treatment of pulmonary inflammatory diseases.

was attributed to aberrant Cx43 transport and reduced Cx43 mRNA levels, respectively (55,56).

Various pharmacologically active substances have been reported to enhance connexin expression in the lungs. Sildenafil, a phosphodiesterase 5 inhibitor, is a common agent used to treat PAH owing to its ability to vasodilate and suppress adverse vessel remodeling (57). Experiments in a mouse model of PAH suggest that it also acts to restore Cx43 to normal levels (Fig. 1) (58). Rotigaptide, a synthetic peptide which acts to enhance gap junction function, is currently under clinical trial for preventing cardiac arrhythmias. It is also being investigated for its potential protective effects in pulmonary inflammatory diseases (41). Expression of various connexins in pulmonary endothelial and smooth muscle cells can be interfered with by using siRNA (54,59), which can potentially be exploited to treat pulmonary inflammatory diseases (41).

5. Liver injury

Hepatic gap junctions are known to play a crucial role in intercellular communication (60) and local propagation of antiviral immune response signaling (61). In chronic liver disease, Cx32 is lost from the hepatocyte membrane by apoptosis as the condition progresses (62). Cx32-knockout mice exhibited resistance to liver cell death induced by D-galactosamine and carbon tetrachloride (63), but increased predisposition to liver cancer (64). In contrast, Cx43 was induced in the cytoplasm of damaged liver cells, and a Cx43 inhibitor downregulated the activity of caspase-3, a major contributor in the apoptotic cascade (62). The underlying mechanism is therefore suggested to be Cx43-induced hepatocyte apoptosis regulated by GJIC. Upon Cx32 removal, injured hepatocytes may escape apoptosis and their persistence may pose as a risk factor in carcinogenesis (62). The exact mechanism remains to be elucidated; however, there is counter evidence against the notion that Cx43 directly induces apoptosis (65,66). In addition to acute liver injury, altered levels and localisation of certain connexins such as Cx26, Cx32, and Cx43 are associated with cholestasis and liver fibrosis (13).

The liver is responsible for the metabolism of drugs, which can often induce liver injury in a dose-dependent manner and produce fulminant hepatic failure (67). Cx32 and Cx40 have been implicated in paracetamol-induced liver injury (65,68,69). Gap junction inhibition was shown to protect against this injury by inhibiting cytochrome P450 enzymes and c-jun N-terminal kinase activation (70) as well as apoptotic signalling (62), thereby preventing fulminant liver failure (71).

6. Neoplastic disorders

Hepatocellular carcinoma (HCC) is associated with the presence of Cx43 expression, while reduced Cx43 levels have been associated with reduced invasion, migration and metastasis (Fig. 2) (72). However, several studies have demonstrated differing results. In one study Cx43 overexpression was noted in HCC and in especially rapidly growing cells with limited differentiation (73). In another, induced Cx43 expression in rat HCC cells reduced the growth rate and even led to cytoskeletal reorganization similar to the effects noted following treatment with all-*trans* retinoic acid, which induces differentiation (74). It is unclear whether Cx43 serves as a definitive oncogene or tumour-suppressor gene, or that its activity depends on its expression level. Cx32 displays characteristics of a tumour-suppressor gene, as its removal in rodents led to a significant increase in hepatocarcinogenesis (75).

Lindane (hexachlorocyclohexane) is an insecticide that is also used to induce carcinogenesis in pre-clinical research. It induces Cx43 endocytosis through activation of extracellular signal-regulated kinases and Ser368 phosphorylation, leading

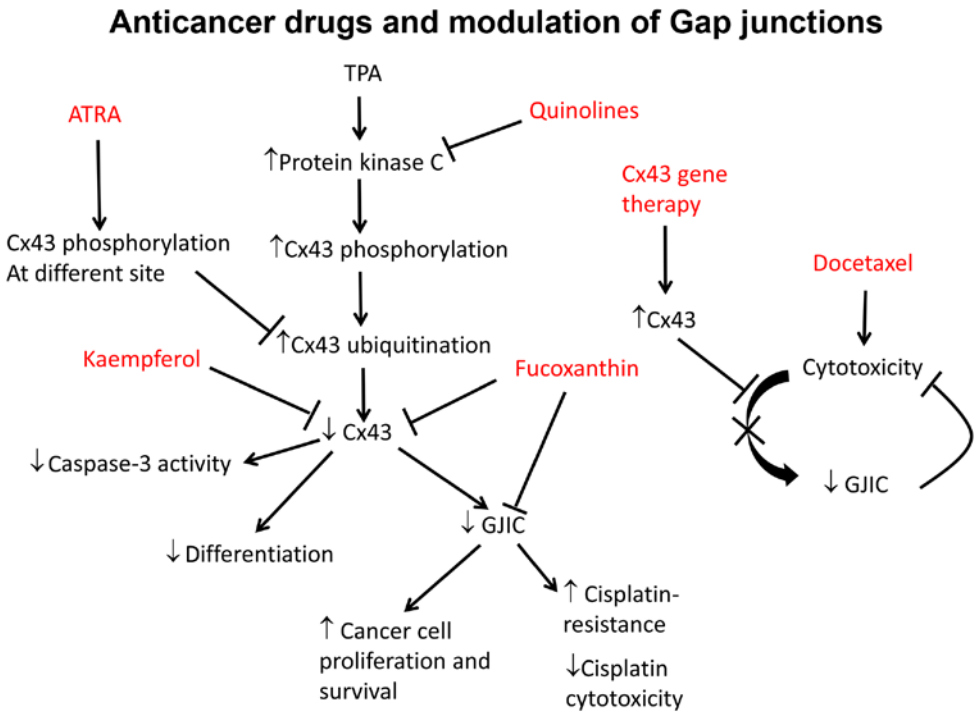

Figure 2. Anticancer drugs and their modulation of the function of gap junctions. TPA, 12-*O*-tetradecanoylphorbol-13-acetate; GJIC, gap junction intercellular communication.

to GJIC uncoupling in liver and myometrial cells (76,77). Oxidation of glutathione was also observed (78). This is thought to contribute to the promotion of neoplastic growth (77,78). Lindane was also found to inhibit GJIC and induce changes in Cx43 and ZO-1 localisation from the membrane to the cytoplasmic perinuclear region (79). Lindane can be used in further investigations to investigate the mechanisms of carcinogenesis and the involvement of connexins to identify therapeutic targets.

Metastatic breast cancer can be aggressive, metastasizing to distant organs such as the lungs, liver, bones or brain (80). Cx43-mutant mice have reduced Cx43 levels, extensive mammary gland hyperplasia but delayed onset of palpable tumours (81). Increased metastasis to the lungs was observed when compared to control mice with normal Cx43 levels. Cx43 therefore appears to exert protective effects. Regarding colon cancer, Cx43 downregulation was found in colon cancer cell lines and in colorectal carcinomas, and was found to be associated with shorter relapse-free and overall survival (82). Normally, Cx43 co-localizes with β-catenin and negatively regulates the Wnt pathway, mediating apoptosis. When Cx43 levels are reduced, apoptosis of cancer cells is lost.

Several chemotherapeutic agents have been studied for their anti-neoplastic effects, in which connexin proteins have been implicated (83-85). Fucoxanthin, a carotenoid, was found to inhibit tumorigenesis in human cancer cells from colon, prostate, leukemia and cervical epithelium (86). At high doses it inhibits the tumour suppressor p53, thereby promoting apoptosis (87) and inducing cell cycle arrest (88). In hepatic cancer SK-Hep-1 cells, fucoxanthin increased Cx32 and Cx43 expression and enhanced GJIC (84). Kaempferol, an antiflavonoid anticancer agent, promoted the differentiation of partially differentiated colon cancer cells with low Cx43 expression. This was associated with higher levels of Cx43 and phosphorylation status (89).

Quinoline, a gap junction enhancer (90), inhibits protein kinase C (PKC). PKC normally phosphorylates Cx43, and interferes with the interaction between Cx43 and Nedd4, an E3 ubiquitin ligase. Therefore quinolone application maintains GJIC, thereby suppressing breast cancer cell proliferation and survival (91). Studies found that tumours may develop cisplatin-resistance through loss of GJIC, preventing the drug from spreading among cancer cells (92,93). The first-generation quinolone, PQ1, was tested in combination with cisplatin, and was shown to potentiate cisplatin cytotoxicity by a GJIC-dependent mechanism (90). Co-treatment with gap junction-enhancing agents therefore represents a possible approach to target drug-resistant tumours.

12-*O*-tetradecanoylphorbol-13-acetate (TPA), a known tumour promoter, was found to activate the PKC pathway through mimicking diacylglycerol (94), thereby stimulating cell proliferation (95). It opposed the anti-proliferative action of the third-generation substituted quinolone PQ15 in T47D breast cancer cells (83). TPA also displayed similar counteracting effects against PQ1 in SW480 colorectal cancer cells (96). It was also found to induce Cx43 ubiquitination in IAR20 rat liver epithelial cells (97). These findings suggest that PQ15 acts by inhibiting TPA-mediated phosphorylation of Cx43 (83), and quinolones can be versatile anticancer drugs (98).

All-*trans* retinoic acid is a natural vitamin A derivative that has been widely used in the chemoprevention and chemotherapy of head and neck cancers (99). In addition to its known mechanisms of action such as the regulation of differentiation and proliferation and induction of apoptosis, previous studies have demonstrated that it upregulated Cx43 phosphorylation

and restored GJIC in hepatoma HepG2 (100) and oral squamous cell carcinoma cells (101). A new antitumour mechanism was proposed in light of the fact that ATRA restored expression of gap junction proteins Cx32 and Cx43 and GJIC in oral cancer cells (101). Contradictory results have been observed in other cell types such as p19 embryonic carcinoma cells, human pluripotent teratocarcinoma cells and cutaneous squamous cell carcinoma SCC-13 cells (102-104). This was hypothesized to be due to variation in tissue-specific transcriptional regulators and connexin expression distribution, leading to opposing cellular mechanics and outcomes (101). The exact underlying mechanism remains unknown and will require further studies before the development of novel treatment options.

Docetaxel is the first cytotoxic drug reported to demonstrate benefits in the treatment for advanced hormone refractory prostate cancer (105). However, resistance against docetaxel has always been a challenge, and is found in more than 50% of patients receiving this drug as first-line therapy (106). Extensive efforts have focused on improving the responsiveness and overcoming resistance in metastatic prostate cancer (107). Cx43 expression has shown promising potential in its application as an adjunct agent to docetaxel. In PC-3 cells, Cx43 expression downregulated Bcl-2 expression, and apoptosis is associated with significantly increased sensitivity to docetaxel both *in vitro* and *in vivo*, and addition of non-viral Cx43 gene therapy to conventional docetaxel treatment caused a significant increment in the tumour xenograft suppression effect (108). Taxels have differential cytotoxicities that are dependent upon the presence of functional gap junctions (109). The distribution and combination of gap junctions may therefore need to be taken into consideration when using taxols in different types of cancers. In another study, forced Cx43 expression enhanced prostate cancer cell sensitivity to TNFα (110). The presence of Cx26, another commonly investigated connexin, has been associated with tumour prognosis, oncogene expression, recurrence and higher tumour grade (111,112). Cx26 may therefore be a good candidate for prediction of prognosis and recurrence (111). Cx26 may also be involved in tumour suppression. It was demonstrated that Cx26 expression suppressed the growth of HeLa cells *in vivo* and *in vitro*, with insignificant changes in GJIC (113). Organic selenium compounds are Cx26 transcriptional upregulators, and have been evaluated in clinical trials for adenomatous polyp recurrence (114).

Suicide gene therapy has become an area of intense investigation in the treatment of different cancers (115). Suicide genes are defined as those with protein products, when expressed, are non-toxic to cells, but are converted into toxic metabolites upon exposure to a pro-drug. However, various suicide gene products may induce a bystander effect (Fig. 3). This describes a situation where a toxic effect, such as cell death, propagates from nongene-modified tumour cells to neighbouring cells. This is dependent on the function of gap junctions, and can be exploited for therapeutic use. For example, the bystander effect can be enhanced by treating cancer cells with both Cx43 and human herpes simplex virus thymidine kinase type (HSV-TK) transfection, leading to cell death (116,117). Similar effects were noted following the replacement of Cx32 with Cx43 (118). By utilizing the bystander effect it may be possible to amplify the cytotoxicity of certain cell type-specific drugs (119). The effect was however limited to cancer cells that were able to utilize and assemble the induced connexins into functional gap junctions (120). When treating prostate cancer, tumour cell responsiveness was significantly enhanced when Cx26 was applied. This bystander effect can also be utilized in therapies using ionizing radiation. Radiation traversed the cell nucleus to induce response or damage in neighboring cells, and nearby non-irradiated cells showed characteristics of damages and responses induced by irradiation. It was then confirmed that Cx43 mediated GJIC that transmited radiation stress from the irradiated cells to the bystander cells (121). This opens up an opportunity for improving therapy to enhance the efficacy of not only chemotherapy, but also radiotherapy in cancer treatment. There are also other limitations to the clinical application, such as the fact that the lipophilicity may be too low to cross the blood-brain barrier and the need to use systemically dangerous dosages that can produce side effects such as cardiac conduction slowing (122), which can precipitate lethal arrhythmias (118,123,124).

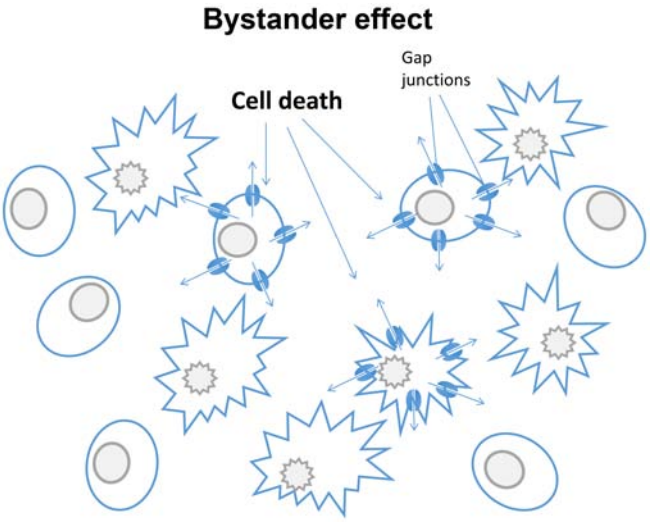

Figure 3. The bystander effect. Cell death can be propagated from affected cells to neighboring cells via gap junctions. Reproduced from Wong *et al* (153) with permission.

7. Conclusion

Gap junction proteins are ubiquitously expressed with some tissue-specific subtypes. Their expression patterns in different diseases are now better characterized. Attempts have been made to examine the consequences of influencing gap junctions by direct modulators or antisense technology, with many successes in pre-clinical disease models. The ability of gap junction proteins to regulate immune responses, cell proliferation, migration, apoptosis and carcinogenesis makes them attractive therapeutic targets to halt the progression of inflammatory and neoplastic disorders. It may be worthwhile to elucidate the gap junction protein pathways to identify more accurate prognostic biomarkers (125). The use of pre-clinical models will continue to provide a platform on which these investigations are conducted (126-139), and for the development of novel therapeutic agents for future clinical applications in these disorders (136,140-152).

Acknowledgements

Dr Gary Tse received a BBSRC Doctoral Training Award at the University of Cambridge and is grateful to the Croucher Foundation for its support of his non-clinical and clinical assistant professorships. Dr Yin Wah Fiona Chan was supported by the ESRC for her research at the University of Cambridge.

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