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The Human Papilloma Virus – Ion Channel Link in Cancer: *An Alternative Opportunity for Diagnosis and Therapy*

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1. Introduction

Despite hundreds of clinical trials being conducted for cancer patients, the overall response is below 4% and cancer remains a major health problem worldwide (Roberts, 2007; Kamb et al., 2007). Indeed, early detection of the disease should help improve diagnosis and treatment leading to a reduction in cancer mortality. The arising link between human papilloma virus (HPV) and ion channels presents a very interesting opportunity for the early diagnosis and therapy of different types of cancer, including cervical, head and neck, oral cavity and lung cancer, some of them within those of the highest incidence in the world.

HPV infection has been proposed as the main etiological factor for cervical cancer (Walboomers et al., 1999; zur Hausen, 2002). Nevertheless, HPV infection has been also suggested to be associated with head, neck and oral cavity cancer (Anaya-Saavedra et al, 2008). Interestingly, in a population of taiwannesse women, more than 90% of lung cancer cases were not associated to cigarrette smoke (Chen et al., 1990). Analysis of HPV expression and its E6 oncoprotein in lung cancer biopsies from non-smoker taiwannesse women, led to suggest HPV as a lung cancer risk factor in such population (Cheng et al., 2001; 2007). Therefore, HPV presence might be used as an early marker for several types of cancer.

Ion channels play important roles in cell physiology, including excitability, neural transmission, cardiac contraction, pancreatic cell metabolism, apoptosis and cell proliferation. Accordingly, alterations in either channel activity or expression are associated to several diseases (Ashcroft, F. 2006), and cancer is not an exception. Actually, several ion channels are suggested as tumor markers and therapeutic targets for different types of cancer, including those malignancies associated to HPV infection.

Ion channels are integral membrane proteins transfering small ions through the hydrophobic lipid bilayer of the cell membrane, such as potassium (K^+), sodium (Na^+), chloride (Cl^-) and calcium (Ca^{2+}). They are present in the plasma and intracellular membranes of every cell type in the human body. Most ion channels require the presence of a stimulus to be activated (*gated*), this can be accomplished by changes in the membrane

potential (*voltaged-gated ion channels*), neurotransmitters or other molecules (*ligand-gated ion channels*), as well as light, temperature, mechanical forces, etc. Ion channels play an important role in a variety of cellular functions regulating every aspect of the cell physiology, the voltage-gated channels provide the ionic currents to generate and spread neuronal activity, calcium channels trigger synaptic transmission, hormonal secretion, and muscle contraction, and some channels participate in the regulation of cell migration, cell cycle progression, apoptosis and gene transcription. An increased number of human diseases has been found to result from defects in ion channel function or expression, including epilepsy, cardiac arrhythmias, skeletal muscle disorders and diabetes (Hübner, C. & Jentsch, T. 2002; Ashcroft, F. 2006). Since channels play an important role in proliferation and growth, and because cancer is a multifactorial disease, these membrane proteins also participate in tumor development. Many types of human cancers show alterations on ion channel expression presumably to help to transform healthy cells into malignant, invasive, and fast growing tissue (Schönherr, R. 2005).

In this Chapter, we begin with a general overview of ion channels in cancer followed by the specific description of the participation of potassium, calcium, sodium and chloride channels in tumor cells. Then we focus on cervical cancer as the best example of a malignancy in which a link between HPV and ion channels can be found. Lastly, we describe in detail the regulation of human oncogenic *ether à-go-go-1* (Eag1) channels by HPV oncogenes and estradiol.

2. Ion channels in cancer

The control of cell proliferation involves diverse signaling pathways, growth factors, and receptors, which have a restrict regulation in order to maintain the cell homeostasis (Vermeulen, et al., 2003). From a general view, the eukaryotic cell cycle consists of four phases (Figure 1) and some checkpoints (Norbury, C. & Nurse, P. 1992; Massagué, J., 2004). Ion channels coordinate the upstream and downstream signals that converge on the cell cycle machinery. Both voltage- and ligand-gated channels have been implicated in the control of different cell cycle checkpoints in normal as well as neoplastic cells. Cell proliferation involves at some point the activation of Cl^- channels, K^+ channels and Ca^{2+} channels; these channels appear to play an active role in the pathways leading to duplication of any given cell (Kunzelmann, K. 2005).

There are more than 400 genes encoding ion channel subunits that regulate the flow of ions across the plasma membrane and the intracellular organelle membrane. In tumor cells, during the change from normal to cancer phenotype, a series of genetic alterations occur in which genes encoding ion channels might be affected. This might lead to changes in either channel expression or activity, which may be responsible, in part, of the pathophysiological features that cause malignant growth.

Many types of ion channels have been described to play a potential role in the development and growth of cancer cells, some of them are listed in Table 1. Hallmarks of cancer have been recently reviewed and include altered cell cycle progression, self sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, adaptation to harsh conditions, sustained angiogenesis, tissue invasion and metastasis (Hanahan, D. & Weinberg, R., 2011). Most of the ion channels that contribute to the development of cancer

have the capacity to induce proliferation by regulating the cell cycle at some point. Cell proliferation is a highly regulated process in which ion channels participate as regulators of the cell cycle, but surprisingly, the same ion channel mechanisms that regulate cell proliferation are involved in the control of apoptosis (programmed cell death) (Wang, Z. 2004). Cell proliferation and apoptosis are two counterparts that are responsible for maintaining normal cellular functions. Abnormal enhanced proliferation and/or impaired apoptosis alters the cell homeostasis leading to loss of control of the cellular growth.

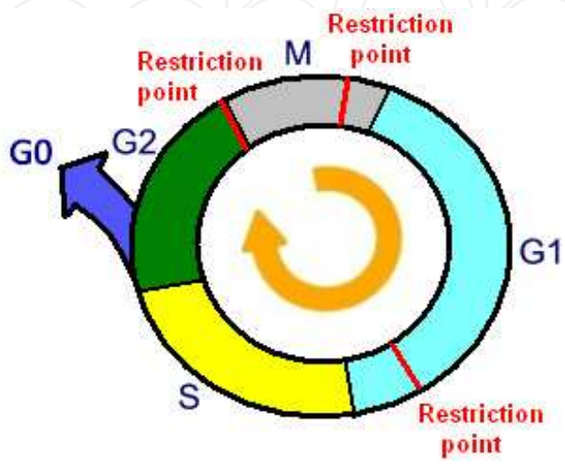


Fig. 1. Phases of the eukayotic cell cycle.

Details of the different types of ion channels involved in proliferation or invasion of tumor cells are described in Table 1.

2.1 Potassium channels

Potassium channels are the most extense family of ion channels and some of the most studied in cancer. Several potassium channels are overexpressed in tumors as compared to the corresponding healthy tissues. Some types of these channels include Kv´s (voltage-gated potassium channels), K_{Ca} (calcium-activated potassium channels), K_{2P} (two-pore domain) and K_{ir} (inward rectifier). All of these classes of potassium channels are further subdivided into subfamilies (Chandy & Gutman, 1993), and they regulate a vast diversity of functions in the cells including maintenance of the cell membrane potential, regulation of the cell volume (Lang, 2007), and cell cycle progression (Blackiston et al., 2009).

Potassium ions are important for the osmotic regulation of cell volume by working in concert with the Na^+-H^+ exchanger and the Na^+-K^+ ATPase, contributing to the regulation of intracellular pH (pH_i) (Ikuma et al., 1998). Thus, K^+ channels participate in physiological and pathological proliferation by playing a role in membrane potential, cell volume and pH_i change during cell-cycle progression. K^+ channels also provide a hyperpolarizing effect on membrane voltage during cell cycle and therefore stimulate calcium influx. This increase in intracellular Ca^{2+} concentration is needed during progression through G1 phase and the G1/S transition (Wonderlin and Strobl, 1996; Kulzenmann, 2005). Usually, cancer cells have less negative voltage membrane than normal cells (Marino et al., 1994); therefore, it is likely that they would require a higher expression of certain types of K^+ channels to produce the transient hyperpolarization required to proceed with cell cycle progression. Therefore, K^+

Channels name IUPHAR	Type of cancer	Reference
K^+ channels		
K_v 1.3	Breast, Colon, Prostate	Abdul, M., et al. (2003) ; Abdul, M. & Hoosein, N. (2002a) ; Abdul, M. & Hoosein, N. (2002c)
K_v 1.5	Glioma	Preussat, K., et al. (2003)
K_v 3.4	Oral Squamous cell carcinoma	Chang, K., et al. (2003)
K_{ca} 1.1	Cervical, Ovarian, Breast, Glioma	Han, et al. (2007); Ouadid, H., et al. (2004a); Liu, X., et al. (2002)
K_{ca} 3.1	Prostate, Breast, Melanoma, Pancreas	Parihar, A., et al. (2003); Ouadid, H., et al. (2004b); Jäger, H., et al. (2004); Gavrilova, O., et al. (2002)
K_v 10.1	Breast, Colon, Cervix, Gastric, Prostate, Sarcoma, Ovarian	Pardo, L., et al. (1999); Hemmerlein, B., et al. (2006); Ousingsawat, J., et al (2007); Farias, L., et al. (2004); Ding, X., et al. (2007); Mello, F., et al. (2006); Asher, V., et al. (2010)
K_v 11.1	Colon, Endometrial, Glioma, Leukemia, Stomach	Lastraioli, E., et al. (2004); Cherubini, A., et al. (2000); Masi, et al., (2008); Smith, G., et al. (2002); Pillozzi, S., et al. (2002); Shao, X., et al. (2008)
K_{2p} 9.1	Breast, Lung	Mu, D., et al. (2003); Pei, L., et al. (2003)
K_{ir} 3.1	Lung	Plummer, H., et al. (2005)
Ca+2 Channels		
Ca_v 1.2	Colon	Wang, X., et al. (2000)
Ca_v 3.2	Prostate	Mariot, P., et al. (2002)
Na+ Channels		
Na_v 1.2	Prostate	Anderson, J., et al. (2003)
Na_v 1.4	Prostate	Bennett, E., et al. (2004)
Na_v 1.5	Breast, Ovarian	Roger, S., et al. (2003); Gao, R., et al. (2010)
Na_v 1.6	Cervical, Glioma	Hernandez, E., et al. (2011); Schrey, M., et al. (2002)
Na_v 1.7	Prostate	Diss, J., et al. (2205)
Other channels		
Cl channels	Breast, Cervical, Hepatoma, Glioma, Prostate	Abdel, M., et al. (2003); Mao, et al. (2009); Roman, R., et al. (2001); Olsen, M., et al. (2003) ; Shuba, Y., et al. (2000).
TRPC1	Prostate	Vanden, F., et al. (2003)
TRPV6	Breast, Colon, Ovarian, Prostate, Thyroid	Bolanz, K., et al. (2008); Vanden, F., et al. (2003); Zhuang, L., et al. (2002); Fixemer, T., et al. (2003)
TRPM8	Breast, Colon, Lung, Melanoma, Prostate	Tsavaler, L., et al. (2001); Yamamura, H., et al. (2008)
P2X7	Cervical, Leukemia, Neuroblastoma,	Feng, Y., et al. (2006); Wiley, J., et al. (2002); Per Larsson, K., et al. (2002)

Table 1. Examples of ion channels involved in cancer.

channel activation is particularly important for the early G1 phase of the cell cycle. During G1/S transition and S phase, cells swell and activate a regulatory volume decrease (RVD) mechanism, which allows shrinkage of the cell after mitosis. RVD requires efflux of water

and solutes, which is due to simultaneous opening of K^+ and Cl^- channels (Kulzenmann, 2005), allowing the cell to proliferate. Another evidence associating K^+ channels with proliferation is that voltage-gated K^+ channels blockers inhibit proliferation in many cell types; this has been observed in normal physiological proliferation (lymphocytes) and in pathological conditions (as in cancer cells). Thus the cells require K^+ channels in order to proceed with cell cycle progression (Wonderlin and Strobl, 1996).

Most studies are devoted to the impact of voltage-gated potassium channels on proliferation of tumor cells, particularly those of epithelial origin (Abdul & Hoosein, 2002; Farias et al., 2004; O'Grady & Lee, 2005; Pardo, 2004; Pardo et al, 2005; Arcangeli et al., 2009). One of the most studied voltage-gated potassium channel in cancer is the Eag1 channel. Eag1 displays oncogenic properties and shows a very restricted distribution in normal tissues (Pardo et al., 1999; Hemmerlein et al., 2006) but it is expressed in many types of tumors including cervical, breast, lung, prostate, liver and colon carcinoma (Farías et al., 2004; Hemmerlein et al., 2006; Ousingsawat et al., 2007). Inhibition of either channel activity or expression leads to decreased tumor cell proliferation both *in vitro* and *in vivo* (Pardo et al., 1999; Gómez-Varela et al., 2007; Ousingsawat et al., 2007). The restricted distribution of Eag1 and its role in proliferation have converted this ion channel in an attractive tool for diagnose and therapy of many cancers.

It has also been shown that several K^+ channels associate with other proteins related to proliferation, for instance Kv11.1 channels associate with 14-3-3 (Kagan et al., 2002), Src (Cayabyab, 2002), or TNF-_ receptors (Wang et al., 2002), Kv1.3 associate with integrins (Levite et al., 2000) and p56lck (Hanada et al., 1997), and Kv10.1 associates with calmodulin (Schönherr et al., 2000). Increased expression of K^+ channels in tumors offers an additional tool for cancer diagnose and treatment.

2.2 Calcium channels

Calcium entry via different channels activates intracellular signalling cascades. Calcium channels play pivotal roles in many human diseases, particularly of the cardiac and nervous systems, for example, epilepsy, hypertension and migraine. In addition, these channels have been involved in pain and cancer. Cytosolic Ca^{2+} activity is necessary throughout the cell cycle since it plays a critical role on the regulation of cell proliferation (Whitfield et al., 1995; Parekh & Penner, 1997; Berridge et al., 1998, 2000, 2003). It has been shown that decreased levels of extracellular Ca^{+2} inhibit the progression through the G1 phase, causing cells to remain at the G1/S boundary. Moreover, Ca^{2+} is highly concentrated in intracellular stores and is released from the endoplasmic reticulum or mitochondria upon mitogenic stimulation (Nilius et al., 1993; Lepple et al., 1996). In excitable tissues, Ca^{2+} influx occurs through voltage-gated Ca^{2+} channels depending on the cell type. In non-excitable tissues, hyperpolarization of the membrane voltage is important for the increase of intracellular Ca^{2+}, providing the driving force for Ca^{2+} entry from the extracellular space.

Among voltage-gated Ca^{2+} channels, members of the Ca_v3 subfamily, and in particular $Ca_v3.2$ channels, are implicated in proliferation. It has been observed that voltage-gated calcium channels Ca_V1 (L-type currents), are expressed in non-proliferative phases, while expression of Ca_V3 channels (T-type currents) often increases during the proliferative phases. This is observed in both normal and cancer cells, although the precise physiological significance is uncertain. $Ca_v3.2$ channels are expressed in several cancer-derived cell lines,

and blockage of the channel generates antiproliferative action (Roger et al., 2006, Panner & Wurster, 2006). T-type calcium channels have been found in lung carcinoma cells (Oguro-Okano et al., 1992) and calcium influx through different ion channels has been suggested to participate in migration and invasion of prostate, breast and fibrosarcoma cells (Monet et al., 2009; Yang et al., 2009; Huang et al., 2004).

Other types of calcium channels have also been involved in cancer progression and prognosis. For instance, expression of the Ca^{+2} channel TRPV6 was correlated with prostate cancer grade, in which patients with positive TRPV6 prostate cancer had a poor prognosis (Fixemer et al., 2003).

2.3 Sodium channels

Voltage gated sodium channels (VGSCs) that selectively conduct sodium due to changes in membrane potential, allow sodium entry and thus the propagation of depolarization along the plasma membrane of nerve, muscle and other electrically excitable cells. Non-voltage-gated sodium channels like the degenerin/epithelial sodium channel (ENaC) superfamily, which are permeable also to lithium and potassium, is a group of proteins involved in diverse biological processes, including sodium homeostasis, salt taste, nociception, pain transduction, touch sensation and mechanotransduction (Goldin et al., 2000). Sodium channels have various functional and pharmacological properties in different tissues and species, and VGSCs in particular play an important role in generating action potentials. There are ten genes that encode VGSCs α subunits, from which nine constitute a single family named Na_V1 ($Na_V1.1$ to $Na_V1.9$), whose members associate with one or more auxiliary β subunits ($Na_V\beta1$ to $Na_V\beta4$) to form the whole channel protein complex (Yu et al., 2003). The remaining isoform, Na_X, shows a structure diverging from the Na_V1 family and seems to be gated by sodium concentration and not by voltage.

VGSCs have been suggested as participants in the development of cancer. Enhanced metastasis correlates with the appearance of membrane channels and currents that are characteristic of excitable membranes. Metastasis is a process where cells escape from a primary tumor, enter circulation (blood or lymph), migrate and invade other tissues, proliferate and form secondary tumors. In *in vitro* experiments, it has been shown that VGSCs are associated to proliferation, motility, and invasion of breast, lung, ovary and prostate cancer (Roger et al., 2003; Gao et al., 2010; Diss et al. 2005; Chioni et al., 2010; Roger et al., 2007; House, et al., 2010; Bennett et al., 2004). In prostate cancer cells, the main VGSC overexpressed is the $Na_V1.7$ subunit, while in breast, colon and ovary the $Na_V1.5$ subunit is the predominant subunit overexpressed. In addition, functional expression of VGSCs (mainly $Na_V1.7$, $Na_V1.6$ and $Na_V1.5$) is often associated with metastasis and VGSCs have been found in biopsies from prostate and breast metastatic cancer (Roger et al., 2006). The mechanisms responsible for VGSCs upregulation and for their pro-invasive roles are still poorly understood, but diverse hypothesis exists. One hypothesis strongly suggests that there is a regulation of growth factors release and/or activity which is common to all the cancers described, highly malignant cancer cell types that overexpress VGSCs also express growth factors such as epidermal growth factor (EGF) and nerve growth factor (NGF) (Brackenbury & Djamgoz, 2007; Uysal & Djamgoz, 2007), empasizing that growth factors could play a major role in upregulating VGSCs. Another hypothesis describes that embryonic genes, which are silent in the cells of the mature organ, are re-expressed in cancer

cells (Monk & Holding, 2001). This might be the case for VGSCs, since highly metastatic cancers (prostate and breast) mostly express embryonic isoforms of VGSCs (Diss et al., 2005; Fraser et al., 2005). Hence overexpresion of VGSCs contributes to the physiological and pathophysiological invasive processes in several metastatic cancers, representing a potential target to inhibit invasion and metastasis.

2.4 Chloride channels

Cl^- channels play a crucial role in controlling the ionic composition of the cytoplasm and the volume of cells. According to their gating mechanisms there are five classes of chloride channels:

- Voltage-gated chloride channels (CLC).
- Volume/swell-regulated/sensitive anion/chloride channels (VRAC).
- Cystic fibrosis transmembrane conductance regulator (CFTR).
- Calcium-activated chloride channels (CLCA).
- Ligand-activated chloride channels, which mainly form synaptic channels.

Cl^- channels play a crucial role in controlling the ionic composition of the cytoplasm and the cell volume. Cl^- channels are expressed in a variety of tumor cells and participate in cell proliferation, invasion and migration. Proliferation is associated with volume increase along the G1 phase, but non-specific cell swelling can inhibit proliferation. To regulate their volume, cells are endowed with various ions and organic osmolyte transport proteins that become activated upon cell swelling or shrinkage. In the presence of a significant water permeability of the plasma membrane, water follows osmotically, resulting in a regulated change of cell volume. This is called regulatory volume increase (RVI) or regulatory volume decrease (RVD). RVI most often involves the uptake of Na^+ and Cl^-, for instance, by the concomitant activation of Na^+/H^+ and Cl^-/HCO_3^- exchangers. Na^+ is replaced by K^+ through the Na^+-K^+-ATPase, resulting in a net intracellular accumulation of KCl. In RVD, intracellular KCl may be extruded by KCl cotransporters or by the concerted activation of swelling-activated Cl^- channels and K^+channels (Jentsch et al., 2002). Cell proliferation has been shown to correlate with increases in cell volume in fibroblasts, mesangial cells, lymphocytes, human promyelocytic leukemia cells (HL-60 cells), hybridoma cells (GAP A3), smooth muscle cells and cervical carcinoma cells (HeLa cells). The signaling of cell proliferation needs at some stage transient cell shrinkage, which may require the activation of Cl^- channels. Usually, intracellular Cl^- is above electrochemical equilibrium and activation of Cl^- channels leads to Cl^- efflux and thus depolarization. As long as K^+ channels are active, the Cl^- outward movement is paralleled by K^+ efflux. The loss of KCl and water shrinks the cells (Lang et al., 1998).

It has been observed that pharmacological inhibition of Cl^- channnels impairs the cell ability to migrate and limits tumor progression in experimental tumor models (McFerrin & Sontheimer, 2006). The outer membrane of mitochondria contains a Cl^- selective porin, the so-called voltage-dependent anion channel (VDAC). On the other hand, VRAC´s modulate progression of nasopharyngeal carcinoma cells through the G1 restriction point and endow nasopharyngeal carcinoma cells with enhanced proliferation ability. In addition, it is reported that VRAC displays cell cycle-dependent expression in tumor cells. Also CLC-3, an important member of the CLC superfamily, plays a crucial role in a variety of cellular

processes, including cell proliferation and cell cycle progression, and it has been demonstrated that inhibition of CLC-3 protein expression down-regulates invasion and migration ability of tumor cells.

3. Ion Channels in apoptosis

Cell homeostasis requires a delicate balance between formation of new cells by cell proliferation and cell elimination by apoptosis (programmed cell death). Apoptosis eliminates abundant and potentially harmful cells (Green & Reed, 1998). Apoptotic pathways involve several proteins with great enzymatic cell degrading potential including Bcl-2, caspases and cytochrome C. This process is initiated by death-promoting molecules such as TNF-α or CD95 Fas ligand, DNA damage, lack of growth factors, or cell exposure to genotoxics like radiation or oxidants. Apoptosis evasion might be one of the first steps for the transformation of nomal cells into cancerous cells, and it is a tightly regulated and highly efficient cell death program which requires the interplay of multiple factors. Upon receving specific signals instructing the cell to enter apoptosis, distinctive changes occur in the cell including shrinkage, nuclear condensation, DNA fragmentation, formation of sub-cellular apoptotic bodies, and mitochondrial depolarization. Ion channels have been involved in the regulation of apoptosis.

Potassium ions must leave the cell as an obligatory step in the apoptotic pathway. Activation of K+ channels and loss of intracellular K+ has been directly correlated to trigger apoptosis (Wang, 2004). Therefore, inhibition of apoptosis might take place by either increasing extracellular K+ concentration (Prehn et al., 1997; Colom et al., 1998) or inhibiting K+ channels (Lang et al., 2003). In any case, cellular K+ loss seems to be an important trigger of apoptosis in a wide variety of cells. Activation of K+ channels leads to hyperpolarization of the cell membrane, thus increasing the electrical driving force for Cl- outflow into the extracellular space. Then, if K+ channel activity is paralleled by Cl- channel activity, it leads to cellular loss of KCl with osmotically obliged water and hence to cell shrinkage, a hallmark of apoptosis (Lang et al., 1998). Subsequently, metabolic enzymes are activated, such as caspases and nucleases, which further propagate death signals. Remarkably, all these enzymes are controlled by the intracellular K+ concentration and while the concentration of various ions may change during apoptotic cell shrinkage, that of K+ plays a necessary and probably pivotal role in the cell death program. Cl- and K+ conductances must stay within a certain values in order to support proliferation, otherwise programmed cell death is triggered (Lang et al., 2004).

Sustained increase of cytosolic Ca2+ activity has been shown to trigger apoptosis in a variety of cells (Green & Reed, 1998; Spassova et al., 2004; Parekh & Putney, Jr., 2005). Cytosolic Ca2+ may trigger mechanisms required for cell proliferation and stimulate enzymes executing apoptosis. Ca2+ signal convergence results in activation of intracellular channels that leads to cytochrome C release from mitocondria. During apoptosis, small amounts of mitochondrial cytochrome C translocate to the endoplasmic reticulum and trigger Ca2+ release via IP3R channels. This leads to a bursting Ca^{2+} overload, which coordinates massive cytochrome C release from mitochondria, leading to activation of the caspase cascade, essential for the development of apoptosis (Boehning, D. *et al.,* 2003). Both the magnitude, space- and time- occurrence of Ca^{2+} entry is a major determinant to trigger apoptosis.

Both cell proliferation and apoptosis involve at some point activation of Cl^- channels, K^+ channels and Ca^{2+} channels. Due to complex interaction with other signaling pathways, a given ion channel may play a dual role in both cell proliferation and apoptosis.

At this point we focus on cervical cancer, a very well recognized cancer type strongly associated to HPV infection and ion channel expression. A potential link between HPV and ion channel expression has been also proposed for this type of cancer.

4. Overview of ion channels in cervical cancer

Expression of several ion channels has been reported in cervical cancer suggesting these proteins as potential markers and/or therapeutic targets for this malignancy. Large Ca^{2+}-activated K^+ (BK) channels are ion channels activated by changes in membrane electrical potential and/or by increases in the intracellular concentration of Ca^{2+}, contributing to cell proliferation and migration (Yuan et al., 2010). BK channels are expressed in HeLa cells, and it has been observed that they play a significant role in the regulation of proliferation of this cell line. Blockage of BK channels in HeLa cells results in tumor cell apoptosis and cycle arrest at G1 phase. The transduction pathway underlying such anti-proliferative effects is linked to the increased expression of apoptotic protein p53 and the decreased expression of its chaperone heat shock proteins (Hsp). Heat shock proteins function as intra-cellular chaperones (proteins that bind to and stabilize an otherwise unstable conformer of another protein) for other proteins, such as p53 (Zylicz M, King FW, Wawrzynow A., 2001); upon cell stress, the levels of these proteins increase dramatically. Other K^+ channels induce expression of heat shock proteins to exert tissue protective effects (Shinohara et al. 2004), suggesting that the intracellular potassium homeostasis may play a certain role in modulating heat shock proteins. The tumor suppressor gene p53 is involved in a variety of cellular processes including induction of G1 arrest and apoptosis by transactivating a number of downstream genes (Jin S, Levine A., 2001). One of those genes is p21 Cip1 (cyclin-dependent kinase inhibitor 1A), which is a cell-cycle regulatory protein that interacts with cyclin-CDK2 and -CDK4, inhibiting cell cycle progression at G1. The expression of p21 is tightly controlled by p53, through which this protein mediates the p53-dependent cell cycle arrest at G1 phase (Zamzami N, Kroemer G., 2005). Blockage of BK channels increases p53, p21Cip1, and Bax protein levels inducing cell arrest and apoptosis. In adition, inhibition of BK channels decreased the expression levels of some Hsp´s, which could be an upstream signaling of the BK channel-mediated p53 change. This would keep p53 under negative control by the activity of BK channels, inhibiting apoptosis in cervical cancer (Han et al., 2007).

Purinergic ATP-gated nonselective ion channels (P2X receptors) have been also suggested to participate in cervical cancer. These channels are permeable to Ca^{2+}, $Na^+$and K^+ (Burnstock, 2004) and several members have been identified and termed P2X1 through P2X7. Extracellular ATP is a physiological ligand that activates P2X7 receptor (Surprenant et al., 1996). Under normal conditions, extracellular ATP is present in only low concentrations, but increases significantly under inflammatory conditions and in response to tissue trauma (e.g., ischemia/hypoxia). The ionotropic purinergic P2X7 receptors activate a diverse range of cellular responses thay play a role in evading apoptosis of cervical cancer cells. In normal cervical epithelial cells, the activation of P2X7 receptors forms a pore that increases calcium influx and induces apoptosis via the Ca^{2+}-dependent mitochondrial pathway. Human

cervical cancer cells express a P2X splice variant (P2X7j) that do not mediates P2X7-dependent apoptosis, causing downregulation of the functional P2X7 receptor, thereby preventing the Ca^{2+} influx required to trigger apoptosis and leading to defective apoptosis and enhanced growth of cervical cancer cells (Feng, et al., 2006).

Voltage-gated sodium channels (VGSC) have also been detected in cervical carcinoma cells that may be involved in metastasis. Expression of $Na_V1.4$, $Na_V1.6$ and $Na_V1.7$ channels has been detected in biopsies from cervical cancer (Díaz et al., 2007). Whether the activity of the sodium channel participates in the invasiveness of cervical cancer cells remains to be determined, but the pharmacological blockade of VGSCs commonly results in the reduced migration of highly metastatic cell lines, whereas the facilitation of channel opening by agonists enhances migration without impairing cell proliferation or viability (Roger et al., 2007). The abnormal expression of these VGSCs might be used as a tumor marker and a potential therapeutic target for cervical carcinoma.

It has been suggested that the expression of volume-activated current ($I_{Cl,vol}$) in HeLa cells contributes to the cell cycle dependent regulation of cell migration. The density of $I_{Cl,vol}$ was positively correlated to the rate of cell migration during cell-cycle progression indicating that volume-activated Cl^- channels are involved in the cell-cycle-dependent migratory behaviour of HeLa cells. Moreover, expression inhibition of the voltage-gated chloride channel ClC-3 arrested HeLa cells in S phase (Mao et al., 2009). The capacity of Cl^- channels to participate in migration could be associated to cell volume regulation, since regulatory volume decrease plays an important role in migration of tumor cells. Cl^- channels helps the cell to undergo changes in their shape and volume, facilitating tumors cells to move trough the extracellular space. In the following section we describe the very interesting oncogenic Eag channels, which are to our best knowledge the only known channels regulated by HPV oncogenes.

5. Oncogenic Eag1 K^+ channels in cervical cancer and regulation by HPV oncogenes

Ether à go go (Eag1) K^+ channel has gained great interest in cervical cancer diagnosis and therapy (Farias et al., 2004). Eag1 is a voltage gated K^+ channel first described as a cell-cycle regulated channel (Brüggemann et a., 1997; Camacho et al., 2000), and was the first ion channel identified to display oncogenic properties (Pardo et al., 1999). These channels are widely distributed in the central nervous system, but their expression in peripheral tissues is very restricted, finding the channel only in placenta, transiently in myoblasts, testis and adrenal glands (Occhiodoro et al., 1998; Pardo et al., 1999; Hemmerlein et al., 2006). This restricted distribution in normal tissues is one of the most attractive features of Eag1 as a potential tumor marker. Eag1 channels are overexpressed in various cancer cell lines including IGR1, IPC298, and IGR39 from melanoma, SH-SY5Y from neuroblastoma, MCF-7 from breast cancer and HeLa from cervical cancer. Eag1 channels have transforming properties, they confer lose of contact inhibition and sustained growth in the absence of serum. Cells transfected with Eag1 channel and implanted into inmunosuppreseed mice induce formation of aggressive tumors (Pardo et al. 1999). Eag1 has been found to be overexpressed in many types of tumors including breast, lung, prostate, liver and colon (Hemmerlein et al., 2006). Thus, Eag is a promising tumor

marker. On the other hand, inhibition of either channel activity or expression decreases proliferation of tumor cells both *in vitro* and *in vivo* (Pardo et al., 1999; Ousingsawat et al., 2007; Gómez-Varela et al. 2007; Downie et al., 2008; Díaz et al., 2009). Therefore, Eag is also a promising therapeutic target for many types of cancer (Camacho, 2006; Pardo & Stühmer, 2008).

Eag1 mRNA expression was found in 100% of cervical cancer human biopsies while only in 33% of normal control samples (Farias et al., 2004). Interestingly, in this study it was observed that in one of the patients that was submitted to hysterectomy without any previous evidence of cervical malignancy (negative pap smears), postsurgery pathological studies showed an unexpected endocervical adenocarcinoma expressing Eag1. This case, although unique in such study, emphasizes the potential significance of Eag1 as a tumor marker in cervical cancer (Farías et al., 2004; Camacho, 2006). In addition, one of the normal cervical samples that were positive for Eag1 expression was correlated with HPV infection. This led to suggest that Eag1 expression in normal cervix could be an early sign of tumor development associated to HPV infection.

The primary transforming activity of high-risk HPVs is provided by the E6 and E7 oncoproteins which act cooperatively in the development of HPV-induced cancers. A primary target of E7 is the retinoblastoma (Rb) family of proteins that control the activity of E2F transcription factors, which are key regulators of S phase genes. The efficient abrogation of Rb function by E7 leads to increased levels of p53 and, consequently, the E6 proteins have evolved to target p53 for degradation. Researchers investigated the potential link between HPV infection and Eag oncogenic channels by transfecting normal human keratinocytes with E6 and/or E7 HPV oncogenes (Díaz et al., 2009). They observed that normal human keratinocytes do not express Eag channels. Interestingly, keratinocytes transfected with either E6, E7 or both HPV oncogenes, displayed a strong Eag channel expression. This finding suggests a novel mechanism by which HPV induces tumor formation, namely, up-regulation of the oncogenic Eag1 channel.

Regulation of Eag1 channels by E6/E7 HPV oncogenes suggests that the regulation of Eag1 in cervical cancer might be via p53 and Rb pathways. A novel signaling pathway has been described that might explain how Eag is regulated by p53. It appears that Eag1 is a terminal component in the p53-miR-34-E2F1 pathway. miR-34 is a micro RNA, which silences expression of target genes through the RNA interference pathway and is commonly downregulated in human cancers; one example is miR-34, which is a direct target of p53. miR-34 transcription is activated by p53, and expression of miR-34 inhibits proliferation by inducing cellular senescence and cell cycle arrest at G1. When cellular stress or damage exist, p53 increases, causing the miR-34 transcription to increase, and the increased miR-34 will decrease the trancription factor E2F1. One of the target genes for transcription of E2F1 is the K^+ channel Eag1. Supression of E2F1 will repress Eag1, this will diminish Eag1 expression and function, resulting in a shut down of the cell proliferation or a cell cycle arrest, thus upregulation of miR-34 represses E2F1 and Eag1. Therefore, p53 negatively regulates Eag1 expression by a negative feed forward mechanism through the p53-miR-34-E2F1 pathway (Lin et al., 2011). This pathway might also help to explain the effect of the E7 oncogene on Eag regulation. E7 binds to Rb disrupting the Rb–E2F complexes, resulting in the constitutive expression of E2F1-responsive genes including Eag1.

6. Effect of estrogens on HPV and eag channels

HPV infection has been suggested as a necessary but not sufficient factor to induce cervical cancer. Thus other contributing factors have been proposed, especially estrogens. The uterine cervix is highly responsive to steroidal hormones and the use of oral contraceptives and multiple pregnancies have been shown to significantly increase the risk for cervical cancer in HPV-infected women (Moreno et al., 2002; Muñoz et al., 2002). In mice models for HPV-associated cancers, estrogen is required for the development of cervical and vaginal cancers (Brake & Lambert, 2005). The estrogen receptor alpha (ERα) is also required in mice for these cancers to develop and ER antagonists can cause efficient regression of cancer, dysplasia, and atypical squamous metaplasia, preventing malignant progression (Chung & Lambert, 2009). Other studies also suggest the relevance of estrogen in the carcinogenesis of cervical cancer. Growth stimulation of SiHa cervical cancer cells by estrogens appeared to be related to the increased expression of HPV E6/E7 oncogenes, estradiol stimulated both cell growth and transcription of E6/E7 viral oncogenes (Rosembaum, et al., 1989; Kim, et al., 2000). In addition, overexpression of aromatase, the enzyme that transforms testosterone into estrogen, is known to increase estrogen activity in breast tissue, and in cervical cancers it has been reported that 35% of human cervical cancer tested express aromatase, but

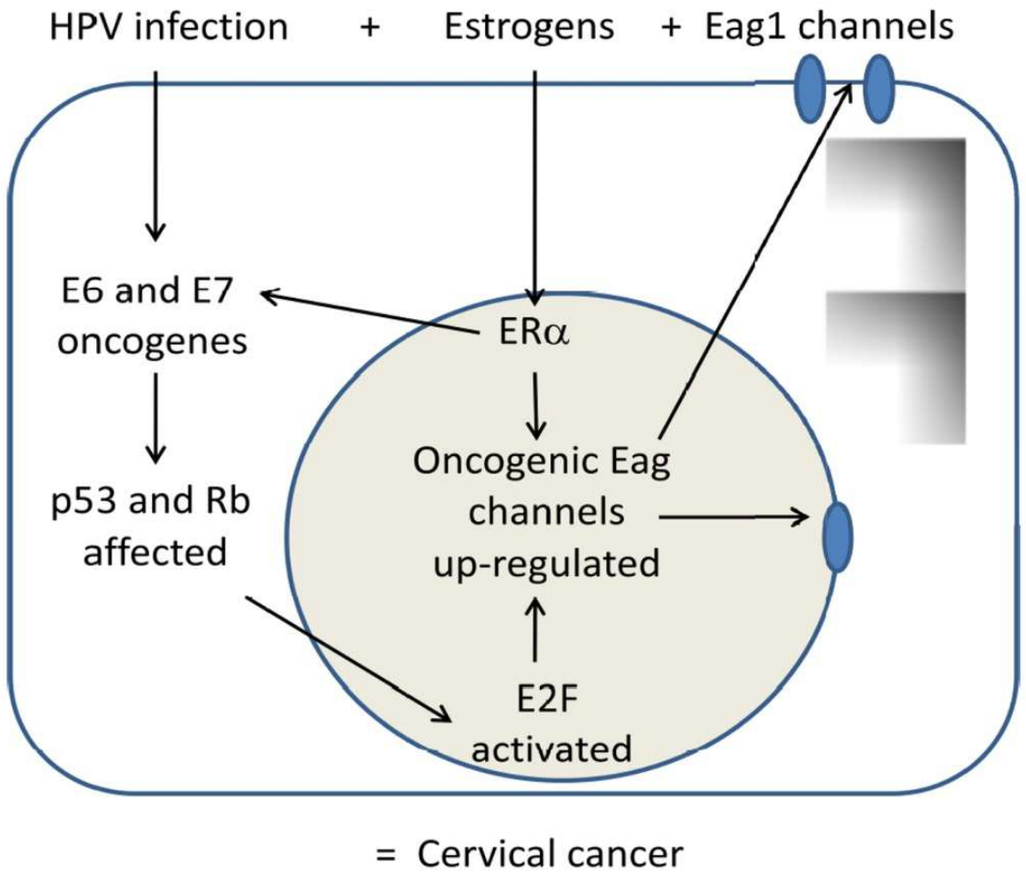


Fig. 2. Regulation of Eag1 oncogenic Eag1 channels by HPV oncogenes and estradiol. Eag1 might become extremely up-regulated since HPV oncogenes are in turn regulated by estradiol, leading cervical cells to cancer.

aromatase expression was not detected in precancerous or normal cervical tissue samples. Aromatase overexpression induced the expression of cyclin D1, proliferating cell nuclear antigen and HPV oncogenes (Nair, et al., 2005). It was also observed that women that expressed higher levels of estrogen receptors transcripts were significantly more likely to have cervical HPV infection; it may be that the presence of the receptor allows cellular acquisition of HPVand increased viral transcription (Shew, M., et al. 2005). These data suggest that a mechanism of synergistic cooperation exist between estrogen exposure and viral oncogenes, so it raises the possibility that steroidal hormones, such as estrogen, might affect cancers of the cervix, much like that of other hormonally responsive female organs. In summary, several studies suggest that estrogens play a critical role not only in the genesis of cervical cancer but also in its persistence and continuous development.

Eag1 channel expression is also up-regulated by estrogens. HeLa cells transfected with ERα and treated with 17-β estradiol, induce a strong up-regulation of Eag1 channels. These results suggest ERα activation as one of the mechanisms of the estrogenic regulation of Eag1. Thus the regulation of the Eag1 channel in cervical cancer is mediated by HPV oncogenes and estrogens (Diaz, L., et al., 2009). HPV-infection in cervical cells might lead to a very significant increase in oncogenic Eag channels. Since estrogens might regulate both HPV-oncogens and Eag1 channels, these related pathways might easily drive the cell into a tumor phenotype (Figure 2).

7. Conclusion

Ion channels are emerging as potential tools for diagnosis and treatment of many types of cancer including those where HPV infection plays a major role. Particularly, up-regulation of the oncogenig human Eag channel by HPV oncoogens offers a novel mechanism by which HPV associates to some types of cancer. Since several ion channels are up-regulated by HPV oncogenes and/or factors closely associated to HPV, for instance estrogens, simultaneous detection of HPV infection and ion channel expression should provide an alternative option for early detection of tumors. Besides, HPV detection might also serve to target ion channels involved in tumor progression. This combined approach should help reduce cancer mortality.

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9. References

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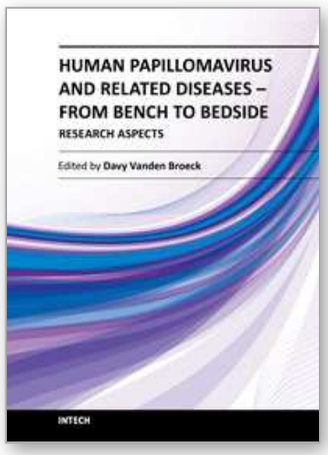
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Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on epidemiological and fundamental research aspects in the area of HPV, and it will update those working in this fast-progressing field with the latest information.

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