1. **Header:**

**Title**: Cancer as a channelopathy: ion channels and pumps in tumor development and progression

**Why did I read this paper:**

**Source:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4362317/pdf/fncel-09-00086.pdf>

**Year of published:** 2015

1. **Summary of abstract**

* Some function of ion channels and pumps
  + Regulate: membrane potential, ion homeostasis, electric signaling
  + Play roles in: cell proliferation, migration, apoptosis and diferentiation
  + Form macromolecular complexes with growth factor, and cell adhesion and other signal molecules
* And while cancer is still not being cataloged as a channelopathy, as the non-traditional roles of ion pumps and channels are being recognized, it is increasingly being suggested that ion channels and ion pumps contribute to cancer progression.
* Research on cancer cells suggests that certain ion channels may be involved in aberrant tumor growth and channel inhibitors often lead to growth arrest.

1. **Outstanding points**

* Cancer is a leading cause of death worldwide.
  + More than 1.6 million new cases were diagnosed in 2013
  + One in four deaths in the US is cancer related.
  + Most cancers are treated with surgery, chemotherapy, and/or radiation therapy
    - patients often experience debilitating side effects that significantly reduce their quality of life
    - cancer relapse with treatment resistance underscores the urgent need to identify novel molecular targets for the development of alternative therapies
* Recently, the role of ion channels in driving malignant cancer cell behavior has been revealed and much has been learned from brain tumors
  + Changes in channel expression have been observed primarily in glioblastoma, the most aggressive malignant brain tumor arising from astrocytes and have also been seen in medulloblastoma, the most common pediatric brain tumor that originates in the cerebellum
  + With our increasing knowledge of ion channels and pumps in tumor development cancer is being classified as a channelopathy, or a disease brought about by disturbed function of ion channels, often due to dysregulation of channel expression (transcriptional channelopathy) or other modifications resulting in altered function
* The proteins that transport ions across cell membranes fall into two general classes: ion channels, through which ions move down their concentration and electrical gradients, and ion pumps that use energy to actively move ions against those gradients
* About 13% of currently known drugs whose primary therapeutic targets are ion channels are being used for the treatment of a variety of human conditions, including cardiovascular and neurological disorders
* With our evolving understanding of the molecular mechanisms of channelopathies, ion channels have now become a promising player for the development of novel anticancer therapies
* Some classes of channels and pumps: sodium, potassium, cloride and calcium channels and ion transport pumps
* Overview of Ion Channels and Pumps with Dysregulated Expression in Cancer Cells

### Potassium Channels

### Can be divided into 4 classes:

### Voltage-gated potassium channel (Kv): gated by changes in membrane potential

### Calcium-activated potassium channels (Kca): activated by intracellular calcium

* + - * Inward rectifying potassium channels (Kir): possess two transmembrane segments flanking one pore loop in each of the four α-subunits
      * Two-pore domain potassium channels (K2P): have two pore domains per α-subunit. Two α-subunits form a K2P channel that is usually constitutively open as a “leak channel” for maintaining a negative membrane potential
    - Multiple studies have reported dysregulated potassium channel expression in human cancer.

### Sodium Channels and Exchangers

* + - Voltage gated sodium channels (VGSCs) are responsible for the rising phase of the action potential in the majority of electrically excitable cells and are therefore important in impulse generation and propagation.
      * Recently, VGSCs have been found to have relatively high expression levels in a range of cell types that are considered non excitable, including immune cells, fibroblasts and cancer cells
      * Moreover, several individual NaV isoforms are differentially expressed in different human cancers.
    - In addition to these sodium channel families, there is also a group of exchanger proteins that involve transport of sodium ions. Some of these exchangers proteins include:
      * Na+/H+ exchanger
      * Na+, HCO−3HCO3− contransporter
      * Na+, K+, 2Cl− cotransporter

### Chloride Channels:

* + - 2 distinct classes
      * CLC
      * Cystic fibrosis transmembrane conductance regulator (CFTR)
    - Functions of chloride channels:
      * ion homeostasis
      * cell volume regulation
      * regulation of excitable cells
    - Dysregulation of chloride channels has been reported in multiple cancer types

### Calcium Channels

* + - Ca2+
      * A ubiquitous second messenger
      * An important signaling molecule for several fundamental cell processes including cell cycle control, migration, and apoptosis.
      * Some human diseases that have been associated with Ca2+ homeostasis include cancer, Alzheimer’s disease, and cardiovascular disease

### Ion Exchangers

* + - The P-type ATPases are a major class of ion pumps and are characterized by an aspartate residue in the cytoplasmic domain that gets phosphorylated by ATP once transported ions have entered the binding pocket
    - Some examples of P-type ATPases are:
      * the Sodium potassium ATPase (**Na,K-ATPase**)
      * the sarcoplasmic and endoplasmic reticulum Ca-ATPase (**SERCA**)
      * the H,K-ATPase
      * the H-ATPase.
    - To date, the best characterized pumps that have been linked to cancer are SERCA and the Na,K-ATPase
* Ion Carriers, Ion Channels and Ion Pumps in Cancer Cell Migration

### Potassium Channels

### Sodium Channels

### Chloride Channels

### Calcium Channels

### Ion Pumps

* Ion Channels and Cell Signaling
* Ion Channels, Proliferation and the Cell Cycle
* Therapeutic Potential
  + Most cancers are treated by surgical resection, chemotherapy, and radiation therapy. However due to the prevalence of cancer relapse with treatment resistance, novel molecular targets must be identified for the development of alternative therapies. Despite the growing evidence of aberrant expression and function of ion channels in oncology, development of cancer treatment using ion channel targeting compounds is still at an early stage.

1. **Lesson learned from the papers**
2. **Terms translated to Vietnamese**

|  |  |
| --- | --- |
| **Term** | **Translated** |
| membrane potential | Điện thế màng |
| ion homeostasis | Cân bằng nội môi ion  Cân bằng nội môi ion là một đặc tính của một hệ thống mở để điều khiển môi trường bên trong nhằm duy trì trạng thái cân bằng, thông qua việc điều chỉnh các cơ chế điều hòa cân bằng động khác nhau |
| apoptosis | Chết rụng tế bào |
| migration | Cư trú, di chuyển |
| aberrant tumor growth | Sự phát triển khác thường của khối u |
| Growth arrest | Sự ngừng phát triển |
| adhesion | Sự kết dính, bám vào |
| inhibitors | Chất ức chế |
| relapse | Tái phát |
| malignant cancer cell | Tế bào ung thư ác tính |
| disturbed function of ion channels | Chức năng bị nhiễu của ion channel |
| channelopathy | are diseases caused by disturbed function of ion channel subunits or the proteins that regulate them |

1. **Novel knowledge**

* Increasing evidence suggests that ion channels and pumps are involved in the regulation of cell proliferation and migration, and channel proteins have been shown to form macromolecular complexes with cell adhesion molecules and other signaling proteins. As these roles of ion channels and pumps are further elucidated, it is being increasingly suggested that regulation of ion channels and pumps could contribute to cancer progression.
* Knowing that these proteins are involved in multiple malignant characteristics of multiple cancers, ion channels and pumps could be potential targets for therapy.

1. **Other notes**