CHAPTER II
LITERATURE REVIEWS

1. Cell cycle

Cell cycle or cell division cycle is an important mechanism to maintain tissue homeostasis. Cell cycle is series of event in a cell that leading to its division and duplication (replication) and produces two daughter cells. Cell cycle can be divided into two periods, interphase and miotic phase: (Diaz-Moralli et al., 2013).

1.1 Interphase is the periods which cell accumulating nutrients required for mitosis and duplicating its DNA. Interphase can be divided into three phase: G_1, S, and G_2.

1.1.1 G_1 phase

G_1 (gap 1) phase, a period between M and S phase, is growth phase. Accumulation of nutrients by the cell is required for DNA replication, active RNA and necessary protein synthesis. This phase is usually the longest and highly variable phase of cell cycle.

1.1.2 S phase

DNA synthesis and replication are occurring in this phase. Event of S phase include DNA replication, histone synthesis and the beginning of centrosome duplication. Thus, amount of DNA in the cell doubles during S phase. The complete duplication of chromosomes during S phase is needed for their appropriate division in mitosis as well as ensures that each daughter cell receives a completely genome complement.

1.1.3 G_2 phase

G_2 phase is the gap between S and M phases, which follow the successful completion of DNA replication. This phase is usually short period of preparation for cell division. Reparation of DNA damage, synthesis of tubulin for the spindle apparatus and ATP accumulation for mitosis are occurring in G_2 phase. The ending of G_2 phase is marked by chromosome condensation and the beginning of mitosis (M phase).

1.2 Mitotic (M) phase is a period of cell division, which consists of 4 phases: Prophase, Metaphase, Anaphase and Telophase. Mitosis followed by a cell division (cytokinesis).

1.2.1 Prophase

The nucleolus and nuclear envelope disappears. The replicated chromatin condenses into threadlike chromosome each consists of two identical arms, called sister chromatid. A pair of sister chromatids attached to each other at the centromere. In this stage, the centrosomes (microtubule organizing center) have moved apart to opposite poles of the cell and each is interacted with microtubules to build a bipolar mitotic spindle.

1.2.2 Metaphase

Chromosomes condense further and each sister chromatid stick to the mitotic spindle at kinetochore, the protein structure on chromatids where the spindle fibers attach to pull sister chromatids apart**.** In this stage, the chromosomes line up along equatorial plane, an imaginary line that is equidistant from the two centrosome poles. This event is due to the opposing kinetochore microtubules generate the counterbalance of the pulling powers**.**

1.2.3 Anaphase

Sister chromatids split from each other to become individual chromosomes and move toward opposite spindle poles of the cell due to the action of the spindle. A complete set of chromosomes has assembled at each pole of the cell in the ending of this phase.

1.2.4 Telophase

The two sets of daughter chromosomes are at the spindle poles and begin reverting to their decondensed state. The nuclear envelope begins to reassemble around each set of chromosomes.

1.2.5 Cytokinesis is the last stage of cell cycle. This stage is the process in which the cytoplasm and its organelles are divided into two daughter cells and each with one nucleus.

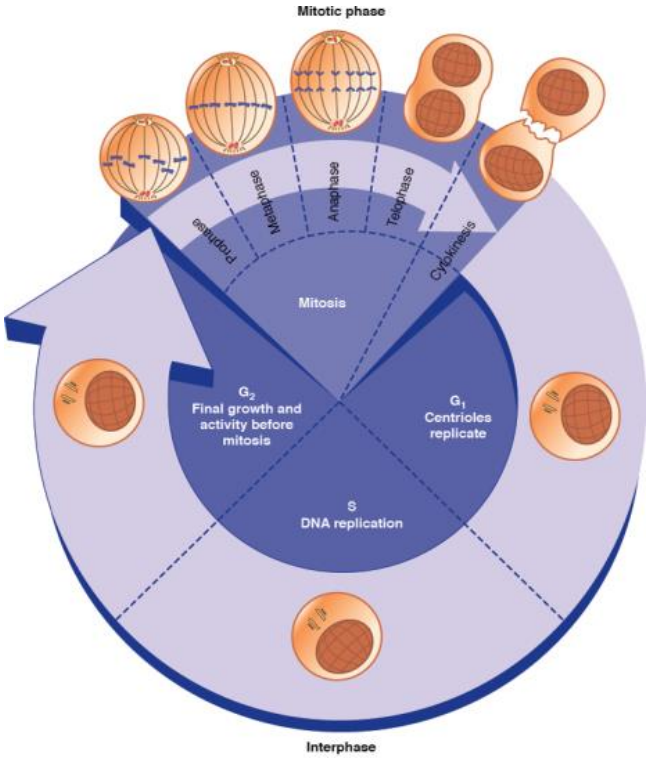

Figure 1 Cell cycle

2. Regulation of cell cycle

Cell cycle is controlled by several mechanisms. A cell cycle checkpoint is the one of important mechanism that regulates proper progression of cell cycle which ensure the fidelity of cell division in eukaryotes (O'Donnell et al., 2013; Recolin et al., 2014). The cell cycle checkpoints regulate cell cycle progression or cell cycle arrest through a regulatory protein, cyclin dependent kinase (CDK) which is activated a specific point of cell cycle. The CDK induces downstream process by phosphorylation of specific protein, cyclins. Level of CDK protein is stable during cell cycle while level of cyclins protein rise and fall during cell cycle. Different cyclins are needed at different phase of cell cycle. There are three interphase CDKs (CDK2, CDK4 and CDK6), a mitotic CDK (CDK1) and ten cyclins that were classified into four different classes (the A-, B-, D- and E-type cyclins), which is monitored the cell cycle (Figure 2) (Vermeulen et al., 2003). If any checkpoints detecting problems, progression through the cycle is interrupted and transit through the cell division cycle is halted until the damage is repaired. Abrogation of checkpoint

may lead to abnormal cell cycle progression and can result in many diseases such as cancer (Diaz-Moralli et al., 2013). Main checkpoints controlling cell division cycle in eukaryotic cell consists of 3 checkpoints: G_1 checkpoint, G_2 checkpoint and Metaphase checkpoint (Figure 3) (Canman, 2001; Golubnitschaja, 2007).

G_1 checkpoint or restriction checkpoint is located at the end of G_1 phase, which is the key decision of whether the cell should divide, delay division or entry to resting stage. If a cell has a variety of adverse conditions that make cell division impossible, this checkpoint is where eukaryotes typically arrest the cell division cycle.

G_2 checkpoint is located at the end of G_2 phase**.** The important role of this checkpoint is ensuring that all of the chromosomes have been exactly replicated without mistakes or damages**.**

Metaphase (M) checkpoint or spindle checkpoint occurs near the end of metaphase, which is determining whether all sister chromatids are exactly attached to the spindle microtubules.

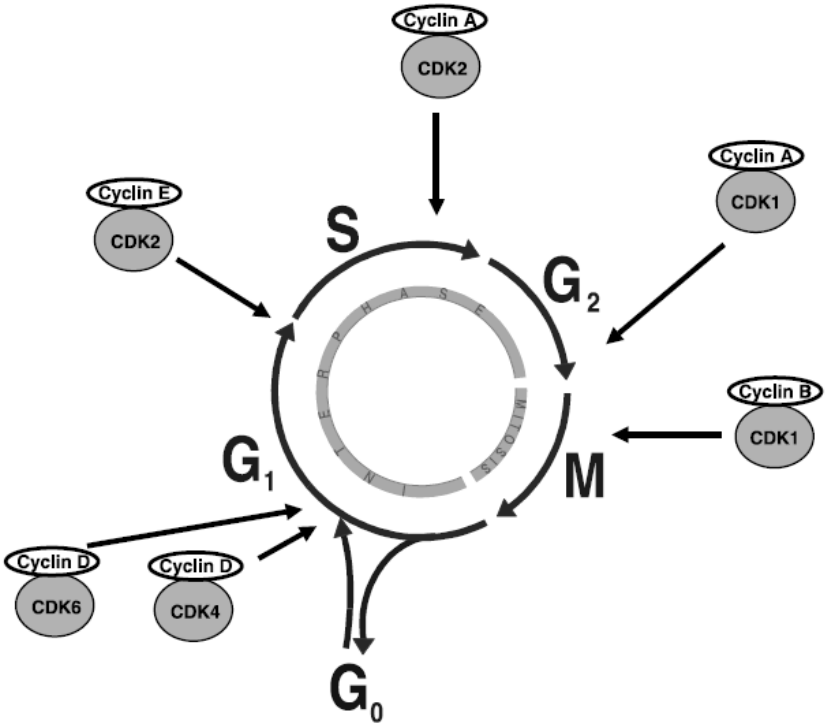

Figure 2 The site of activity of regulatory CDK/cyclin complexes (Vermeulen et al., 2003)

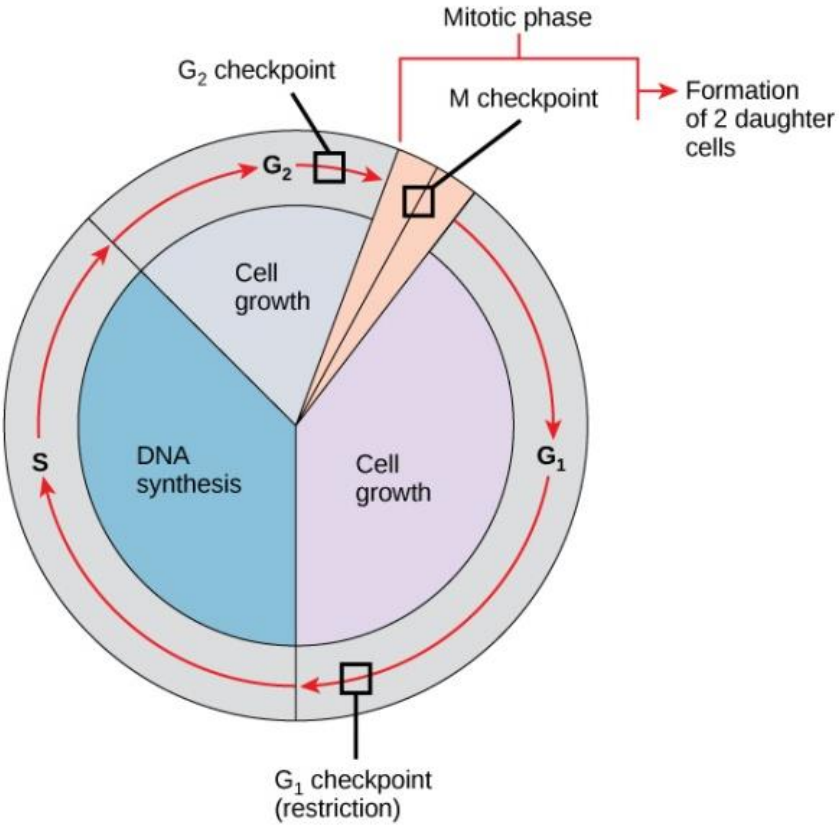

Figure 3 Cell cycle checkpoints

3. Cancer

Cancer is a disease which result from the cell uncontrolled proliferation (Diaz-Moralli et al., 2013). Characteristic of cancer cell are include self-adequacy in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, invade local tissues and can spread to other parts of the body through the blood and lymph systems (metastasis) (Figure 4) (Hanahan and Weinberg, 2000). Abnormality of cell proliferation may due to any cell cycle checkpoints defect and result in accumulation of abnormal DNA to daughter cell (Diaz-Moralli et al., 2013; Foster, 2008; Gabrielli et al., 2012).

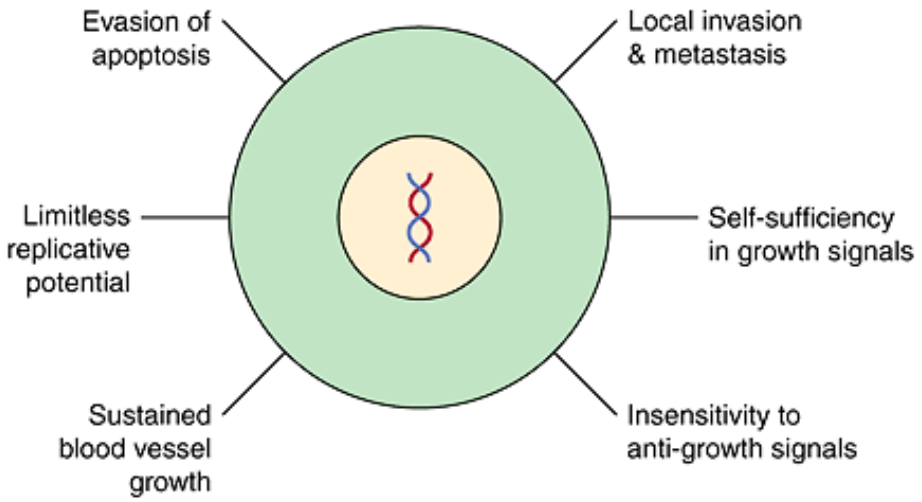

Figure 4 Six major features of cancer cells (Hanahan and Weinberg, 2000)

Process of Carcinogenesis (Stelzner, 2006)

Process of carcinogenesis is a multistep process, which can be divided into three main phases: initiation, promotion and progression.

1) Initiation: Initiation stage is the first step of carcinogenesis, which involves the alterations of irreversible in appropriate target somatic cells. Stable cellular changes arising spontaneously or induced by exposure to a carcinogen, which lead to potential for neoplastic development and follow by neoplastic transformation of progeny.

2) Promotion: The subsequent changes of a transformed cell results in neoplastic transformation may involve more than one step and requires repeated and prolonged exposures to promoting stimuli, which is harmful condition.

3) Progression: Progression is characterized by irreversibility, genetic instability, faster growth, invasion, metastization, and changes in the biochemical, metabolical and morphological characteristics of cells. During progression, this balance is modified and form there malignancy arises.

4. Cervical cancer

The cervix is located in the lower part of uterus and connected to the vagina. The anatomy of cervix is generally divided into the endocervix with columnar glandular epithelium and ectocervix or exocervix with squamous epithelium. Squamocolumnar junction or called transformation zone is the point between squamous and glandular epithelium, which is the most common place that cervical cancer start. Cervical cancer is a type of cancer that occurs in the cervical cell which grows out of control. Cellular classification of cervical cancer consists of squamous cell carcinoma, which is a most common type of cervical cancer with approximately 90% and adenocarcinoma with approximately 10% of cervical cancer.

Squamous cell carcinoma usually arises at the squamocolumnar junction. Developments of cervical cancer do not rapidly occur but the normal cells of cervix gradually change into cancer. The pre-cancerous stage before the cells turn cancerous is called cervical intraepithelial neoplasia or CIN, which is dysplasia of the cervical epithelium. CIN can be divided into 3 grades: CIN1, CIN2 and CIN3 depend on the proportion of the thickness of the epithelium showing mature and differentiated cells. Most of case follows persistence HPV infection, which may progress to CIN. HPV induced pre-invasive lesion by integration of HPV into host genome, which lead to overexpression of E6 and E7 of HPV resulting in increased proliferative ability and may cause progression to invasive cervical cancer. However, progression of pre-invasive lesion depends on many factors such as host immunity, chemical substances and somatic cell genomic variations (Figure 5).

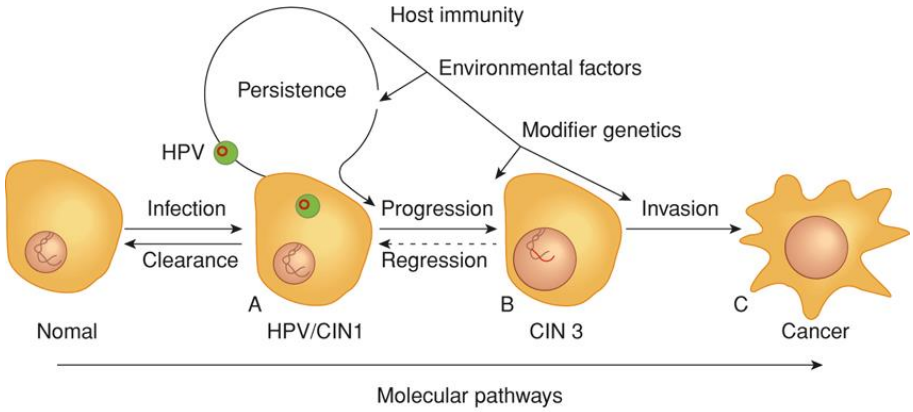

Figure 5 Genesis of cervical cancer

4.1 Stage of cervical cancer

The cervical cancer is classified into 5 stages, stage 0 to stage IV according to the International Federation of Gynecologists and Obstetricians as following (Figure 6) (Pecorelli, 2009).

Stage 0 is carcinoma in situ. The tumor present only intraepithelial which is the cells lining the cervix.

Stage I is carcinoma strictly confined to the cervix (extension to the uterine corpus would be disregarded). Stage I is subdivided as follows:

Stage IA is invasive carcinoma which can be identified only by microscopy. Invasion is limited to measured stromal invasion with deepest invasion ≤5 mm and largest extension ≥7 mm.

Stage IA1: Measured stromal invasion of no greater than 3.0 mm in depth and no wider than ≤7.0 mm.

Stage IA2: Measured stromal invasion of greater than 3.0 mm and no greater than 5.0 mm in depth and less than 7.0 mm in width.

Stage IB is clinically visible lesions limited to the cervix or preclinical lesions greater than stage 1A.

Stage IB1: Clinically visible lesion no greater than 4.0 cm in dimension.

Stage IB2: Clinically visible lesion greater than 4.0 cm in dimension.

Stage II is invasive carcinoma that invades beyond the uterus, but not into the pelvic wall or to the lower third of the vagina.

Stage IIA: Spreading tumor without parametrial invasion.

Stage IIA1: Clinically visible lesion no greater than 4.0 cm in dimension.

Stage IIA2: Clinically visible lesion greater than 4.0 cm in dimension.

Stage IIB: Spreading tumor with obvious parametrial invasion.

Stage III is invasive carcinoma that extends to the pelvic wall and/or involves lower third of the vagina. The tumor in this stage may be causes hydronephrosis or non-functioning kidney.

Stage IIIA: Tumor involves lower third of the vagina but no extension into the pelvic wall.

Stage IIIB: Tumor extends to the pelvic wall and/or hydronephrosis or non-functioning kidney.

Stage IV is carcinoma that has extended beyond the true pelvis or involvement of the mucosa of the bladder or rectum.

Stage IVA: Tumor has spread to adjacent pelvic organs.

Stage IVB: Tumor has spreads to distant organs.

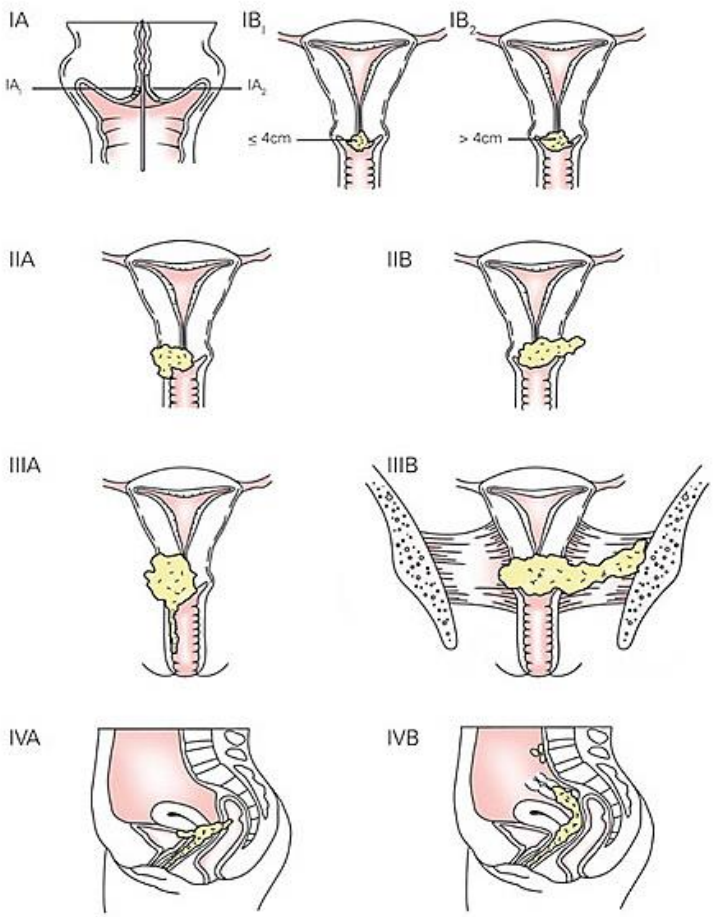

Figure 6 Stage of cervical cancer

4.2 Risk factors of cervical cancer

4.2.1 Human papilloma virus (HPV) infection

Human papilloma virus is a non-enveloped, double-stranded circular DNA virus consisting of approximately 8,000 bp. The genome of HPV can be divided into three regions: a long control region (LCR) with ~1-kb, an early region (E) with ~4-kb and a late region (L) with ~3-kb. LCR is a non-encoding region that contains the origin of viral DNA replication and a variety of transcriptional regulatory elements. The E region contains eight genes and the two genes in L region. These genes in both regions encode viral necessary protein. At present, there are over 100 genotypes of HPV. HPV can be classified as either high-risk (HR) or low-risk (LR) depending upon their capacity to promote malignant transformation in host cells

(Rathfisch et al., 2014). Examples of those classified as HR viruses are HPV 16, 18, 31, 33, 35, 45, 52, 58 and 82 (Rijkaart et al., 2012) . HPV of any types can be found in approximately 95% of cervical cancers. However, HPV types 16 and 18 play an important role in medical field which are the critical factor for cervical cancer development (Woods et al., 2014). Persistent infection with high-risk HPV is an essential factor for the developing cervical cancer because HPV integration into the host genomes can be leading to carcinogenesis (de Freitas et al., 2014; Dochez et al., 2014). The integration of HPV leads to the functional elimination of the viral E2 repressor and remodeling of the E6/E7 promoter. The E6 and E7 open reading frames are virtually always retained and result in continued expression of the E6 and E7 oncoproteins. HPV type 16 and 18, most common type of HPV infection has two transcriptional units: E6 and E7. The E6 gene produce E6 oncoprotein which inactivate the function of *p53* tumor suppressor protein by ubiquitin degradation, which disrupts an inherent checkpoint of cell-cycle while E7 gene of E region produce E7 oncoprotein which bind to and inactivate products of retinoblastoma (RB) gene which allows unchecked cell-cycle progression and finally, lead to cervical cancer development (Amirian et al., 2013; Rijkaart et al., 2012). The time course of HPV infection induced the invasive cervical cancer development usually take many years. However, many studies suggested that HPV infection alone is not sufficient for the cervical cancer development. Other factors related to the host such as genetics polymorphism play an important role in the persistence infection of HPV and progression of cervical carcinogenesis (de Freitas et al., 2014). The association between HPV infection and cervical cancer risk has been reported for long time. For instance, an increased risk of developing high-grade CIN/cancer was observed in correlation of HPV16 non-European variants in several studies (Pientong et al., 2013; Schiffman et al., 2010). In the studies of multiple HPV infections, some investigators suggested that HPV co-infections may affecting viral oncogenic potential and may have influence on risk and severity of premalignant lesions (Carrillo-Garcia et al., 2014; Trottier et al., 2008).

4.2.2 Chemical substances

(1) Contraceptives

Contraception is used for preventing pregnancy among women (Haider and D'Souza, 2009). Common types of contraception that are used include oral contraceptive and injected contraceptive. Oral contraceptives are hormonal preparations that may contain combinations of the hormones estrogen and progestin or progestin alone. Several studies have been shown association between long term uses of oral contraceptive and increasing risk of cervical cancer. However, hormonal contraception less than 5 years did not increased cervical cancer risk (Smith et al., 2003). Oral contraceptive has been related with increased cervical cancer risk. Nevertheless, HPV infection is a mainly causative of cervical cancer development. Thus, oral contraceptive is likely act as a cofactor of HPV for development of cervical cancer. Hormonal-related mechanism may affect the progression pre-malignant to malignant cervical lesions by promoting integration of HPV-DNA into host genome, which results in deregulation of E6 and E7 expression (Castellsague et al., 2002). Furthermore, experimental studies in cell line that contain integrated HPV type 16 have shown that estradiol may stimulate transcription of E6 and E7 of HPV16 (Mitrani-Rosenbaum et al., 1989).

(2) Smoking

Various compounds of cigarette are carcinogen such as nicotine derivative cotinine and tobacco-specific nitrosamines. Smoking has been related with several types of cancer: lung cancer, oral cancer, prostate cancer as well as cervical cancer (Juarez-Cedillo et al., 2007; Madani et al., 2014; Peres, 2013; Rohrmann et al., 2013). Cigarette smoking is considered a causative factor in development of cervical cancer which is an independent factor (Moralejo, 2009; Winkelstein, 1977). In addition, several studies found that smoking increased the risk for cervical cancer in HPV-positive women. Thus, data from various studies demonstrate the propose mechanism of smoking for cervical cancer development that the compounds in cigarette can bind to and damage cellular DNA and might cooperate with HPV to produce malignant transformation (Braun and Gavey, 1999).

4.2.3 Reproductive behaviors

Many reproductive behaviors such as number of sexual partners, age at first sexual intercourse as well as male factors have been associated with developing cervical cancer.

Number of sexual partners is one of the mainly risk factors for both pre-invasive and invasive cervical cancer. Several studies have shown an increased relative risk of cervical cancer in female who had more than six sexual partners (Munoz et al., 1993). In addition, numbers of sexual partners has been strongly related to the HPV infection, a sexually transmitted infection. Thus, a higher number of sexual partners may increase risk of developing cervical cancer (Lenselink et al., 2008).

Early age at first sexual intercourse has been associated with an increased infection of HPV and also increased risk of invasive cervical carcinoma. Many investigations have been speculated that the increased risk of HPV is due to a biological predisposition of the immature cervix during adolescence that may be more susceptible to persistent HPV infections and therefore have a greater risk of cancer development (Louie et al., 2009).

Male factors are correlated with the risk for cervical cancer. The sexual transmission of HPV both women and men are acceptable as a risk factor for cervical cancer. Cervical cancer patient often report a history of having a male partner who has multiple other female partners. Furthermore, study of HPV DNA detection observed that in couples which was detected HPV DNA in husband's penis associated with cervical cancer risk in their wives (Bosch et al., 1996). Thus, several investigators have been suggested that sexual behaviors of male partners have influence to increased risk of cervical cancer (Bosch et al., 1996; Verhoeven et al., 2006).

4.2.4 Genetic polymorphism

Genes are the basic units of heredity that code for and transfer traits from cell to cell and from parents to children. Alteration of gene is called a gene mutation which can affect the structure of the gene and stop it from working properly and lead to carcinogenesis. Single nucleotide polymorphism, one type of gene mutation is a DNA sequence variation occurring commonly within a population.

Many investigators have been reported about single nucleotide polymorphism such as *MDR1* polymorphism that might influence cervical cancer development (Calhoun et al., 2002; Wang et al., 2013).

5. *MDR1* gene polymorphism

The *MDR1* gene is located on chromosomal region 7q21.1 which consists of 28 exons in a 600 kilobases (kb) and ranging in size from 49 to 587 base pairs (bp) (Fung and Gottesman, 2009; Li et al., 2006; Sakaeda, 2005). *MDR1* gene is a highly polymorphic gene, which has been reported at least 100 SNPs and 3 insertion/deletion polymorphisms (Hu et al., 2013; Marzolini et al., 2004). Many of these SNPs are silent type mutation (synonymous); do not change amino acid sequence. The most three common SNPs including C1236T, G2667T/A and C3435T SNPs were studies in various diseases such as respiratory disease, epilepsy as well as several types of cancer (Johnatty et al., 2013; Milojkovic et al., 2014; Seven et al., 2014; Yue et al., 2013). The *MDR1* gene encodes a polypeptide with 1280 amino acids which has 170 kDa of molecular weight, a member of ATP-binding cassette (ABC) transporter superfamily and also known as P-glycoprotein (P-gp) (Li et al., 2006; Milojkovic et al., 2014). Several studies have been reported that polymorphisms of *MDR1* gene have effect on P-gp expression and function (Milojkovic et al., 2014; Seven et al., 2014; Siegsmund, 2002).

P-gp was first identified in cancer cell which is a protein responsible for resistance to multiple cytotoxic anticancer agents (Seven et al., 2014). This protein is a phosphorylated and glycosylated transmembrane protein consisting of two halves, each containing six putative hydrophobic transmembrane domains and an intracellular ATP-binding domain (Sakaeda, 2005). ATP hydrolysis supply the energy for active drug transport which capacitates the transporter to function against concentration gradients (Figure 7) (Marzolini et al., 2004). P-gp is not found only cancer cells, but also found in many normal tissues of human with excretory functions such as in the liver, intestine, kidney and blood-brain barrier (Figure 8) (Fromm, 2002; Marzolini et al., 2004).

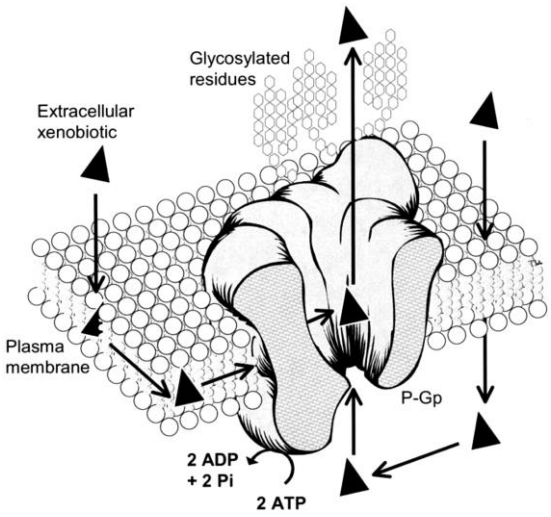

Figure 7 P-glycoprotein function (Marzolini et al., 2004)

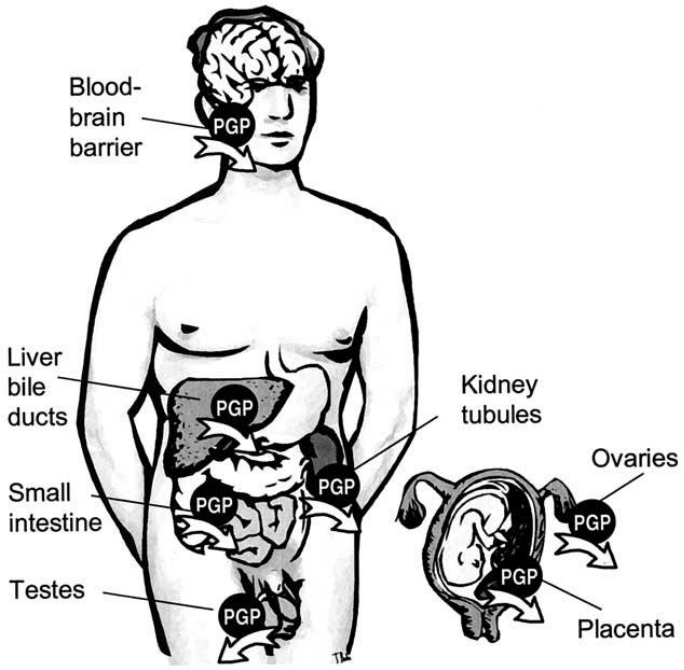

Figure 8 P-glycoprotein tissue distribution (Marzolini et al., 2004)

The physiological role of P-gp is an ATP-dependent efflux transporter that protects and reduces intracellular accumulation of wide range of xenobiotic and potentially toxic substances (Brinkmann, 2002). Furthermore, P-gp is also preventing the entry of substrates into the central nervous system as a part of blood-brain barrier.

The physiological function and distribution of this transporter illustrate that P-gp acts as a protective barrier to remove toxins out of the body by extruding these toxins into bile, urine and intestinal lumen. Therefore, P-gp is an important transporter to prevent accumulation of toxins in critical organs, brain, gonad, bone marrow and fetus (Marzolini et al., 2004). In addition, P-gp plays an important role in the development of multidrug resistance of tumor cells against various anticancer agents (Samanian et al., 2011). The substrate of P-gp has a broad specificity. It is usually hydrophobic and amphipathic (Aller et al., 2009; Fromm, 2002). The lipophilicity and amount of hydrogen bonds have been related with affinity of substrates for P-gp. Various drugs that used in cancer chemotherapy, hypertension, allergy, infection, immunosuppression, neurology, and inflammation are usually substrate of P-gp. Numerous studies have been shown that many drug substrates of P-gp are also substrates of drug-metabolizing enzymes, particularly, cytochrome P450 (CYP) 3A4 (Marzolini et al., 2004). Thus, P-gp may have effect on the treatment of many diseases such as cancer and acquired immunodeficiency syndrome (AIDS) (Bellusci et al., 2013; Taheri et al., 2010).

Numerous studies have been found that some SNPs of the *MDR1* gene are related with P-gp expression and function in different populations and ethnicities. Expression of P-gp with high level may lead to reduction of intracellular drug concentration due to activity of P-gp to pump various drugs out of the cell. In contrast, low level expression of P-gp may increase intracellular accumulation of drugs. Therefore, expression and activity level of P-gp may determine tissue distribution of drugs (Li et al., 2006). For example, in the study of C3435T SNP found that subject with TT genotype has lower intestinal P-gp expression with two-fold than subjects who have CC genotype, leading to higher steady state plasma concentrations after administration of drug such as digoxin (Kurata et al., 2002). Moreover, low level of P-gp expression and activity may influence the accumulation of potentially toxics in normal tissues which may leads to diseases development, respiratory disease and many types of cancer (Li et al., 2006; Milojkovic et al., 2014; Rubis et al., 2012).

Mutation of gene encodes transmembrane protein pumps that excrete several substrates out of the cell leads to significantly increase accumulation of intracellular

toxics and mutagenic substances. Most three common SNPs included C1236T, G2677T/A and C3435T in exon 12, 21 and 26, respectively (Figure 9). They have been studied repeatedly in different populations and various disease conditions and also associated with altered P-gp which leading to increased risk for development of cancer (Hu et al., 2013; Yue et al., 2013). However, in the cases of cancer treatment, the cancer cells usually have increased P-gp activity may result in poorly respond to chemotherapy (Rubis et al., 2012).

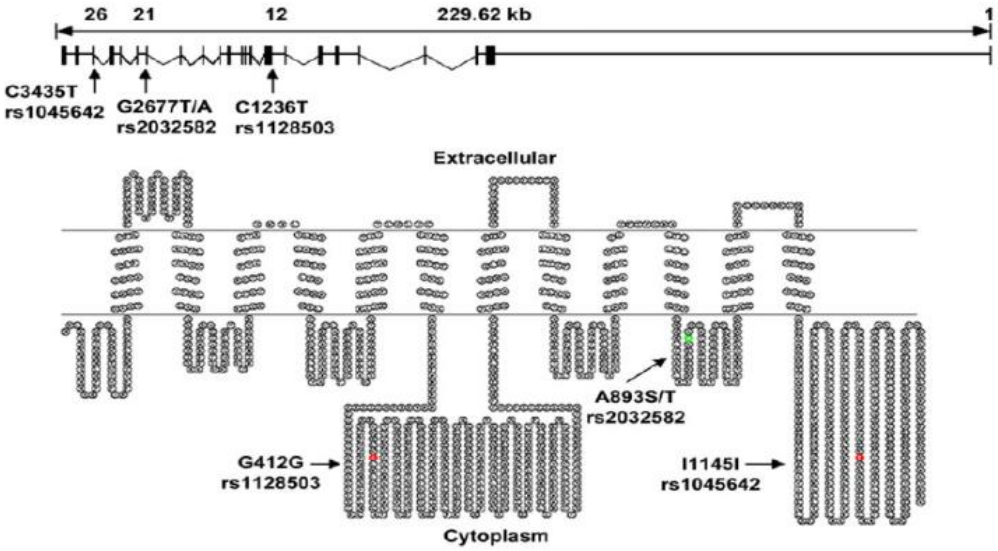

Figure 9 Genomic structure and protein structure of *MDR1* (Wang and Sadee, 2006)

Polymorphism at position C1236T in exon 12 is the one of most common SNPs that has been studied intensively over the last few years. C1236T SNP is a silent type mutation, amino acid exchange from cytosine to thymine (Gly412Gly) but does not produce altered coding sequences and also known as synonymous polymorphism. This SNP is divided into 3 genotypes: CC genotype (cytosine/cytosine, wild type), CT genotype (cytosine/thymine, heterozygous type) and TT genotype (thymine/ thymine, mutant type) (Vaclavikova et al., 2008). C1236T SNP provided changes in both protein expression and function of MDR1 (Fung and Gottesman, 2009). Several investigations revealed a significantly association between C1236T SNP and risk for cancer development. The T allele of C1236T was shown increased risk of breast

cancer (Alsaif et al., 2013) and also found that heterozygous individuals had significantly lower *MDR1* mRNA expression levels than those with a homozygous wide type about three-fold (Vaclavikova et al., 2008). However in the breast cancer treatment, individuals with CT C1236T genotype have been shown to be associated with poor response to anthracycline (Chaturvedi et al., 2013). Therefore, genetic differences in transporters of drug may contribute to the inter-individual variations in treatment outcome. In addition, *MDR1* polymorphism has also been found to be associated with response to chemotherapy (Chaturvedi et al., 2013).

G2677T/A is a triallelic SNP in exon 21, which divided into 6 genotypes including GG genotype (guanine/guanine, wide type), GT genotype (guanine/ thymine, heterozygous type), GA genotype (guanine/adenine, heterozygous type), TA genotype (thymine/adenine, mutant type), TT genotype (thymine/ thymine, mutant type) and AA genotype (adenine/adenine, mutant type). This SNP is a nonsynonymous SNP, amino acid exchanges from Ala to Ser or Thr (Ala893Ser/Thr). Polymorphism in this SNP has been found to be associated with altered P-gp and has also been linked to the risk of cancer development as well as the inter-individuals difference of response to several drugs (Yue et al., 2013). The presence of T allele results in increased efflux function of P-pg in the European Americans and African Americans population (Kim et al., 2001). However, in the study of P-gp expression in colorectal cancer patients found that GG genotype has highest expression of P-gp while lowest level P-gp expression was observed in AT genotype (Samanian et al., 2011). Nevertheless, study of colorectal cancer in Chinese population was not found association between G2677T/A SNP and colorectal cancer risk (Yue et al., 2013). Moreover, in other studies were also not revealed correlation between this SNP and risk for various diseases such as diffuse large B-cell lymphoma (DLBCL), inflammatory bowel disease and colorectal cancer (Hu et al., 2013; Sapmaz et al., 2008; Yue et al., 2013).

C3435T SNP on exon 26 is a silent mutation encoding the amino acid isoleucine (Ile). This SNP is provided 3 genotypes; CC genotype (cytosine/cytosine, wild type), CT genotype (cytosine/thymine, heterozygous type) and TT genotype (thymine/thymine, mutant type). C3435T SNP is one of the most popular *MDR1* polymorphisms, which affects the expression and functions of P-gp both *in vitro* and

in vivo and involves in the risk of developing cancer (Taheri et al., 2010; Wang et al., 2013). Many studies had shown association between C3435T SNP and cancer risk. A significantly association of T allele was found in various type of cancers; endometrial cancer, lymphoblastic leukemia and colon cancer (Kurzawski et al., 2005; Wang et al., 2013). In the study of colorectal cancer, however, was found association between C allele and colorectal cancer susceptibility (Andersen et al., 2009). Moreover, some studies have failed to observe an association between C3435T SNP and cancer susceptibility such as breast cancer (Rubis et al., 2012).

As described earlier, each SNP, C1236T, G2677T/A and C3435T SNPs have an influence on either various diseases risk or diseases progression. A strongly association of these three SNPs was also reported in some type of cancers (Hu et al., 2013; Sohn et al., 2006). Therefore, *MDR1* polymorphism (C1236T, G2677T and C3435T SNPs) may influence on cervical cancer risk in Thai women.