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# MUSCARINIC RECEPTORS

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## Introduction

Muscarinic receptors (MRs) are G-protein coupled acetylcholine receptors. Acetylcholine is a neurotransmitter involved in parasympathetic nervous system. These special receptors are located in peripheral nervous system ganglions as well as in several organs such as hearth, smooth muscle, brain, and exocrine glands. MRs are also a member of metabotropic receptor class which utilizes G proteins for signal mechanism (Novik et al., 2005; Pluchino & Martino, 2005; Uccelli, Laroni, & Freedman, 2011).

The characterization of MRs in several cell and tissue types is crucial in development of selective drugs. MRs reside in; neurons of both central and peripheral nervous systems, hearth that is under control of autonomic nervous system, respiratory track, gastrointestinal system, urinary track, and ocular and exocrine system glands and mediates several regulations comprising important basic physiological processes (Papadaki et al., 2005).

## Characteristics and classification of MRs

The classification of MRs is based on their structures and aminoacid sequences. MRs are designated with lower case "m" letter in molecular classification and with upper case "M" in pharmacological classification. So far 4 muscarinic acetylcholine receptor subtypes have been detected *in vivo* ($M_1$-$M_4$). Besides 5 muscarinic receptor subtypes have been defined in cloned genes ($M_1$-$M_5$). These receptors and their bodily locations were represented in Figure 1. In general, while $M_1$, $M_3$, and $M_5$ receptors activate multiple signal effectors including phospholipases C, $A_2$, and D, it was shown in several studies that $M_2$ and $M_4$ increases the levels of phospholipases $A_2$, by inhibiting adenylyl cyclase enzyme (Goyal, 1989; Nathanson, 2008).

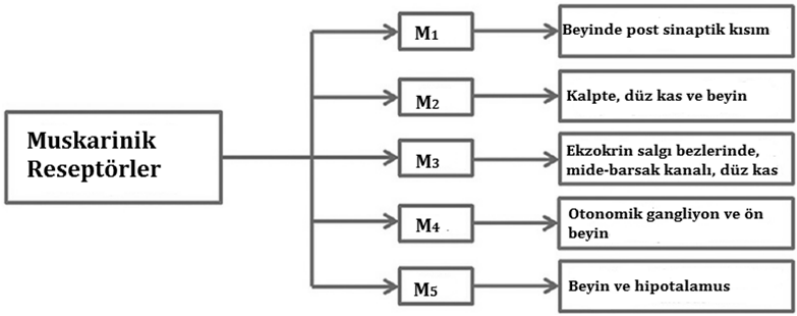


**Figure 1.** MR subtypes and their locations in the body.

## Structure of muscarinic receptors

MRs are members of G-protein coupled receptor family, and are 7-pass transmembrane glycoproteins with single subunit and a size of 50-70 kDa. The stimulation of membrane-bound effector proteins of MRs occur via G proteins. α subunit of MRs is responsible for binding of GTP and the

interaction with other receptors and macromolecules. MRs comprise 2 binding sites. One of them is the ligand binding site on the extracellular site of the cell membrane and the other is G-protein binding site on the cytoplasmic site of the cell membrane. The amino group and carboxyl group tails of MRs locate in extracellular matrix and cytoplasm respectively. When MRs pass through cell membrane, they form 6 loops of which 3 are intracellular ($i_1$-$i_3$) and 3 are extracellular ($e_1$-$e_3$) (Cabadak, 2006; Caulfield & Birdsall, 1998; Felder, 1995).

## Molecular events taking place after MR action

The induction of muscarinic receptors by acetylcholine leads to the activation of Gq protein. In general, although $M_2$ and $M_4$ receptors and $M_1$, $M_3$, and $M_5$ receptors have similar aminoacid sequences, they are divided into 2 groups regarding their receptor signaling pathways. $M_1$, $M_3$, and $M_5$ receptors initially activate phospholipase C (PLC) by recruiting Gq protein family which is insensitive to the pertussis toxin. On the other hand, $M_2$ and $M_4$ receptors inhibit adenylyl cyclase enzyme by using Gi and Go protein families (Figure 2) (Cabadak, 2006; Felder, 1995; van Zwieten & Doods, 1995).

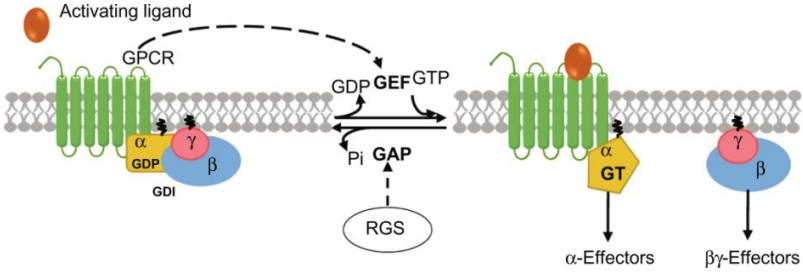


**Figure 2.** G-protein coupled receptor activation and initiation of intracellular pathways (Senarath et al., 2018).

Heterotrimeric G proteins (Guanine nucleotide binding proteins), residing on the intracellular surface of the cell membrane, are the members of large GTPase super family which also includes small monomeric GTP binding proteins. G proteins, consisting of α, β, and γ subunits, mediate signal transduction through several effectors such as enzyme and ion channels by binding to more than one thousand cell surface receptors (Wess, 1996).

The stimulation of muscarinic acetylcholine receptors causes the hydrolysis of phosphatidylinositol phosphates, suppression of adenylyl and guanylyl cyclases, and the regulation of calcium-dependent potassium and chlorine channels together with voltage-dependent calcium channels. First of all, α-subunit of G protein activates effector phospholipase-C which then produces inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) 14 by catalyzing phosphatidylinositol 4,5-bisphosphate. IP3 increases calcium secretion from calcium deposits which augments cytoplasmic calcium

concentration. DAG increases calcium- and phospholipid-dependent protein kinase activity. The following responses are triggered by the direct effects of calcium on calcium-regulated proteins and by calcium-calmodulin and protein kinase C mediated phosphorylation. Moreover, during muscarinic receptor activation, phospholipase D, which hydrolyses phosphatidylcholine, is also activated as a result of secondary activation of protein kinase C which supports secondary increase of DAG (Figure 3). At the same time, increased levels of intracellular calcium concentration bring about the stimulation of several molecular reactions such as (Caulfield & Birdsall, 1998; Felder, 1995);

1- Activation of calmodulin-dependent protein kinases,
2- Activation of calmodulin-dependent adenylyl cyclases,
3- Activation of calmodulin-dependent phosphodiesterases,
4- Activation of nitric oxide synthase.

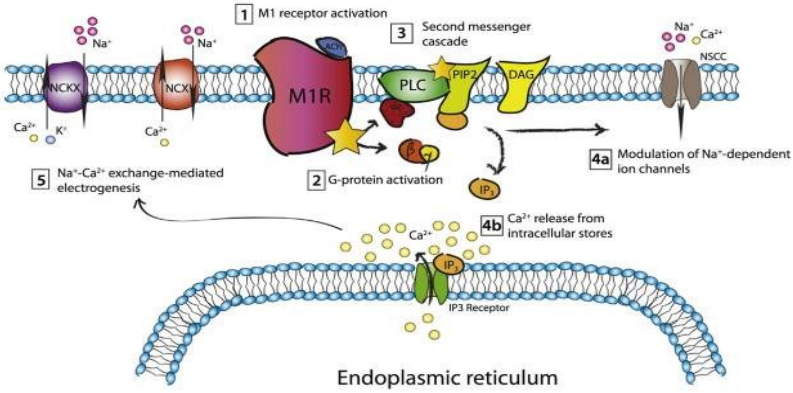


**Figure 3.** Action mechanism of muscarinic receptors (Proulx, Suri, Heximer, Vaidya, & Lambe, 2014).

## Functions of muscarinic receptors

Muscarinic receptors take action in regulation of many physiological processes such as control of heart beat rate and muscle contraction level, constriction of pulmonary air track, contraction of smooth muscle, and regulation of controlling motor and sensory perceptions. Apart from this, it was demonstrated in several pharmacologic studies that MRs are also functional in more complex processes like memory. Besides, it was considered that MRs play role in some of the neurological disorders such as Alzheimer's disease, down syndrome, and Parkinson's disease. It was also shown that MRs had role in the induction of REM sleep during which acetylcholine secretion increases by cholinergic nerves in brainstem and the treatment with muscarinic receptor antagonists resulted in reduction of REM sleep. MRs have also crucial involvement in the regulation of the function of

basal ganglia. Moreover, it was reported in many studies that MRs have effects on other pathologic conditions including central nervous system-mediated hypotension, bradycardia, epilepsy progression, and alcoholic behavior. Basically, neuronal cells express the MRs in central and peripheral nervous systems. More specifically, MRs present in some axon terminal and dendrites and somas of cholinergic and non-cholinergic neurons ("Cardiac Hypertrophy Cell Biology," 2012; Goktas, 2011; Wettschureck & Offermanns, 2005).

## MR subtypes

### 1. $M_1$ receptor

$M_1$ receptor is a 460 aminoacid-long protein in human which mediates the stimulation of phospholipase C and is considered to have a role in learning and memory. The $M_1$ receptor is encoded by *CHRM1* gene. $M_1$ receptor is present in central and autonomous nervous system, especially in autonomous ganglion cells of telencephalon and in exocrine tissues. $M_1$ is the only muscarinic receptor involved in the mediation of MAP kinase activation induced by acetylcholine in central nervous system. MAP kinase activation via acetylcholine, which quite often takes place in central nervous system and exocrine glands, is an important step in memory. $M_1$ receptor has an intermediate role for slow inducing post-synaptic potential in postganglionic nerves. Besides, it was assessed in several studies that $M_1$ receptor structurally resembles to $GABA_A$ receptors that regulate GABA secretion. There is a binding region for benzodiazepine receptors on the α-subunit of $GABA_A$ receptor complex. Some of the antagonists of $M_1$ receptor are atropine, scopolamine, dicycloverine, tolterodine, oxybutynin, ipratropium, and telenzepine (Hulme, Birdsall, & Buckley, 1990; Patrik Maďa, 2014; Pepitoni, Wood, & Buckley, 1997).

### 2. $M_2$ receptor

$M_2$ receptor is a 466 aminoacid-long protein in human which is encoded by *CHRM2* gene. While $M_2$ receptor is mostly expressed in heart and cerebellum in the first place, it is also present in central nervous system and on the terminals of autonomous nerves. While $M_2$ receptor inhibits adenylyl cyclase in smooth muscles, it activates potassium channels via acetylcholine $G_{i/o}$ proteins in order to hyperpolarize heart muscle and thus contributes to decrease in heart beat rate. $M_2$ receptor inhibits the secretion of acetylcholine from cholinergic neurons in lung. In parasympathetic neurons of respiratory track, while $M_2$ receptor expression decreases due to viral infection and interferon γ treatment, the secretion of acetylcholine increases. On the other hand, dexamethasone increases the expression of $M_2$ receptor but decreases the secretion of acetylcholine. Some of the antagonists of $M_2$ receptor are atropine, scopolamine, dicycloverine, tolterodine, oxybutynin, ipratropium, metoctramine, tripitamine, and gallamine (Wess, 1996; Zhou, Fryer, & Jacoby, 2001).

### 3. $M_3$ receptor

Human muscarinic $M_3$ receptor consists of 590 aminoacids and is encoded by *CHRM3* gene. This receptor type is located in various parts of the body. Especially it is highly expressed in exocrine glands and smooth muscles. $M_3$ receptor provides contraction of smooth muscles in blood vessels and lungs. Besides, it is functional in brain, eye sphincher muscles, lungs, smooth muscle of bladder, stomach, and intestines. PLC causes the formation of IP3/DAG by means of Gq/11 protein family. Thereafter, while IP3 leads to Ca+2 secretion and DAG activates protein kinase signaling pathway. $M_3$ receptor also has a pivotal role in saliva secretion as well as the regulation of food uptake. The lack of $M_3$ receptor causes less food uptake and therefore loss of body weight and eventually peripheral fat deposition appears. Some of the antagonists of $M_3$ receptor are atropine, scopolamine, dicycloverine, tolterodine, oxybutynin, ipratropium, tiotropium, and darifenacin (Matsui et al., 2004; Wess, 1996).

### 4. $M_4$ receptor

$M_3$ receptor is 479 aminoacid-long in human and encoded by $CHRM_4$ gene. $M_3$ receptor is mostly present in central nervous system. It plays role in the regulation of central dopaminergic responses and the contraction of smooth muscles. The activation of these receptors results in reduction of these muscles' movement. Some of the antagonists of $M_4$ receptor are atropine, scopolamine, dicycloverine, tolterodine, oxybutynin, and ipratropium (Eglen, Hegde, & Watson, 1996; Wess, 1996).

### 5. $M_5$ receptor

M5 receptor consists of 532 aminoacids in human and mouse and is encoded by $CHRM_5$ gene. It is highly expressed in cerebral cortex of the brain. Besides, it is considered that $M_5$ receptor has a role in the contraction of gastrointestinal smooth muscle. Some of the antagonists of $M_5$ receptor are atropine, scopolamine, dicycloverine, tolterodine, oxybutynin, and ipratropium (Bonner, 1989; Wess, 1996).

### Non-specific blocker of muscarinic receptors: Atropine

Atropine is an alkaloid with parasympatholytic activity which is extracted from a plant called *Atropa belladonna*. Its chemical formula is $C_{17}H_{23}NO_3$ (Figure 4). The primary function of atropine is inhibiting the muscarinic action of acetylcholine. Tertiary amine group of atropine is a drug that can pass through the lipid barrier and thus it functions by passing over the blood-brain barrier and placenta. Cardiac vagolytic effect of atropine is more than the other anticholinergic drugs (scopolamine, glycopyrrolate) used in premedication. As mentioned above, muscarinic receptors, which are located in effector organs, postsynaptic ganglia, cholinergic and adrenergic nerve terminals, have 5 subtypes. And atropine equally affects all muscarinic

receptor subtypes except $M_5$ (Kayaalp, 1996; "Premedikasyon ilaclari," 2010).

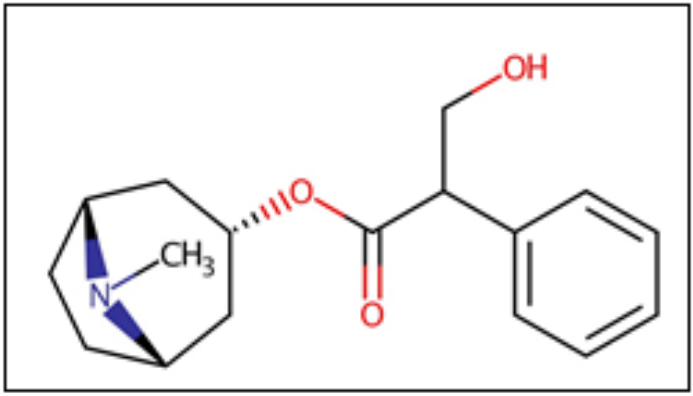


**Figure 4.** The chemical structure of atropine ("Atropine," 2019).

Atropine is taken parenteral or orally. When taken orally, it is fully and fast absorbed from stomach-intestine channel. Atropine, of which effects start within an hour and continues till 3-4 hours, broadly disperses in the body upon uptake. It can pass over the blood-brain barrier and placenta. In liver atropine is metabolized to tropic acid and other metabolites. The constant part and metabolites of atropine are removed from primarily kidneys via urination and slightly via respiratory air and feces. Atropine is taken especially to attenuate secretion during oral operations. Atropine advised to be used combined with opioids. Atropine has inhibitory effects on bradycardia and bronchial spasm triggered by opioids. Additionally, atropine is used in combination with neostigmine in order to antagonize the non-depolarizing muscle relaxants. In case of low blood pressure during acute myocardial infarction, atropine can be administered in order to increase heart rhythm and blood pressure. Last but not the least atropine can be used to reduce frequent urination together with cystitis and also for palliative treatment against Parkinson's disease ("Atropine," 2019; Brunton, Lazo, Parker, & Felitti, 2014).

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# MITOCHONDRIAL MIRNAS (MITOMIRS) IN BREAST CANCER

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## Breast Cancer

Breast cancer is the most common cancer among women worlwide. It takes the second line after lung cancer. The prevalance is 1/100 compared to men. 5% of breast cancer is related to genetic susceptibility and inheritance pattern is autosomal dominant. BRCA1 and BRCA2 mutations were found to be highly related with breast/over cancer. Women with these mutations have a significantly increased lifetime risk of invasive breast (65-85%) and ovarian cancer (15–65%) (Chattarjee et al., 2006; Plak et al., 2009). Except from BRCA1 and BRCA2 genes TP53, PTEN, CHEK2, ATM, XPD and HER-2 genes were also found to be related with Breast cancer prognosis (Aral and Özer., 2007; Modica-Napolitano et al., 2007).

## Mitochondrial Genome and its Role in Breast Cancer

Mitochondria is a very dinamic organel and besides the ATP production it plays important roles on regulating several physiological events including apoptosis, disease and aging. Although mitochondrial function is essential for cell life and death, deregulation of mitochondrial methabolism is critical for pathogenesis of several diseases (Kushnareva and Newmeyer, 2010; Bienervota-Vasku et al., 2013). Mammalian cells includes >1000 mitochondria and almost 10000 copies of mitochondrial DNA (mtDNA). Human mitochondrial DNA is circular and double stranded with the size of 16,6kb and does not cointain intronic regions. It encodes 37 genes coding of 2 rRNA, 22 tRNA and 13 polypeptides (Figure 1). Although mitochondrial genome encodes 13 polypeptides almost 1500 protein is synthesised. Due to the limited capacity of mtDNA it needs nuclear genes in order to its biological functions and structural components. Replication and transcription start in D-loop region. Mitochondrial proteins are synthesized as precursor forms in the cytosol and imported into mitochondria with the help of different protein translocases (Bertram, 2000; Sripada et al., 2012; Bienervota-Vasku et al., 2013). Mitochondria-targeted proteins that encoded by nuclear genome are transported with the help of several accessory proteins via TOM/TIM complex proteins including presequence carrying proteins, β-barrel preteins, etc (Mesecke et al., 2005; Dudek et al., 2013). Transcription, translation and transkript processing are regulated by mitochondria genome or nuclear encoded non-coding RNAs (Tomasetti et al., 2014). Mitochondrial RNAs are transcribed as long polycistronic precursor transcripts from both strands and then processed according to the 'tRNA punctuation model' in order to release individual rRNAs and mRNAs (Mercer et al., 2011). Our knowledge is limited about the features of mitochondrial transcriptome especially about the RNA processing and modification sites, harbouring non-coding RNAs or the regulation of transcipt abundance. Likewise the related mechanisms have not been enlightened yet, RNA transport is quite important.

Through its location around the ROS production region mitochondria is rendered to be unprotected across the oxidative damage and there comes the increased mtDNA mutation ratio causing cancer too often (Li et al., 2012). Warburg in 1930s suggested that cancer occurs as a result of malfunctions in

oxidative fosforilation or mitochondria and there is a significant difference in the glycolysis ratio between normal and cancer cells. Those findings is also known as "Warburg Effect". According to Warburg hyphothesis cancer, malignant development and tumor development come true with the energy formation by glycolysis in tumor cells. Unlike to tumor cells, normal cells provide these energy by oxidative degredation of pyruvate. Pyruvat is the last product of glycolysis and oxidates in mitochondria. Therefore according to Warburg cancer cell formation is a result of decrease in mitochondrial respiration (Jemal et al., 2007). Oxidative phosphorilation activity in cancer cells work as a biomarker on detecting tumor grades, prognosis and planning of theuropatic strategies. For example after revealing the mutations in ND6 gene regulate tumor cell metastasis it gives rise that similar mutations could occur and could be use as prognostic markers in breast cancer.

Mitochondrial genome is also scanned in the sense of spesific mutations and it is reported that D-loop mutations at nucleotide position 204, 207 and 16293 may be an independent prognostic marker in breast cancer (Tan et al.,2002). mtDNA compared to nuclear genome has 6-17 fold more mutation ratio. Thus mutations are permanent due to low mtDNA polymerase activity and absence of DNA repair mechanisms (Imanishi et al., 2011). mtDNA mutations are idendified almost in every cancer. Especially mutations in D-loop region were shown to be hot-spot. D-loop region is the non-coding region of mtDNA and it harbours cis-regulator elements essential for replication and transcription. Therefore, it could be imagined that mtDNA mutations in this region could affect gene expression and copy number (Sripada, 2012). Somatic mutations in D loop region were found in breast, gastric, hepatocellular, over, colorectal carsinomas and melanoma. In addition to those, deletions, point mutations, insertions and duplications were also detected in some cancers including breast, over, tyroid, lung etc (Sripada et al., 2012; Michel et al., 2012).

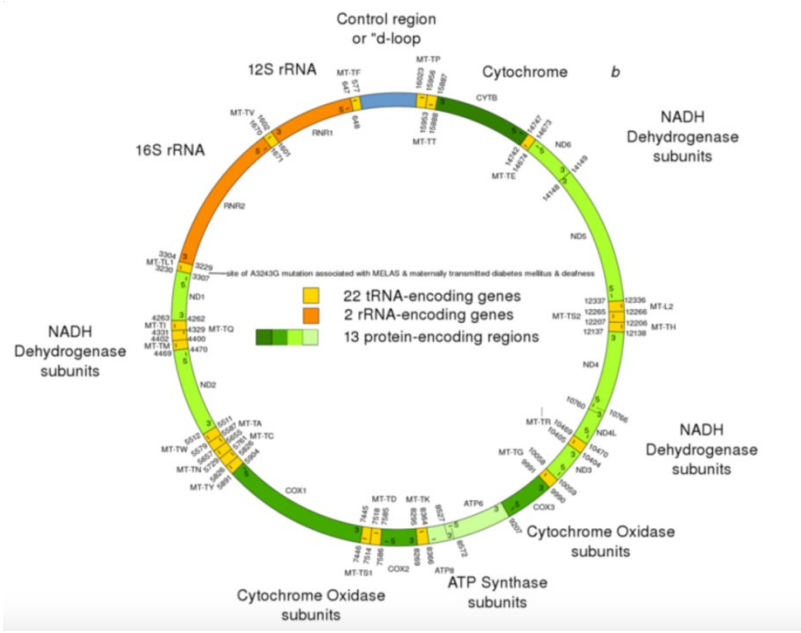


**Figure 1.** Mitochondrial Genes (web_1)

## MicroRNA Biogenesis and Their Roles in Gene Expression

Non-coding RNAs (ncRNA) have roles on several processes such as catalysation of biological reactions, cellular defense, cell response etc. In addition they play effective roles on gene silencing (transcriptional, post-transcriptional) and chromosome remodelling. Small non-coding RNAs (miRNA, piRNA, tiRNA) generates the most of the ncRNAs and these ncRNAs are the molecules responsible for gene silencing via RNA interference mechanism (Akkaya and Dinçer, 2013). Their mechanism of action in cytoplasm was executed with several studies but they are started to be discovered in different cell compartments as mitochondria, endoplasmic reticulum and nucleus (Figure 2).

miRNAs are encoded by the non-coding regions of DNA by RNA polymerase II and/or as 100-1000 nt length pri-miRNA (Lee et al., 2002; Borchert et al., 2006). pri-miRNA then sequentially processed by the Drosha/Pasha to produce 70 nt pre-miRNAs that contains 5' phosphate and 2 nt overhang at 3' end (Denli et al., 2004; Gregory et al., 2004). 2 nt overhang of pre-miRNA is recognized by Exportin 5 and exported to cytoplasm where they bind to the ribonuclease Dicer (Yi et al., 2003; Lund et al., 2004) in order to form approximately 20 nt long miRNA/miRNA* duplex. Double helix miRNA Dicer then binds to miRISC complex which consists of Argounate,

RNA binding proteins TRBP and PACT (Bernstein et al., 2001; Martinez et al., 2002; Kok et al., 2007). While miRNA duplex unwinds to produce mature miRNAs (Nykanen, 2001), its complementary sequence is degraded by miRISC complex (Matranga et al., 2005; Leuschener et al., 2006). Mature miRNA binds to the complementary 3' UTR of the target mRNA. This miRNA/mRNA complex is recognized by argounate protein and 182 kDA glycine-tryptophan protein which play key roles on miRISC complex. This either results in inhibition of mRNA translation and degredation of target mRNA (Sripada et al., 2012).

miRNA expression studies reveal the importance and potential areas of usage of miRNAs with regards to disease taxonomy and improvement of prognostic tools in breast cancer. Cell cycle, proliferation and tumorigenesis are shown to be regulated by miRNAs and Increase on protein levels of cyclines, cycline dependent kinases (CDK) and CDK inhibitors that controls cell cycle and abnormal miRNA expressions are reported to be seen in breast cancer pathogenesis. miRNAs by regulating the mRNA expression play essential roles on controlling cancer cell methabolism. They target directly key molecules (transporter or enzymes/kinases) in cell methabolism and regulate several oncogenic signalling pathways. Besides, they can gain oncogenic or tumor suppressor features depending on the features of target mRNAs on molecular pathways such as regulating the expression levels of transcription factors, p53, c-Myc, AMPK and AKT signalling pathways (Chen et al., 2012).

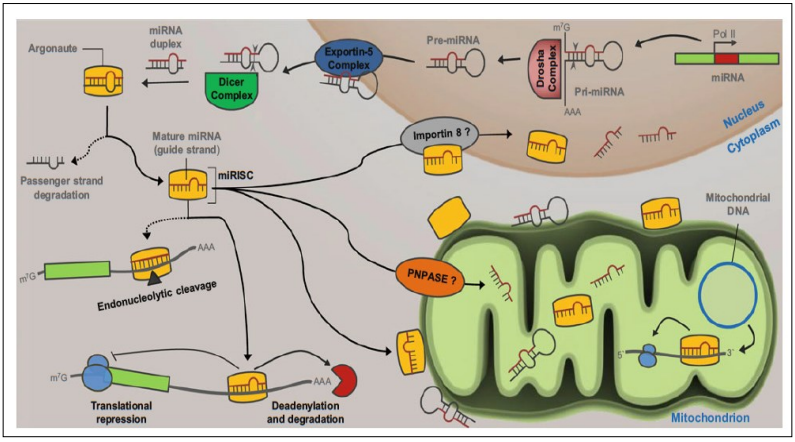


**Figure 2.** miRNA regulation in human cells (Borralho et al., 2015)

## Mitochondria as a Host For Non-Coding RNAs

Mitochondria hosts its own genome and plays important roles on the pathogenesis of cancer, methabolic diseases, neurodegenerative and cardiovascular diseases. mtDNA replication and transcription is regulated by coding/non-coding RNAs. Mitochondrial genome hosts almost 1500 protein

even encoding of 13 polypeptides. Therefore most of these proteins are synthesized in cytoplasm and transported into mitochondria. Controversially, several non-coding RNAs that functions in mitochondria are also encoded by nuclear DNA (Entelis et al., 2001). However it is known that variety of RNA types are in and out of mitochondria. For example, tRNAs, RNAse MRP, RNAse P and 5S rRNA which abundance in mitochondria are nuclear encoded and transported to mitochondria (Puranam and Attardi, 2001; Alfonzo and Soll, 2009). Mitochondria also horbours several miRNAs like miRNA,snRNA, piRNA,srpRNA and snoRNA within itself (Mercer et al., 2011; Sripada et al., 2012). Outher surface of mitochondria works as a platform for miRNA cohort and components. And also miRNA may translocate to mitochondrial matrix in order to regulate mitochondrial gene expression. Very few miRNA sequences can make a complementary with mitochondrial DNA sequences. pre-miRNA and mature miRNA can be directed to several subcellular localizations as mitochondria. Ago2/3 which is a core component of pre-miRNA, mature miRNA and RISC complex is related to mitochondria (Walsh et al., 2006; Debniak et al., 2006; Imanishi et al., 2011). Even though mitochondrial miRNA biogenesis has enlightened yet there are several hypothesis. There are supposed to be 3 ways for the mechanism of action. First; nuclear encoded miRNA targets nuclear encoded proteins and inhibits mRNA translation in cytoplasm affecting the transportation of sprsific mitochondrial proteins to mitochondria, second; nuclear encoded miRNAs are transported to mitochondria and regulate translation of mitochondrial encoded proteins third; mitochondrial encoded miRNA regulates the translation of mitochondrial encoded proteins (Wang, 2015). Some pre-miRNA sequences are thought to be processed in mitochondria and might synthesize mature miRNAs (Imanishi et al., 2011).

First evidence that RNAi contents localize into mitochondria is the discovery of tRNAmet interacting with mitochondria (Dudek et al., 2013). Lately it is revealed that mitochondria has the potential for carrying unique intracellular nisch for RNAi mediated gene silencing after showing that Ago2 and Ago3 localize in mitochondria together (Bian et al., 2010; Bandiera et al., 2011; Sripada et al., 2012). Second clue is that systematic sequencing of small RNAs from rat liver mitochondrias ascertain to identify some miRNAs by coincidance. Latronico and Condorelli (2012) have found 15 nuclear encoded miRNAs in the mitochondria isolated from rat liver, 20 miRNAs from the Mouse liver mitochondria and 13 miRNAs from Hela cells by microaaray. Barrey et al. (2011) scanned for 742 miRNAs by qRT-PCR and have shown that 243 miRNAs have significant expression in the mitochondrial RNA samples isolated from human myotubes by in situ hybridization. This study becomes as the first clue for showing that pre-miRNAs could localize in mitochondria. Nonetheless, next generation sequencing methodologies provide the characterisation of small RNAs in mitochondria. Mercer et al. (2011) examined human mitochondrial transcriptome and have shown 3 miRNAs (miR-146a, miR-103 and miR-16) have quite high expression in intrermembranal region compared to matrix. Likewise, Sripada et al. (2012) questioned the relationship between small RNAs in the surface of

mitochondria and full scale small non-coding RNAs by deep sequencing. Up to now, several findings for showing the most of the mitochondrial proteins are nuclear encoded and transported to mitochondria post-transcriptionally remark the interesting relation between nucleus and mitochondria. Coene et al. (2005) have demonstrated the existance of BRCA1 proteins in nucleus, cytoplasm and mitochondria of human cells (Coene et al.,2005).

**Mitochondrial miRNAs (mitomiRs)**

Barrey et al. (2011) showed that mitochondrial miRNAs both target nuclear and mitochondrial genes by discovering a group of miRNAs that have different expression profiles in nucleus and mitochondria named as "MitomiR". miRNA expressions in mitochondria can vary depending on the type of tissue (Sripada et al.,2012; Wang et al., 2017). mitomiRs unlike to canonocal miRNAs have the size of 17-27 nt and have been thought to have different thermodinamic features (Bandiera et al., 2011). When compared to miRNAs in cytosol mitomiRs preferably do not target nuclear encoded mitochondrial genes. But RNA22, RegRNA, miRWalk or TargetScan algorithms could be used for prediction of multiple mtDNA targets of most miRNAs (Latronico and Condorelli, 2012).

Although the mechanism how mitomiRs are transported to mitochondria remains unclear it is thought to be some translocases could be related to mitochondrial protein transport. It was shown that mitomiRs can affect several pathways including TCA cycle, electron transport chain, intracellular ion hemostasis, oxidative stress, lipid methabolism, aminoacid methabolism (Das et al., 2017). Recently, miRNA characterization in the regulation of mitochondria in cancer cells is started to be investigated. It is shown that miR-23b and miR-210 affect the ROS production and shown to be expressed in breast and colorectal cancers (Duarte et al., 2014).

As functions of mitomiRs are unknown generally, there are very limited knowledge of their roles in cancer types including breast cancer. In view of the fact that the size of mitochondrial genome and limited numbers of mitochondrial encoded mRNA, it is seen to be very easy to identify the targets of mitomiRs. But it has to be taken in consideration that the expression paterns of mitomiRs might be tissue spesific. While Barrey et al. (yıl) were identifying mitomiRs in myoblasts they also discovered cardiac spesific mitomiRs in another study. Therefore, it is possible that some mitomiRs might be spesific for breast cancer and further studies are need to detect their roles.

In our study we evaluated mitomiRs in breast cancer cell lines by small RNA sequence. hsa-miR-6087-5p, hsa-miR-3960-3p, hsa-miR-7641-5p, hsa-miR-3648-3p, hsa-miR-4488-5p, hsa-miR-4485-5p, hsa-miR-4449-3p, hsa-miR-4484, let-7 family members, hsa-miR-1290-3p and hsa-miR-423-5p was found to be most relevant with mitochondria as well as miR-221-3p, miR-92a-3p, hsa-miR-1246-5p, hsa-miR-1275-5p, hsa-miR-663a-5p, miR-25-3p, miR-23a-3p, hsa-miR-423-5p, hsa-miR-320a-3p. hsa-miR-4461, hsa-miR-4484 and hsa-miR-4485 aligned to mitochondrial genome at positions

(10689–10711), (5747–5763) and (2539–2554) corresponding to ND4L, L-ORF and 16S rRNA genes respectively. Besides known miRNAs, novel miRNAs which are predicted to be encoded by mitochondrial genom were also identified (Tokgün and Tomatır, 2018).

Nuclear encoded tRNA and rRNAs are shown to be transported into mitochondria by the recent studies (Smirnov et al., 2011; Schneider et al., 2011). But how these small noncoding RNAs transport remains unclear. With the discovery of mitomiRs there is a issue about enlighting the underlying molecular mechanisms of the transportation. Several studies focused on a number of ways for the transport and reported that this transport could be ATP dependent. And molecular mechanisms of mitochondrial RNA transport may vary between species (Bandiera et al., 2013). Alongside the mature miRNAs, also pre-miRNAs are shown to be located in mitochondria thus increasing the possibility of mitochondrial miRNA biosynthesis (Sripada et al., 2012). It is thought that some pre-miRNA sequences could process in mitochondria and generate mature miRNAs that affects on mitochondrial transcripts or interact with genome-derived mRNAs. Therefore mitochondrial processed miRNAs might contribute to relevant gene expression of mitochondrial functions post-transcriptionally (Bienertova-Vasku et al., 2013).

The roles of miRNAs on mRNA degredation and translation are very clear. Existance of miRNAs in mitochondria make us think that they have roles on the regulation of mitochondrial genome encoded transcripts. Recently, it was shown that miR-181c was present in mitochondria and it is regulated differently in mitochondrial encoded transcripts of ventricular cardiac cells (Das et al., 2014). By the help of enlightening the mitochondrial transport mechanisms it might be executed to show the importance of miRNAs in the regulation of cellular hemostasis. More studies are needed for elucidating the affects of miRNAs that localize in mitochondria or relevant on human health, diseases and biological importance. This kind of studies will also become more of an issue in order to point clinical targets for theuropeutic treatment.

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# MALPRACTICE OF MIDWIFERY PRACTICES AND LEGAL DIMENCION

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## INTRODUCTION

Patient safety is one of the current and important issues discussed in the context of improving healthcare services. According to the National Patient Safety Foundation definition, "patient safety is defined as all of the measures taken by healthcare institutions and the professionals working in these institutions in order to prevent harm to the patient from the services provided in healthcare services" (1,2,3). Prevention from malpractice in ensuring the safety of the caregiver and in all stages of this implementation is among the primary task and objectives. (1).

Malpractice is the improper medical practices which are caused by an unintentional disruption at any stage of the healthcare service provided to the patient and which cause an unexpected result that affects the patient's life and health (2,4,5). In order to reduce malpractice, everyone in the healthcare service needs training on patient safety, malpractice, status notification systems and legal dimension (2,6).

Medical errors in the field of gynecology and obstetrics have the largest share in malpractice. Malpractice is an important issue for midwifery profession because midwives are directly involved in medical practices and their malpractice directly threatens the patient's life (6,7). Therefore, it is aimed in the article to examine the malpractice and its legal dimensions along with the medical errors in the midwifery profession and what can be done to prevent them.

## Malpractice

The Institute of Medicine defines malpractice as "using a faulty plan to accomplish a goal or intentionally ignore and perform a planned action" (8,9,10).

Malpractice results in the extension of hospital stay of the patient, increase in mortality and morbidity rate, psychological problems in patient and patient relatives, and consequently causes negative impact on caregiver professionals as well. Errors in the field of healthcare may occur at any stage of treatment and care (1). Many studies support the view that preventive interventions for malpractice are an effective policy in the short term to reduce healthcare costs (11).

In the report published by the National Institute of Medicine on malpractice; it has been emphasized the importance of making necessary arrangements in order to examine and prevent the misapplications of healthcare professionals and notifying if they are experienced (1,12,13). According to the US Institute of Medicine 1999 data, the incidence of death due to medical errors in inpatient clinics has been reported as 44,000-98,000 per year (10,13,14). Although the incidence of health errors in our country is not known exactly, it is believed to show parallelism with world countries (9).

A study conducted in 2004 to investigate the malpractice rates and causes in the field of gynecology and obstetrics in Turkey revealed that the errors made have the largest share with a 31% rate, and that the majority of these errors are caused by the staff's carelessness and it was concluded that 22,5 % of the errors are made by midwives and nurses (15).

In another study conducted between the years 1990 and 2000, it was found that of the errors made, %16.8 was in the field of gynecology and obstetrics and the %3.7 was in the field of pediatry.

In a study discussing the 371 malpractices related to nurses and midwives which were reported to the Higher Health Council (207), the Forensic Medicine Institute (125), the Istanbul Provincial Health Directorate (39) between 1992 and 2002, the number and rate of occupational branches referred to law were specified as nurse + physician (126, 34.0%), midwife (86, 23.2%), nurse (78, 21.0%), midwife + physician (57, 15.4%), midwife + nurse (11, 3.0%), midwife + physician + nurses (5, 1.3%), management + nurse + physician (7, 1.9%) (16). According to the Forensic Medicine Institute data, the highest number of files found to be defective was reported as gynecological and obstetric fields.

**Malpractice Classification**

- ✓ **Errors in Diagnosis**

Errors leading to late diagnosis, deficiencies in diagnostic tests, failure to use new tests, errors in the evaluation of results and tests.

- ✓ **Errors in Treatment**

Errors occurring during the surgical procedure, errors related to the calculation of the drug dose during the treatment or the way of administration, improper or inadequate healthcare, response to abnormal tests.

- ✓ **Prevention Errors**

Errors seen in preventive treatments and inadequate observation or follow-up of treatment.

- ✓ **Other errors**

Communication errors, errors related to insufficient hardware or equipment and other system deficiencies (1).

Errors associated with patient care stem more from the conditions such as failure in the application of care services, lack of records or incomplete registration, inadequate patient safety practices, careless behavior, lack of professional knowledge and experience, not behaving according to ethical rules, high number of patients per person, lack of communication, overwork and working with shift system, and heavy working conditions (9,17).

According to the studies conducted in this area, the most common types of errors can be listed as the drug errors, transfusion errors, errors related to patient follow-up, care and material reliability, falls, and communication errors (6, 17,18,19).

## Malpractice in Midwifery Practices and Prevention Interventions

Due to injuries occurring during labor, the number of lawsuits filed against the midwives is quite high. Among the lawsuits due to obstetric malpractice, vaginal delivery shoulder dystocia comes first. For this reason, the most common fetal complications are transient brachial plexus injury, clavicle and humerus injuries, permanent plexus injury, hypoxic ischemic encephalopathy and death (20).

Other complications during delivery in the newborn include soft tissue traumas; head traumas during intervened labor, peripheral nerve injuries, extremity fractures; genital area traumas in the breech birth, liver injury as a result of pressure on the liver, splenic rupture and kidney damage (20).

In the study performed by Yaman et al. in order to determine patient safety practices for the first care of newborn, it was concluded that midwives / nurses working in the delivery room performed different applications in the umbilical cord cutting time, navel care and intramuscular vitamin K injection applications during delivery (21).

As a result of 7237 malpractice allegations between 1986 and 2010, the rate of babies born with neurological disorder due to malpractice at birth was found to be 31.6%, brachial injury was 26% and fetal mortality rate was 22.2% (22).

In a study conducted in Iran, requests made to the Forensic Medicine Institute between 2011 and 2013 were examined, and gynecology and midwifery malpractice claims files were found as 1165. In regard to malpractice related to pregnancy and delivery; newborn death was found to be 43.3%, fetal death was 28.52% and maternal death was 28.16%. The maternal causes of death during pregnancy were stated as bleeding 40%, preeclampsia and eclampsia 20%, dangerous conditions leading to newborn deaths 14.63% and the reasons not stated 25.37% (23).

In the studies conducted by the Institute of Forensic Medicine in Turkey between 2001 and 2005, 525 death cases referred to malpractice were found. 15.4% of these cases are perinatal deaths and 7.3% are deaths between 8 days-12 months. It was stated that 7.2% of the malpractice claims in these cases were the result of faulty practices of the midwives (24).

In a study conducted on the analysis of medical malpractice cases related to birth in Japan, 64 possible cases of malpractice were examined and it was seen that 44 of the lawsuits were decided in favor of the complainants. The study covers almost all cases published in Japan in the last 10 years and opened for legal action (25).

The causes of malpractices by midwives include careless behavior, imprudence, negligence, misdiagnosis, wrong decision-making, lack of knowledge and skills, making unnecessary attempts, intervening beyond the limits of authority, and not keeping accurate records. Therefore, midwives

must be cautious, follow up-to-date information, be aware of their duties, authorities and responsibilities, work in cooperation with the physician in an emergency situation, avoid unnecessary intervention, and keep accurate and adequate records to prevent faulty practices (20).

There are four basic ethical principles that are international and are adopted in our country, which should be applied by healthcare personnel in providing care;

a. Non-damaging (Pirimum Nihil Nocere: First Do Not Damage).

b. Benefit (Pirimum Util Esse: Provide Benefit First).

c. Autonomy: Being Autonomous and Respecting for the Autonomy of the Patient.

d. Being Fair (26,27).

## Legal Aspect of Malpractice

The lawsuits related to medical errors and malpractice in Turkey are tried according to private law and criminal law. In the determination of the penal and legal obligations of healthcare professionals and the application of these penalties, it is referred to the Articles 55 and 459 of the Turkish Penal Code [T.C.K] and according to Article 4 of T.C.K. "It is not an excuse not to know the law and its obligation" (15).

Along with the continuous change in health technology, the current responsibilities of the professionals working in the field are also changing. Midwives in this group may be punished in case of delaying or not fulfilling their obligations in patient care practices (16).

In determining the negligence of healthcare professional in medical malpractice cases, the courts refer mainly to the High Health Council. In addition to criminal liability, healthcare personnel are also legally responsible for their negligent practices. The patient may also claim material and immaterial compensation based on unfair practice or contract (28).

## Result

Although malpractice cases in midwifery application field have increased in recent years, there are not many studies conducted on this subject. For this reason, researches should be made by midwife academicians in order to determine the causes of the mistakes made by midwives and the measures to be taken should be determined. Midwives in the field should follow the regulations, ethical principles and rules, malpracticed/ neglected initiatives should be recorded, and it should be ensured that their awareness about the subject is increased both by undergraduate / graduate education and post-graduation in-service trainings in order for them to be aware of the midwifery duties and responsibilities.

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