CHAPTER II

LITERATURE REVIEW

2.1 Cornea

Cornea is a part of eyeball which is transparent and located in front of pupil. Cornea is one of the refracting elements of the eyes and consists of five layers: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium.[18] Epithelium consists of stratified non-keratinised epithelial cells lies in outer part of cornea. Bowman's layer is composed of collagen fibrils but with smaller diameter compare to the stromal layer. Stroma is the biggest part of corneal thickness, consists of collagen fibers which keeps corneal transparency. Descemet's membrane is a basement for endothelial cells. Endothelium act as active bicarbonate pump to maintain the corneal hydration.

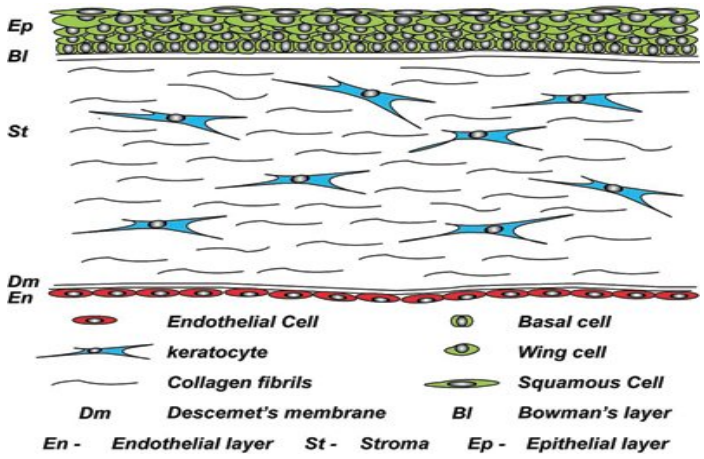

Figure 1. Corneal layers[18]
Five layers of corneal tissue are (from outer to inner): epithelium, Bowman's layer, stroma, Descemet's membrane, endothelium.

The curvature of cornea must be well coordinated with other refracting elements to get the optimal light focus in retina. The failure of this coordination will leads to a refractive error.

Investigation of the age-related changes of ocular parameters in 19-82 years old Korean people found that corneal curvatures are increased in accordance with age.[19] Singapore Malay Eye Study found that the average of corneal curvature is 7.65 mm and it is increased with greater age, greater height, and greater weight.[20] The average of corneal curvature radius in older white population was 7.70 mm in a study about association of age, stature and education with ocular dimensions. In this study, participants under 65 years old are having greater corneal curvature radius compare to participants over 75 years old.[21]

The result of a study about optical and biometric characteristics of emmetropic eyes was that male had 0.16 mm higher of anterior corneal curvature than female.[22] In Greater Beijing, the mean of flattest meridian refractive power is 43.16 ± 1.45D and the steepest meridian is 43.98 ± 1.52D. Steep cornea was found to be associated with high myopia and high cylindrical refractive error.[23]

Diurnal variation is found to have a role in corneal curvature. Cornea is thickest and flattest after people awake in the morning.[24] High myopia eyes had steeper central corneal curvature and a tendency for flattened cornea in periphery with increasing myopia.[25] Mean of corneal curvature in myopic patients in Thailand was 44.6 ± 13.8 D (ranging from 39.05-47.65).[26]

Corneal curvature was flatter and corneal thickness decreased as the eyeball elongates in myopia in Korean adults.[27] There was a correlation between cornea and myopia in a study in Greater Beijing. [23]

2.2 Myopia

Normal refraction of human eye is called emetropia. The abnormality of refraction is called ametropia. There are 3 types of ametropia i.e myopia, hyperopia, and presbiopia. Myopia is a condition where the shadow of object is fall in front of retina while the eye is not accommodate.[2]

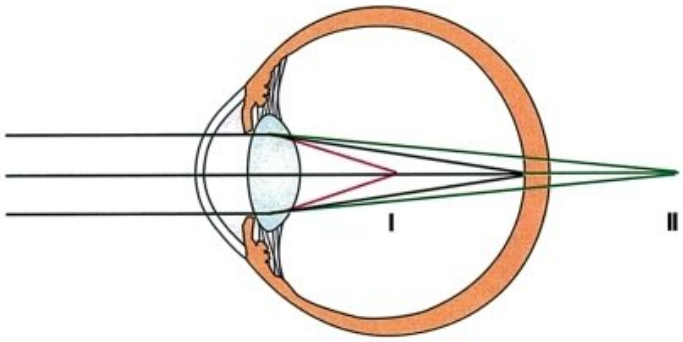

Figure 2. Myopic refractive error[28]
I is the focus point of myopic eye. II is the focus point of hyperopic eye.
In between is the focus point of emmetropic eye.

Myopia onset in a high school students in Palembang, South Sumatera was 70 out of 150 (46.7%) students and the onset was before 15 years old.[9]

2.2.1 Risk Factors in Myopia

Risk factors for myopia development are:

a. Genetic factors

There was an association between corneal curvature and *PDGFRA* gene and *FRAP1* gene in Singaporean population.[11] Area at 47 cM on chromosome 7p15 (*MYP17* gene) was significant for ocular refraction among African American people.[29] *MYP3* gene in chromosome 12, region q21.2-24.12 showed significant linkage at rs337663 in Duke, Asian, and Caucasian population, but rs163016 and rs1520724 were more relevant in Asian population.[30] *COL2A1* gene was associated with high-grade myopia in two independent Caucasian family but *COL1A1* gene polymorphisms was not associated with myopia.[31]

b. Parental history of myopia

Children with myopic parents are having high risk for myopia development.[32,33,34] Children who have both parents with myopia have greater risk for having higher degree of myopia than children who have only one myopic parent or even none.[35]

c. Near work

Reading, watching television, or using computer are categorized as near work. Myopic children were having more time studying and reading.[34] There was a positive association between myopia and the close distance while reading in Australian school children.[36] There was a correlation between myopia and shorter duration in watching television.[37] But, one study found that children with myopia was spent more time watching television compare to non-myopia children.[38] The odds ratio for children who read more than 2 hours per day to have higher myopia was 2.16.[39]

d. Reading in dim light

There was a correlation between myopia with reading in dim light in an investigation of risk factors for myopia in Greater Beijing school children.[37]

e. Outdoor activity

The lower the outdoor activities, the bigger chance for having myopia in children.[33,38,40,41] The odds ratio was 0.93 (p value <0.001) for children with less daily exercise to have myopia. But, when the data adjusted for some parameters, this result became unsignificant.[37] When rhesus monkey exposed to various type of light, the result suggests that natural outdoor light reduced the myopia.[42]

f. Sex

Female sex has higher risk for having myopia than male.[43,44] This gender risk factor in myopia maybe due to the hormonal effect. The experiment on porcine corneas showed oestrogen effect on corneal thickness and corneal biomechanics.[45] Level of estradiol (E2) was affecting spherical lens, cylindrical lens, axis, and interpupillary distance during menstrual cycle.[46]

g. Corneal curvature

Some studies found an association between corneal curvature and refractive anomaly. Myopic eye has steeper corneal curvature than normal eye.[23,25]

2.3 *PDGFRA* Gene

Platelet-derived growth factor receptor, alpha polypeptide (*PDGFRA*) is a gene that located on chromosome 4q12. This gene has other names such as

CD140A, CD140a antigen, CD140 antigen-like family member A, PDGFR2, PDGFR-alpha, PGFRA_HUMAN, platelet-derived growth factor receptor 2, platelet-derived growth factor receptor alpha.[47]

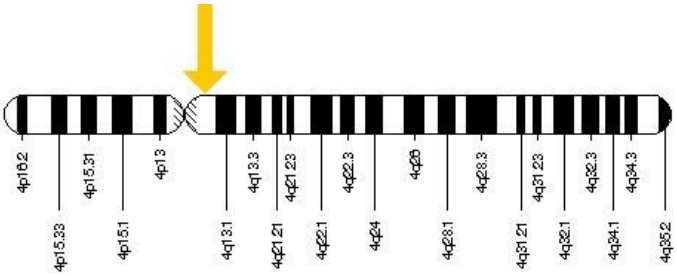

Figure 3. *PDGFRA* gene[48]
PDGFRA gene is located on chromosome 4q12 from basepair 55,095,263 to 55,164,411

The function of this gene is to provides instructions for making a protein called platelet-derived growth factor receptor alpha (PDGFRA).[48] PDGF receptor alpha is mainly expressed in mesenchymal tissue.[16]

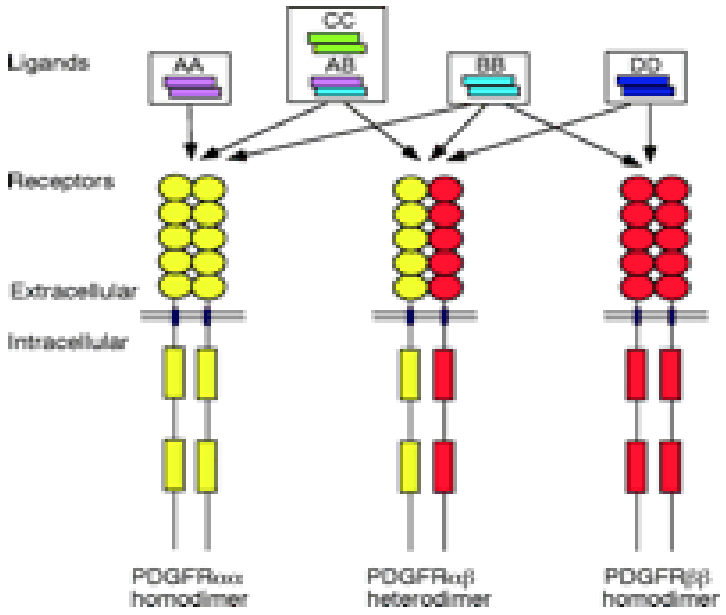

Figure 4. Platelet-derived Growth Factor Receptors[49]
This receptor has one extracellular part (loops) and intracellular part (rectangle). Extracellular part consists of immunoglobulin, intracellular part consists of amino acid tyrosine.

This receptor was present on epithelial cells, stromal fibroblast, and endothelial cells.[49] Stromal fibroblasts synthesize the collagen type I, V, and VI. These collagen fibrils contribute to maintain optical transparency, stabilize, and organize corneal stroma.[50]

PDGF receptor is part of receptor tyrosine kinases (RTKs).[16] RTK are essential for normal growth, development, and cell survival. When activated, this receptor will provide some cellular responses.[15]

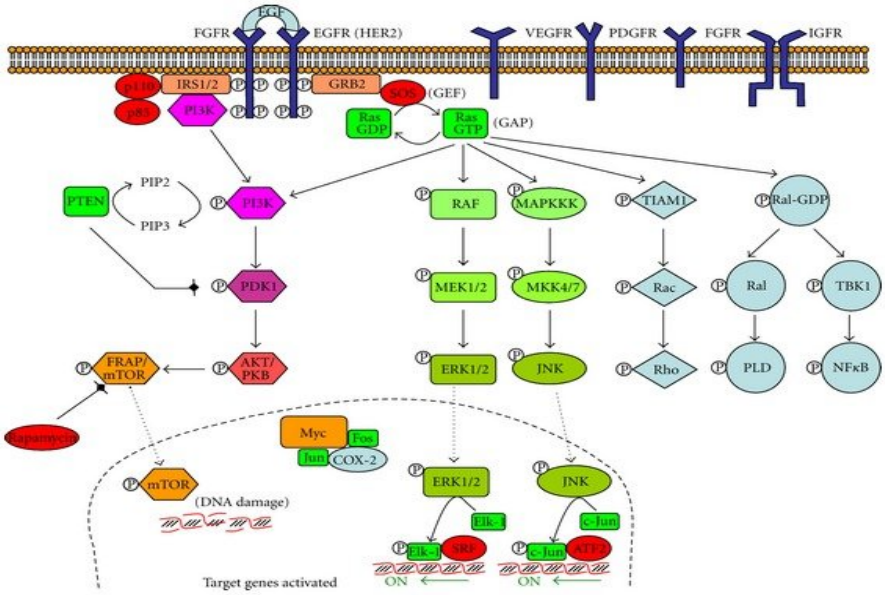

Figure 5. Receptor tyrosine kinase activation[51]
Ligand binding to extracellular part of RTK will make a RTK dimer. The dimer RTK will be phosphorylated and activated other intracellular protein to create some cellular responses that can change transcription.

Investigation for the specific architecture of cornea that maintenance the corneal curvature showed that corneal stroma was playing a role in corneal curvature maintenance.[52] Cornea will becomes more susceptible to any pressure if there is a structural alteration that weakening the cornea. This condition will make corneal shape canges more easily such as corneal steepening.[53]

PDGFRA protein was expressed in 70.2% synovial sarcoma tumors. [54] Forty percent of glioblastoma multiformes were having mutation in *PDGFRA* gene. There was an elevation in tyrosine kinase activity in tumors with *PDGFRA* rearrangement.[55] High level of PDGFRA was correlated with older age, high grade malignancy, and over expression of PDGFRA protein in

gliomas.[56] There were seven single nucleotide substitutions in *PDGFRA* gene from 9 of 102 subjects (p value <0.0001) which correlated to cleft palate.[57]

There are some research about cornea involvement in the eye diseases. A GWAS about corneal curvature in three main races in Singapore found some SNPs that may play a role in corneal curvature. From these SNPs, they tried to locate the nearest gene 5 kb upstream and 5 kb downstream. *PDGFRA* gene is determined to be the nearest gene to 7 SNPs, which were[11]:

Table 2. SNPs that were nearest to the *PDGFRA* gene[11]

SNP	Effect Allele	Frequency in SiMes	Frequency in SP2	Frequency in SINDI	Frequency in SCORM
rs7676985	A	0.26	0.25	0.26	0.24
rs17084051	A	0.25	0.21	0.26	0.20
rs7677751	T	0.25	0.19	0.26	0.19
rs2307049	A	0.25	0.18	0.26	0.18
rs7682912	G	0.26	0.23	0.26	0.22
rs7660560	A	0.25	0.18	0.26	0.19
rs2114039	C	0.30	0.28	0.27	0.29

SiMES = Singapore Malay Eye Study, SP2= Singapore Prospective Study Program (for Singaporean Chinese), SINDI= Singapore Indian Eye Study, SCORM= Singapore Cohort study of the Risk factors for Myopia (for Singaporean Chinese children).

This study was partly repeated in Australian population and White Europeans and found positive association between corneal curvature and *PDGFRA* gene, but not with *FRAP1* gene.[12,13] In White Europeans population, this locus was found to be affecting the eye size rather than corneal curvature.[13]