

Institute for Christian Teaching
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**God's Fingerprint: The EGFR in the Biological Membrane
and the Mechanism of Primary Signal Transduction**

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INTRODUCTION

God's fingerprint in His creation is revealed in the book of Isaiah, "I made the earth and created humankind upon it, it was my hands that stretched out the heavens and I commanded all their hosts. Likewise, the book *Education* by E.G. White declares, "Upon every page of the great volume of His created works may be traced His handwriting." The creation of man is described in the book *Healthful Living* "Man came from the hand of his Creator, perfect in organization and beautiful in form."

In the book *Testimonies*, E.G. White states that not only does God created the heaven and all the host of them, the earth and all the things therein by the work of his hands but He has given life by the breath of His mouth. The realization that life comes only from God creates in man a desire to unravel God's fingerprint in every living organism. One interesting area of biological research is the understanding of the biochemical processes that control the proliferation of mammalian cells.

Growth hormone receptors are among the most intensively studied intrinsic plasma membrane proteins. The involvement of the epidermal growth factor (EGF) in the regulatory network of cell proliferation is well established. EGF can induce cell proliferation by binding to a cell surface receptor known as epidermal growth factor receptor (EGFR). To paraphrase Ellen White: Everything known about the molecular basis of the EGF and its receptor and its mechanism of action declares God's sustaining power.

The primary objective of this paper is to present biochemical evidence of God's fingerprint on the molecular basis of EGF and its receptor in the biological membrane and its role in primary signal transduction. The secondary objective is to examine whether the biochemical system of EGFR in the biological membrane fits into the theory of intelligent design and irreducible complexity.

The Biological Membrane

The identity and very existence of a cell and its organelles are not possible without a membrane which separates the internal from the surrounding environment. The primary functions of biological membranes are containing, compartmentalization and regulating the transfer of metabolites and macromolecules in living organisms. To mediate such functions, membranes contain lipids which act as barriers, solvents, anchors and conformational stabilizers for proteins that perform specific catalytic and translocation reactions. Biological membranes are organized assemblies of 40% lipids, 60% protein and small amount of carbohydrates (Jain, 1988).

Fluid Mosaic Model of the Biological Membrane

Several models were reported about the structure of the biological membrane. The most popular is the Fluid Mosaic model shown in Figure 1 and was postulated in 1972 by Singer and Nicholson.

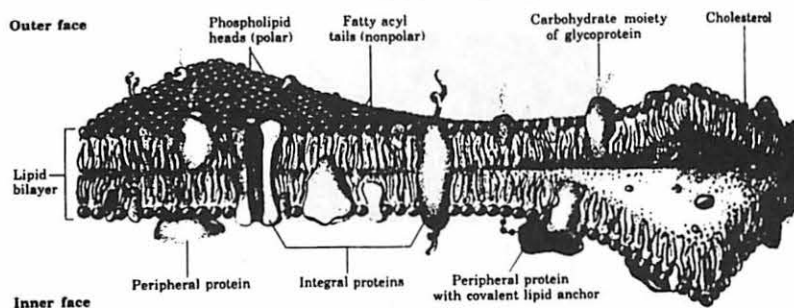


Figure 1. Fluid Mosaic Model of Biological Membrane
(Taken from Lehninger, 1993)

This model describes the membrane containing integral membrane proteins as iceberg floating in a two-dimensional lipid "sea". These proteins freely diffuse laterally in the lipid matrix unless their movements are restricted by association with other cell components. Membrane proteins once in place within the bilayer do not flip their orientation with respect to the sides of the bilayer. They are placed in the membrane with absolute asymmetry and remain kinetically trapped for their lifetime (Lehninger, 1993).

In contrast, membrane lipids, exhibit rapid lateral diffusion (see Figure 2) of individual molecules within one face of the bilayer. The bilayer matrix provides a surface for specific distribution, orientation and sidedness for a variety of functional molecules.

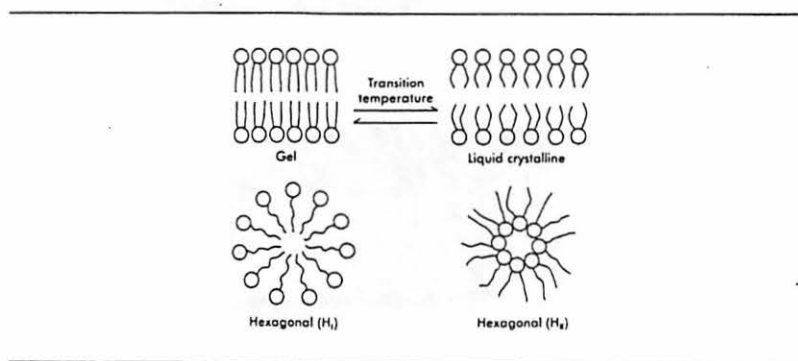


Figure 2. Lipid Motion within the bilayer
(Taken from Lehninger, 1993)

Flip-flop as shown in Figure 3, a process involving rotation of 180° about an axis on the plane of the membrane and a transfer of a lipid molecule across a bilayer is a very slow or rare event.

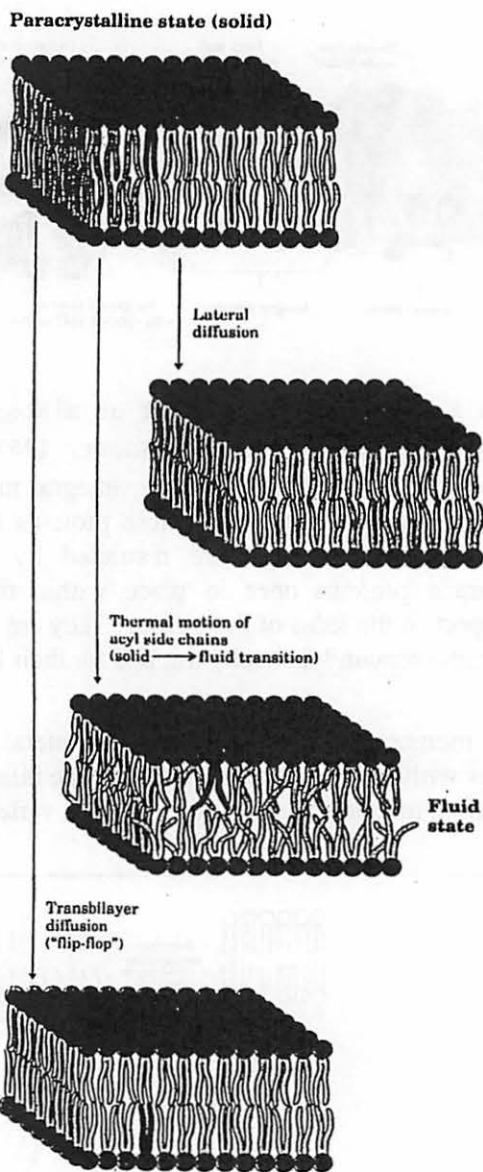


Figure 3. Flip-flop Motion
(Taken from Lehninger, 1993)

Creative love for order, harmony and unity: In the diversity of the structure and composition of the cell membrane, we see the Fingerprint of Jesus, the Creator, the Biochemist and the Intelligent Designer. It reflects God's creative love for order, harmony and unity in diversity. As stated by Gibson (Vol. 11), "Diversity is not the result of chance but of planning". E.G. White noted that --

...unity in diversity is God's plan. Every individual has his place in the filling up of a great plan bearing the stamp of Christ's image. The spirit of God working in and through the diverse elements will produce harmony of action. One is fitted to do a certain work, another has a different work for which he is adopted, another has a different line but each is to be the complement of others (MCP 745).

If the cells and their organelles do the specific task assigned to them in harmony, how much more should we as God's children created in His own image?

The Fluidity of the Biological Membrane

The lateral motion of the lipid bilayer endorses the biological membrane with fluidity and flexibility, high electrical resistance, and relative impermeability to highly polar substances. The fluidity of biological membrane permits embedded proteins to interact. Above its transition temperature, the membrane is in its fluid state. The transition temperature of most biological membranes are in the range of 10°C to 40°C. Below the transition temperature, the lipid molecules exist as a gel-like solid. The transition temperatures of mammalian membranes are well below body temperature thus, these membranes have a fluid-like character. The transition temperature of a bilayer is directly proportional with the chain length and with the degree of saturation of its component fatty acid residues. (Voet & Voet, 1995).

Voet and his colleague (1995) described the physiological consequences of the fluidity and flexibility of the biological membrane on an erythrocyte skeleton. They compared a slurry of solid particles of a size and concentration equal to that of the red blood cell with the flow characteristic equal to that of sand. They reported that in order for the blood to flow continuously, the RBC membrane skeleton must be in the fluid state and easily deformable. They define the ability of organisms to regulate the phase transition to keep membranes fluid in cold environments as *homeoniscous adaptation*. Furthermore, they mentioned that this property is detected in many eukaryotic organisms including algae, higher plants, protozoa and hibernating animals.

Voet & Voet (1995) cited that when a golden hamster enters hibernation, its body temperature falls from about 37°C to as low as 5°C. Consequently, the proportion of double bonds in the membrane phospholipids increases, keeping the membrane fluid at the reduced temperature. This ability to keep membranes fluid at low temperature is particularly significant in the nervous system of hibernating mammals. This enables the cells of the nervous system to be active in transmitting nerve impulses, and the animal, although in its inactive stage, can maintain the basic body functions and respond to external stimuli. Higher plants with resistance to chilling are equipped with membrane lipids containing higher proportions of double bonds.

God's Omnipotence. How such apparently diverse functions are mediated and regulated by and thru membranes is an area of active investigation until now. God's ownership and creatorship in everything that exists is expressed in Colossians 1:17. "And He is before all things and in Him all things consist". The minutest atom of the cell and its organelle, in its perfect beauty, versatility, order and complexity suggests that life was designed by an all-knowing God.

Is it a coincidence that the food sources specified by the Creator help maintain the fluidity of the biological membrane? "And God said, Behold, I have given you every herb bearing seed, which is upon the face of all the earth, and every tree, in which is the fruit of a tree yielding seed, to you it shall be for meat" (Gen 1:29). These plant sources are rich in unsaturated fatty acids that maintain the fluidity of the biological membrane which delays the aging process. Research has proven that the fluidity of the biological membranes slows down the aging process. God's infinite love enables us to enjoy life to the fullest. The harmonious action of all the parts of the cell is necessary to the full and healthful development of the living organism.

On the other hand, the bad cholesterol which is obtained from animals was reported by Voet, 1995 to decrease membrane fluidity because of its rigid steroid ring system which interferes with the motions of the fatty acid side chains. E. G. White, in her book, *Counsels on Diet and Foods* instructs us to refrain from eating meat.

Integral Membrane Proteins

Integral or intrinsic proteins are tightly bound to membranes by hydrophobic forces and can only be separated from the membrane by treatment with agents that disrupt membranes like organic solvents and detergents. They tend to aggregate and precipitate in aqueous solutions or in water-miscible organic solvents. Transmembrane integral proteins span the bilayer whereby the nonpolar portions are embedded in the lipid interior, whereas, the polar residues are extended into the aqueous environment. An example of a transmembrane integral protein is the epidermal growth factor receptor (EGFR).

Epidermal Growth Factor (EGF)

EGF is a growth hormone containing 6045 kDA polypeptide with 53 amino acids (Savage, et al., 1972). The discovery and characterization of EGF as a result of the pioneering work carried out by Stanley Cohen paved the way for the modern field of growth factor research. EGF was discovered in 1960 by Stanley Cohen in a submaxillary gland of a mouse and was also found in human urine. It was originally called tooth-lid-

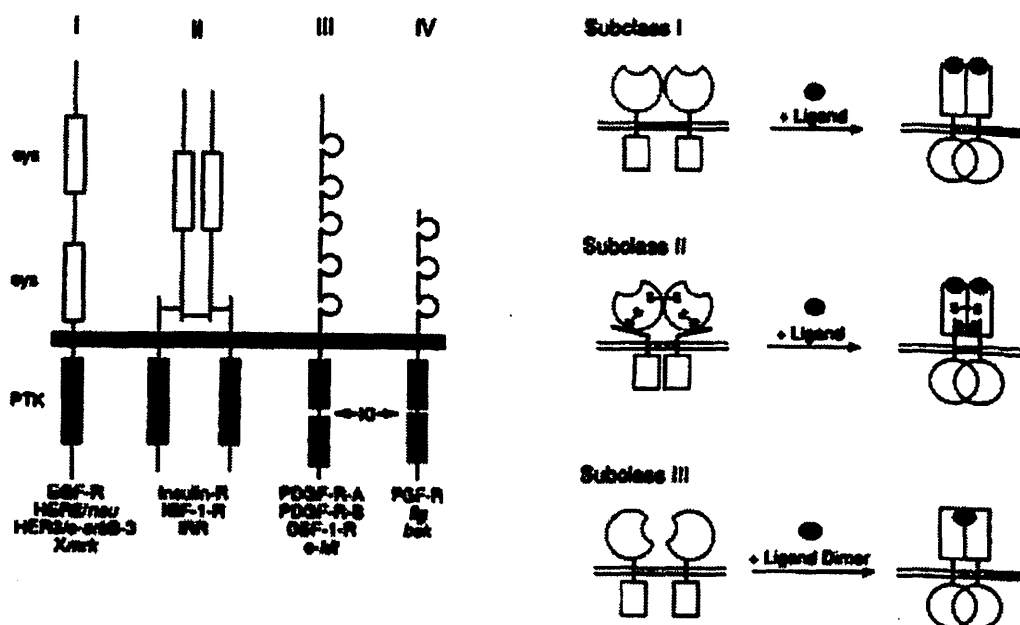


Figure 4. Receptor Tyrosine Kinase family (Taken from Ulrich and Schlessinger, 1990)

factor, because it causes tooth development and induces premature eyelid opening and incisor eruption when injected into newborn animals (Cohen, 1962). The said event was induced by epidermal proliferation and keratinization (Carpenter & Cohen, 1979). Thus the term EGF was coined. Raman (1985) placed EGF as a member of the receptor tyrosine kinase RTK family as shown in Figure 4 (I).

Thirty-two percent sequence conservation between transforming growth factor (TGF) and EGF was reported, and all bind with 1:1 stoichiometry. Rall et al. (1985) observed EGF expression at the mRNA and on protein levels on kidney, pancreas, small intestine and brain of an adult mouse. Furthermore, Raman (1985) reported homology sequences found in a variety of proteins-like LDL receptors and *Drosophila* genes.

Mouse EGF (mEGF) and human EGF (hEGF)

The hEGF was reported by Carpenter and Cohen (1975) as a potent mitogen from human fibroblasts in cell cultures, stimulating both RNA and DNA synthesis and cell proliferation. Carpenter (1977) identified the hEGF as the major growth-promoting agent in human milk. Staros, et al. (1985) stated that hEGF participates in normal regulation of genetic and duodenal function.

A superimposed structure of the mEGF and hEGF in Figure 5 shows that they share a homologous sequence with Aspartic acid as the N-terminal and Arginine as the C-terminal. EGF contains 6 half-cysteine residues corresponding to three S-S required for

biological activity which were located in the same position in the mEGF and hEGF which were observed to be necessary for ligand binding. Staros, et al., 1985 observed that mEGF and hEGF bind with their receptors with the same affinity and produces the same response in target cells.

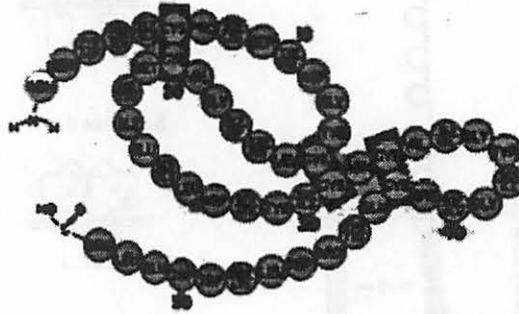


Figure 5. A superimposed structure of mEGF and hEGF (Taken from Staros, et al., 1985)

Epidermal Growth Factor Receptor (EGFR)

Receptors are membrane glycoproteins designed to recognize and bind molecules interacting with the cell surface called ligands. One large and highly important group of receptors binds growth factors. The cell surface may contain from hundreds to thousands of individual receptor molecules. EGF can induce cell proliferation by binding to a cell surface receptor known as the epidermal growth factor receptor (EGFR).

EGFR is a 170 kDa transmembrane glycoprotein with 1,186 amino-acid residues (Sunada et al., 1985). The EGFR is present in a variety of cell types *in vivo* and *in vitro*. It is a single polypeptide chain with three domains (see Figure 6). First is the amino terminal or the extracellular domain where ligand binding occurs. Then comes the intracellular or the C-terminal (the site of tyrosine kinase activity and autophosphorylation), and between the extracellular and the intracellular is a single putative transmembrane sequence that consists of 23 amino acids.

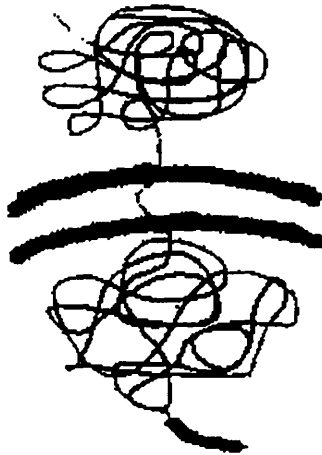


Figure 6. Schematic Diagram of Epidermal Growth Factor Receptor (EGFR) (Copied from Raman,1995)

Finally, within the segment immediately adjacent to the transmembrane domain is the juxtamembrane domain with 13 amino acid residues highly enriched with basic amino acids Argine and Lysine. Livneh, et al. (1986) reported that this domain functions as a stop transfer signal after the insertion of the amino terminal end of the receptor in the lumen of the endoplasmic reticulum. They also mentioned that Threonine 254 is located in this region which is the autophosphorylation site for tyrosine kinase C.

Uniformity in Design & Specificity in Function: Discovering these highly intricate structures of EGF and its receptor together with other homologous proteins declares God's fingerprint: of specificity amidst complexity.

What attribute of God can we observe from the uniform design of the EGF and that of the other receptors of the living cell? Is it by chance, or does it portray a superior intelligence of a master designer?

The chances of randomly forming the right sequence of amino acids in a protein containing 100 units from the 20 common amino acids was reported to be about 10^{130} . In the case of the EGF with 53 and its receptor with 1,180 amino acids, the chances of a random ordering would be infinitesimally small. Thus to attribute the existence of these EGFR family of homologous proteins to evolution subscribing from a common ancestry is definitely questionable.

Mechanism of Primary Signal Transduction

In cells, binding of EGF to the extracellular domain of EGFR triggers a primary signal which traverse the 23 amino acid transmembrane domain of the receptor. This activates the tyrosine kinase activity inside the cell, causing phosphorylation of EGFR and other intracellular substrates, and initiating a cascade of reactions that leads to cellular proliferation. The transmembrane domain is undoubtedly important in primary signal transduction, which is the mechanism of activation of this internal enzymatic activity after ligand binding to the external ligand-binding domain of the receptor.

Two different mechanisms have been proposed (Staros, et. al., 1985) to account for kinase activation after ligand binding to the EGFR.

Communication is essential: Cells communicate with each other through chemical signaling, just like the EGF and its receptor. Likewise, there must be a link that binds men with God and with one another. There must be a connection between God's moral law and laws of the physical world. E.G. White states that if men would be obedient to the laws of God, the principle of righteousness that it teaches would be a safeguard against wrong habits (MCP 569).

“All parts of the living machinery were put in motion. The heart, the arteries, the veins, the tongue, the hands, the feet, the perceptions of the mind, the senses were placed under physical laws. It was then that man became a living soul” (*This Day with God*, p.273).

Flush Chain or Intramolecular Model

The flush chain or intramolecular model (see Figure 7) suggests that ligand binding causes the transmembrane portion of the receptor to move vertically, which may be responsible for the conformational changes through the transmembrane region. The conformational change due to EGF binding is propagated across the bilayer to the tyrosine kinase domain, resulting in an activated tyrosine kinase activity (Bertics & Gill, 1985). The conformational change appears to be brought about by a push on the transmembrane domain of the EGFR so that the sequence is moved toward the inside of the cell with the movement occurring perpendicular to the plane of the membrane. This vertical movement is hypothesized to cause a conformational change in the intracellular portion of the EGFR that coincides with the activation of the tyrosine kinase activity (Ulrich & Schlessinger, 1990).

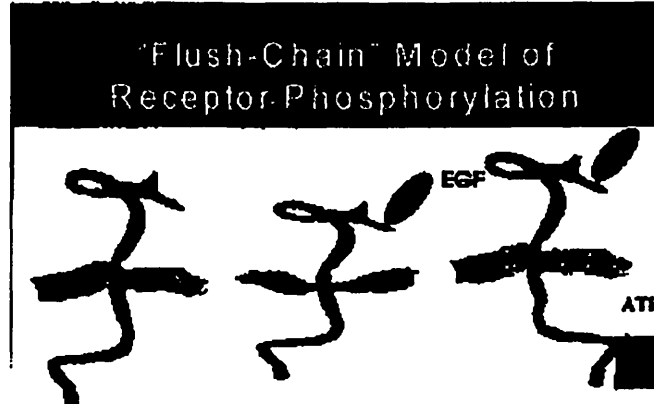


Figure 7. Flush Chain or Intramolecular Mode
(Taken From Raman, 1995)

Vertical Communication

This intramolecular model of primary signal transduction in the lipid bilayer brought about by the binding of the EGF to its receptor can be compared to our need as Christians to maintain a vertical relationship with Jesus. "The closer our connection with God, the more fully we can comprehend the value of true science, for the fingerprints of God as seen in His created works can best be appreciated by him who has a knowledge of the Creator of all things, the Author of all truth" (CT 38 [1913]).

Through faith in Christ and His sacrifice we may have restored connection with God. Through prayer we can talk to God anywhere and anytime. We should listen to the voice of God and follow His instructions. Only then can we find joy and peace in everything that we do.

Intermolecular or the Dimerization Model

In this model, Carpenter (1987) suggests that the receptor must dimerize in the membrane for kinase activity to be activated as a result of the binding of the EGF to the receptor. Schlessinger (1966) noted that the binding of EGF to monomeric receptor enhances receptor aggregation. In contrast to the flush-chain model, this theory suggests that receptors phosphorylate each other and that one receptor cannot phosphorylate itself. The schematic diagram of the dimerization model is given in Figure 8.

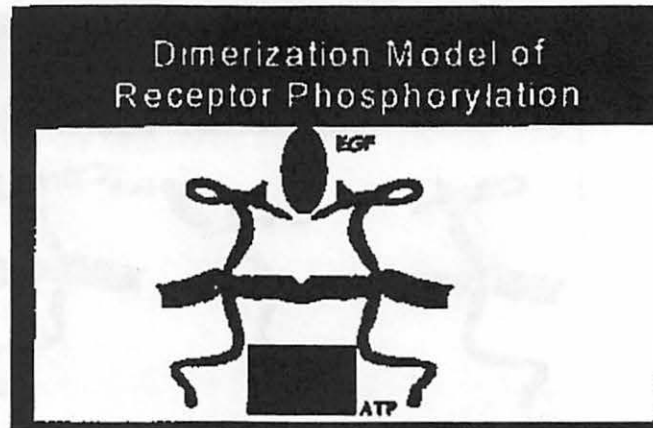


Figure 8. Dimerization Model
(Taken from Raman, 1995)

According to this model, oligomeric EGF receptors have a higher binding affinity than receptor monomers, and therefore the binding of EGF will stabilize the oligomeric state. This leads to the activation of the catalytic properties of the kinase domain by subunit interaction between neighboring cytoplasmic domain.

Horizontal Communication

The intermolecular model of primary signal transduction that requires formation of dimers for activation to occur portrays the horizontal relationship among Christians. As the English poet/clergyman John Donne has so appropriately written, “No man is an island”. We cannot live alone. E. G. White states that “we are all woven together in the great web of humanity. Whatever we can do to uplift others will reflect in blessing upon ourselves. The law of mutual dependence runs through all classes of society” (PP 534 [1890]).

Intelligent Design and Irreducible complexity

Gibson (1997) presented Paley’s argument which claimed the existence in living organism of features that function like a mechanical devices to achieve some purpose are proof that they were created by a designer. This principle holds true for the biological membrane, EGF and its receptor and the mechanism of primary signal transduction. Each of which are made up of intricate parts and were designed for a purpose.

Behe (1996) defines irreducible complexity as a simple system composed of several well-matched interacting parts that contribute to the basic function whereby the removal of any of one of the parts causes the system to effectively cease functioning. The complexity and functional interdependence of the biological membrane, EGF and its receptor and the mechanism of primary signal transduction as shown in the

biochemical system presented supports the theory of intelligent design and irreducible complexity.

Oncogenic Potential of the EGFR_{td}

If an "alien" cell is introduced among the cells of the body of an organism, it will be identified as an "intruder" and be rejected and destroyed. This transforms a normal cell into a cancer cell.

The oncogenic potential of the EGFR_{td} was evident by the discovery of the sequence homology with different transmembrane oncogene of the EGFR family. In principle, every receptor with tyrosine kinase activity has oncogenic potential (Ulrich & Schlessinger, 1990). Tables 1 & 2 summarize the different transmembrane oncogenes of the EGFR and the predicted sequences of the TD of the EGFR family.

Table 1. Transmembrane Oncogene of the Epidermal Growth Factor Receptor Transmembrane Domain (EGFR_{td})

| PROTO-ONCOGENE | ONCOGENE | ORIGIN | CHARACTERISTIC | REFERENCES |
|----------------|-------------|-------------------------|--|------------------------|
| EGFR | v-erbB | Avian erythro-Blastosis | Lacks extracellular domain | Downward et al., 1984 |
| EGF-like neu | c-erbB2/neu | Neuroblastoma cells | Val ₆₅₉ → Glu ₆₅₉ | Hudziak & Ulrich 1991 |
| Unknown ligand | P185 | Rat | Val ₆₆₄ → Glu ₆₆₄ | Bargmann et al., 1988 |
| EGFR | DER | Drosophila | Val ₄₂₈ → Glu ₄₂₈ | Livneh et al., 1986 |
| EGFR | | Human | Val ₆₂₇ → Glu ₆₂₇ | Carpenter et al., 1991 |

Table 2. Transmembrane Domain of Epidermal Growth Factor Receptor (EGFR) Family Members

| GENE | SPECIES | PREDICTED SEQUENCES | REFERENCES |
|-----------------------------------|------------|---------------------------|---------------|
| EGFR | human | IATGM-V-GALLLLLVALGIGLFM | Kashles, 1988 |
| <i>C-erbB2</i> et al., 1984 | human | IVSAV-V-GILLVVVLGVVFGILIK | Brandt-Rauf |
| <i>Neu (p185)</i> et al., 1986 | rat | IIATV-V-GVLLFLILVVVGILIP | Bargmann |
| DER al., 1985 | Drosophila | IITGA-V-LVPTICILCVVTYICR | Livneh et |

Single Point Mutation in the EGFR Transmembrane Domain

If the intramolecular model is correct, then the mutation made by Miloso et al. (1996) could be predicted to cause a change to the vertical orientation of the transmembrane segment of EGFR. Miloso et al. (1996) proposed that an alteration of a single amino acid in the transmembrane domain of the EGFR from a nonpolar to a polar residue can cause constitutive activation of the ability of the receptor to phosphorylate itself and several other cellular proteins.

The sequence of residues 613-647 of the EGFR is:

PTNGPKIPS(IATGM-V-GALLLLLVALG-I-GLFM) RRR

Residues 622-644 (within the parenthesis) represent the putative single transmembrane segment. Synthetic peptides corresponding to the EGFR_{td} were prepared. In each peptide a hydrophobic amino acid Isoleucine was changed to the fluorescent amino acid tryptophan to allow localization of the position of the residue in the membrane by parallax analysis of fluorescence quenching by spin-labelled phospholipids.

Synthesis of the Peptides

Diagram of the steps involved in obtaining a synthetic peptide is shown in Figure 6. It involves design, synthesis, evaluation, purification and application. The design of any specific peptide depends primarily on the use for which the peptide is intended. The physical and chemical properties of proteins and peptides are determined by the nature of the constituent amino acid side chain and by the polypeptide backbone itself. The success of the work is determined by the evaluation and purification process (Grant, 1988).

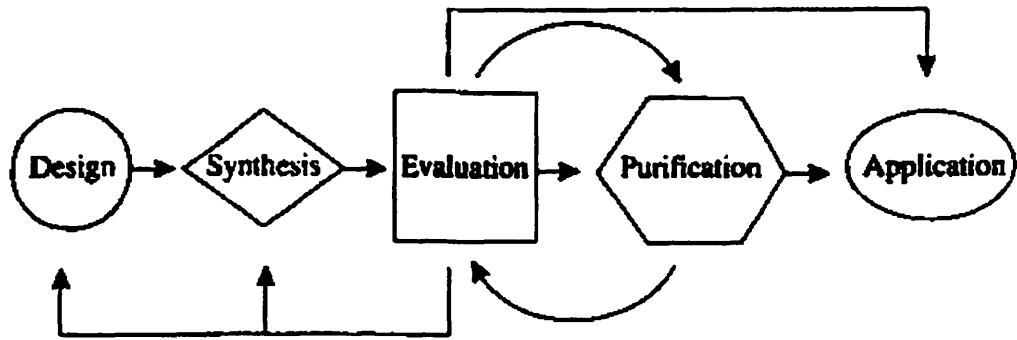


Figure 9. Diagram of the steps involved in obtaining a synthetic Peptide (Taken from Grant, 1992)

Vertical Localization of EGFR Transmembrane Sequence

Each of the synthetic peptides were reconstituted in the lipid bilayer vesicles and the distance between the center of the membrane bilayer and each tryptophan fluorophore was determined by the parallax method utilizing fluorescence quenching by spin-labeled lipids (Chattopadhyay & London, 1987).

The result of the study demonstrates no significant differences in the membrane depth of both the control and the mutant EGFR_{td}. This implies the passive role of the EGFR_{ts} in primary signal transduction, and most likely by the dimerization model. The results obtained in this study showed that the possible mechanism of primary signal transduction does not involve vertical localization of the EGFR_{td} and could be the intermolecular or the dimerization model, contrary to the hypothesis proposed by Miloso et al. 1996.

Abundant evidences are available in the literature supporting any of the validity of the two models of primary signal transduction involving the EGFR_{td}. However, until now the mechanism has remained unclear.

Conclusion

Before the fall man was created perfect. The mechanism of the human body cannot be fully understood. It presents mysteries that puzzle the most intelligent. But one thing is certain: Amidst the perplexities of the mechanism of life, a creationist sees the fingerprint of a living God, full of wisdom and power, our father, friend and, above all, Creator and Savior.

“The living God is worthy of our thoughts, our praise, our adoration, as the Creator of the world; as the creator of man. We are to praise God, for we are fearfully and wonderfully made” (*The Upward Look*, p.278).

In the biochemical evidences of the structure, organization, function and mechanism of EGF and its receptor we see God’s Fingerprint — the Fingerprint of a true God who perfectly balanced the physical forces that hold the atoms which comprise the EGF and its receptor in every living cell; a versatile and an all-knowing God who is the Master Designer and the source of life. The extrinsic beauty, capability, and versatility of the human being as shown by the mechanism involved in primary signal transduction in a lipid bilayer all constitute a brilliant and awesome display of the products of a divine handicraft in His infinite workshop

Every manifestation of created power is an expression of Infinite love. By Him were all things created. Because God is the creator of all mankind we belong to one family. Since the art of creation of the first forms of life cannot be replicated, despite the biochemical evidences brought about by scientific discoveries, it takes faith to accept the reality of creation. E. G. White explicitly mentioned: “In the formation of our world, God was not indebted to pre-existing matter. On the contrary, all things material or spiritual, stood up before the Lord at His word and were created for His own purpose” (*Testimonies*, Vol.8, pp. 289).

“He who set the starry world on high and tinted with delicate skill the flowers of the field, who filled the earth and the heavens with the wonders of His power, when He came to crown His glorious work, to place one in the midst to stand as ruler of the fair earth, did not fail to create a body worthy of the hand that gave him life. Next to the angelic beings, the human family, formed in the image of God are the noblest of His created works” (*The Faith I Live By*, p.29).

Perfection exists in the least as well as in the greatest of the works of God. When God made man in His image, the human form was perfect in all its arrangements but it was without life. Then a personal self-existing God breathed into that form the breath of life, and man became a living intelligent being. All parts of the human organs were set in action

“Yet God is ever seeking to instruct finite men, that they may exercise faith in him and trust themselves wholly in his hands” (*Healthful Living*, p 295).

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