Cell and molecular biology for diagnostic and therapeutic technology

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M I Tan[1]

[1] School of Life Sciences and Technology, Institut Teknologi Bandung, Bandung 40132, Indonesia

E-mail: marsel@sith.itb.ac.id

Abstract. Our body contains 100 trillion cells. However, each cell has certain function and structure. For maintaining their integrity, cells will be collaborating with each other and with extracellular matrix surround them to form a tissue. These interactions effect internally on many networks or pathway such as signalling pathway, metabolic pathway and transport network in the cell. These networks interact with each other to maintain cell survival, cell structure and function and moreover the tissue as well as the organ which the cells built. Therefore, as part of a tissue, genetic and epigenetic abnormality of a cell can also alter these networks, and moreover disturb the function of the tissue itself. Hence, condition of genetic and epigenetic of the cell may affect other conditions in omics level such as transcriptomic, proteomic, metabolomics characteristics which can be differentiated by a particular unique molecular profile from each level, which can be used for diagnostic as well as for targeted therapy.

1. Cells and other components in our body – Complexity in our body

As we know from several decades, that cells are the smallest functional unit in our body [1]. In the human body, there are 100 trillion cells. Each cell in our body has a particular structure and function (figure 1). The cells collaborate with similar cell type or other cell type and acellular components such as connective tissue and construct a particular complex system which is then arranged to develop to specific organs, such as heart, liver, bone.

In keeping their functions and integrity, the cells interacts with cells and other acellular components. Interaction with other cells can be regulated intrinsically or externally through communication with other cells in the vicinity (local interaction) or with cells from a distant place. Interaction with cells in the vicinity could be occurred through interaction between molecules on cell membrane directly with molecules from of neighboring cell membrane (contact-dependent) or through secreted molecules from a cell which influence themselves (autocrine) or other surrounded cell types (paracrine). Distant communications can be happened with the help of blood vessel (endocrine), where the molecule communications delivered through the blood vessels or with the help of nerve cells (synaptic communication) [2] (figure 2).

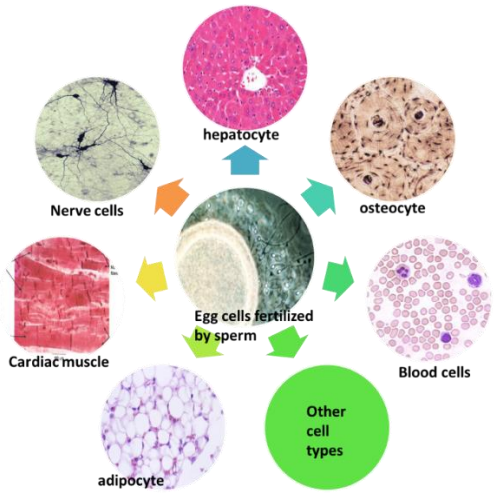

Figure 1. Cells are differentiated into many types of cells

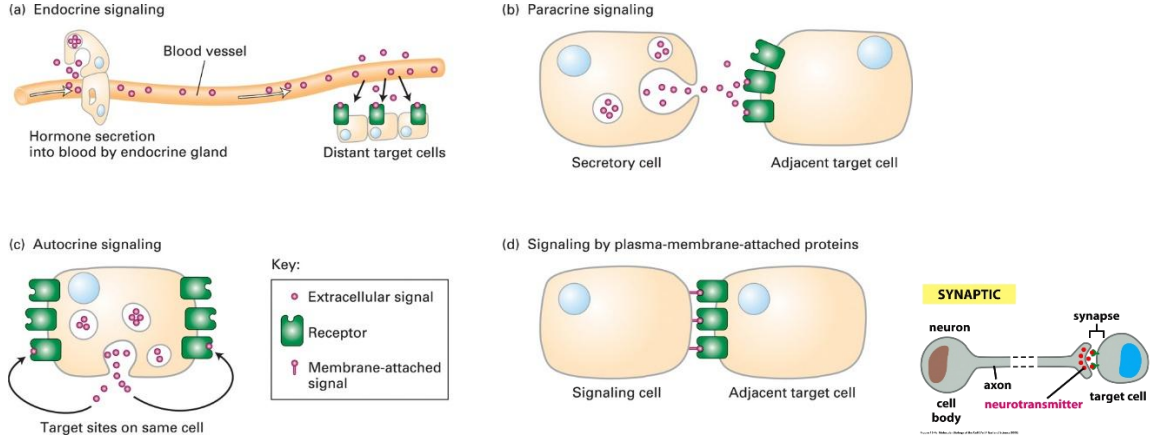

Figure 2. Cell communication type: (a) endocrine signaling; (b) paracrine signaling; (c) autocrine signaling; (d) contact dependent communication; (e) synaptic communication) (adopted from [2]).

Besides interaction with cells, the interaction also occurs with acellular components, extracellular matrix components such as laminin, collagen, etc [3]. Processes that take place in these cells are intrinsically reacted with a variety of cell proteins that work as signaling proteins, or cytoskeletal protein. This component should continue extracellular signals that have been delivered to the cells, and affects the activity of gene expression, metabolism or other cell activity that can further specify the processes that occur in these cells such as cell differentiation, apoptosis, cell proliferation, cell migration (figure 3). The processes that occur in response to a signal received by cell involve genetic and epigenetic signaling pathways related to the intracellular networks dynamics (figure 4).

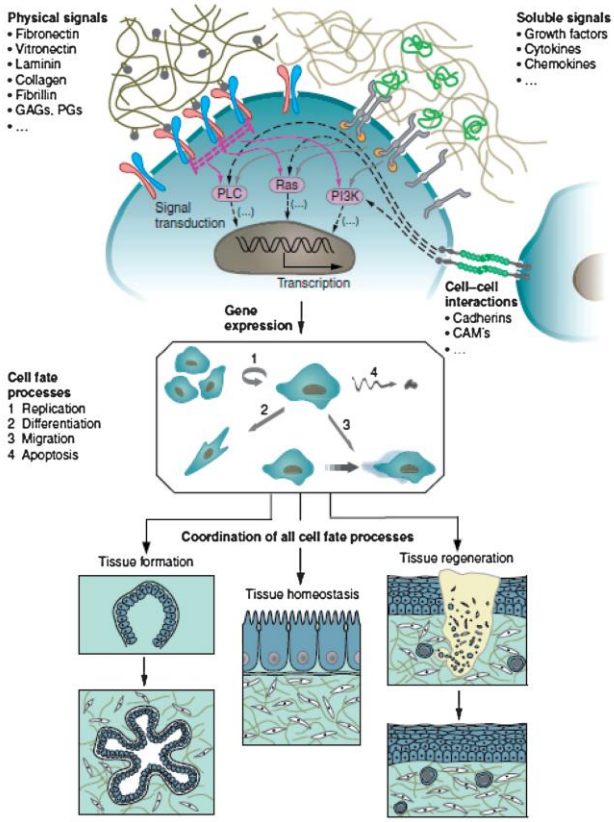

Figure 3. The cell's surrounding is comprised of a highly hydrated atmosphere containing physical and soluble signals, which can control signalling and activation of particular target genes. The activation of these genes will regulate the phenotype of the cell. (adopted from [3])

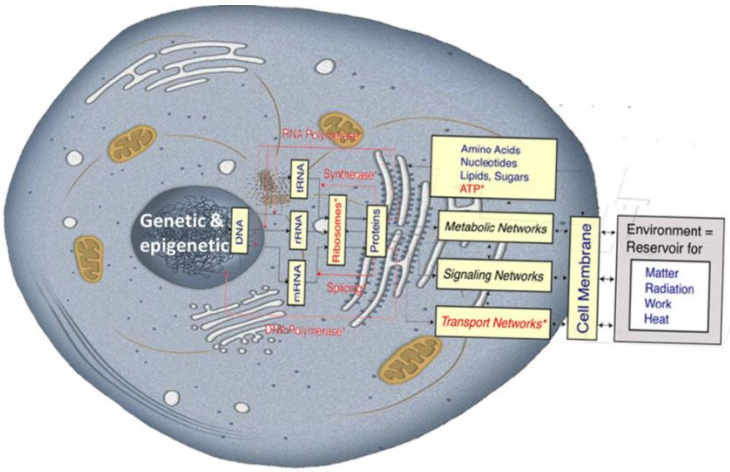

Figure 4. Genetic and epigenetic factors from a cell which are supported by circumstances will regulate metabolic networks, signaling networks, and transport networks (modified from [4]).

There are a variety of intracellular networks participating in the presence of signals from their environment, namely in a metabolic pathway, signaling pathways, transport networks [4]. Overall, the entire pathways collaborate with a very complex network however mutually supporting. Inside the cells, there are different signaling pathways such as MAPK pathway, JAK-Stat pathway, etc., which work together to determine the response of cells as shown in the image below. This signaling pathway will furthermore influence cell response such as cells proliferation or programmed cell death (apoptosis) [5].

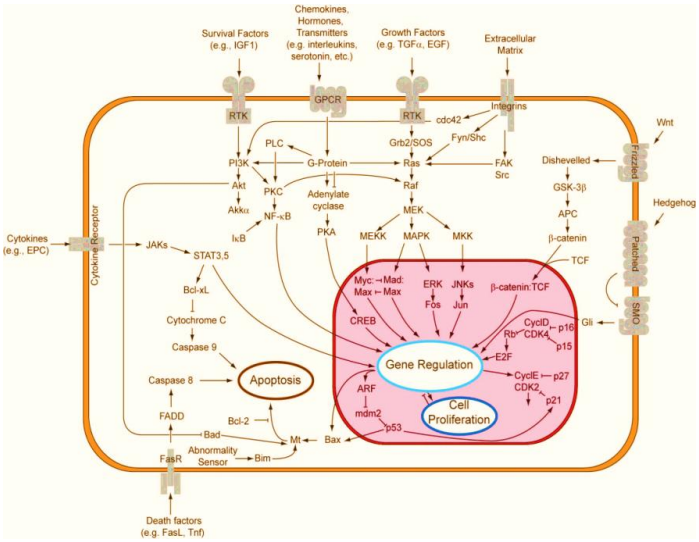

Figure 5. Extracellular molecules activate signaling pathway through specific transmembrane protein such as GPCR, Growth factor receptor, integrin etc. There are variety signaling pathway in eukaryotic cells, such as MAPK pathway, JNK pathway. Activation of signaling pathway cause cell proliferation or apoptosis etc. [5].

This signaling pathway is not operating alone to stimulate the response of cells but also in collaboration with other networks such as metabolic networks. As can be seen in the figure 6, activated myc protein in the MAPK pathway [6], for example, can also play a role in regulating glycolysis, protein metabolism, fatty acid metabolism, or indirectly affect the Krebs cycle.

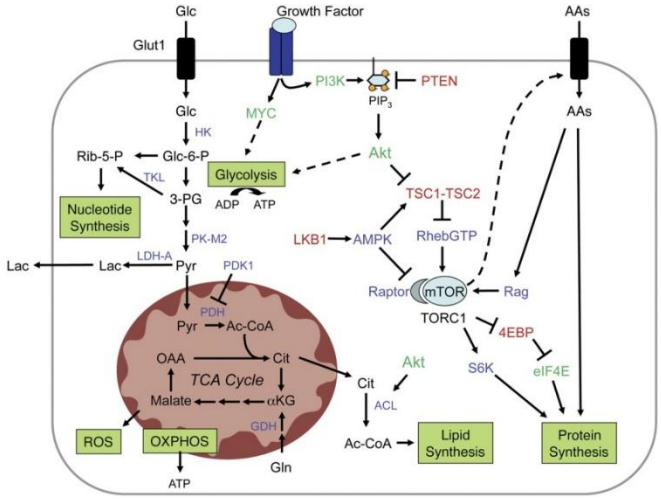

Figure 6. Growth factor-independent activation of the c-Myc pathways stimulates alterations in cellular metabolism to support cell growth and proliferation. c-Myc promote increased rates of glucose uptake and glycolysis (adopted from [6]).

Moreover, transport network, which involving the transport of proteins/other cells products in vesicles that also transferred to its target within or secreted out of the cell. This transport network is not also independent of other systems; nevertheless this network can cooperate with the signaling pathways as show in the picture below [7]. In the image below, some of the components that play a role in the MAPK pathway as Erk1/2, Raf also played a role in the secretory pathway, which furthermore eliciting cell response.

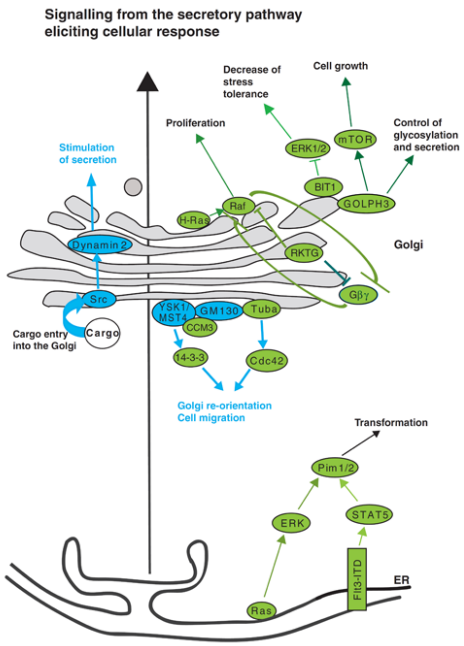

Figure 7. Signalling from the secretory pathway, displays a confirmation on how organelles of the secretory pathway contribute to the compartmentalization of signal transduction to obtain differential cell responses, such as proliferation, transformation and migration (adopted from [7]).

Changes in the secretory or signaling or metabolic pathways will transform cell homeostasis which effect on cell response such as in the figure below. In the figure below as an example, quiescent fibroblast cells can be turned into active proliferative cells when these cells change their metabolic network. When quiescent fibroblast cells transform into an active fibroblast cell in cell division, the cell will increase glucose intake and consequently glycolysis and Krebs cycle, the cells also produce nucleotides and macromolecules, which they need for replication and other activities. Besides that, the active fibroblast cell also activates glutamine and lactate metabolism [8]. This situation shows that alteration in these networks can cause changes in cell activity which could further affect the physiological state of a person. It means that unhealthy cells can cause a disease.

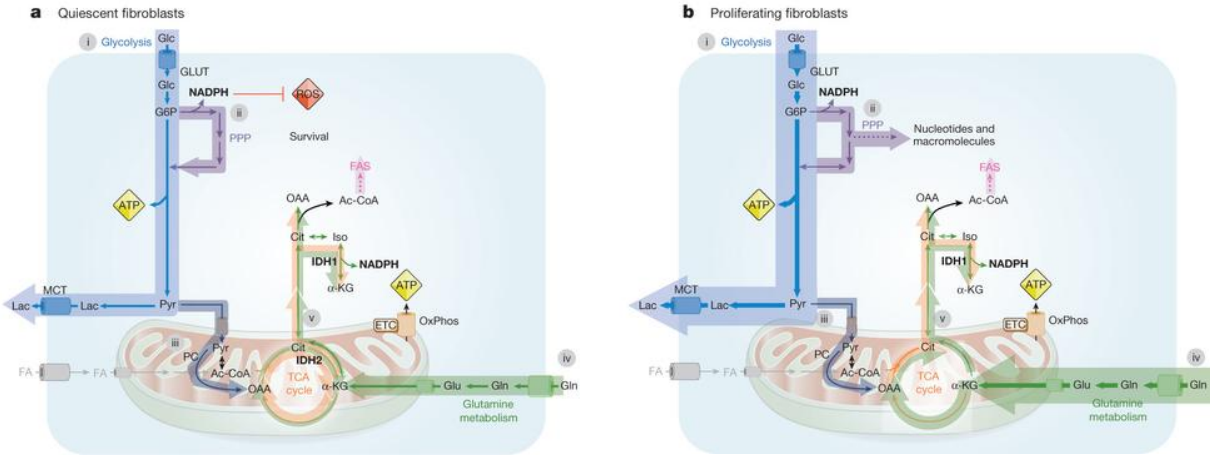

Figure 8. Alteration of fibroblast metabolism could modify proliferation activity of the cells (adopted from [8]).

2. Abnormal cells vs healthy cells

A variety of factors can effect abnormal cells. The prominent causes of the abnormality are genetic and epigenetic alterations. Genetic change might have no impact on the cells when the alteration is only causing silent mutation or is a mutation in the non-coding part of the gene. However, it might

also cause severe changes in phenotype, such as sickle cell. In a patient who suffered from sickle cell, there is a mutation in codon 6 of the gene encoding hemoglobin (figure 9). In codon six of hemoglobin gene, nucleotide T is changed to A, which causes a change in amino acid, namely from the glutamic acid into valine, which furthermore resulted in an alteration of hemoglobin function regarding reduced ability for oxygen binding. The blood cell structure furthermore turned into a crescent-shaped and, as a result, people with this disease has some problem in oxygen binding.

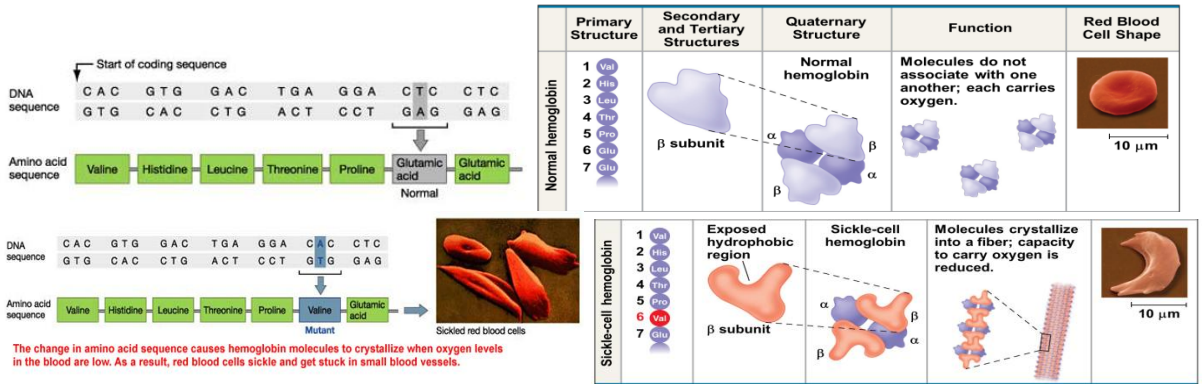

Figure 9. Hemoglobin mutation in sickle cell patient. Alteration of hemoglobin gene in codon 6 from T to A alter amino acid from glutamic acid to valine and furthermore alter structure and function of red blood cell (adopted from [9] and [10]).

As mention before, phenotype alteration can also occur due to epigenetic changes. These epigenetic changes took place in several types of cancer, for example in colorectal cancer. Changes in genetic and epigenetic might further alter structure and organization of cells, or cellular sensing and signaling or secreted products such as the extracellular matrix that are subsequently affecting changes in mechanotransduction signaling that cause a particular disease (figure 10) [11]. Furthermore, these alteration might also change a different profile of molecules on cell surfaces [12]. For example in breast cancer cells, EGFR is found more in membrane cells of breast cancer than in normal cells (figure 11). On the membrane of embryonic stem cells, the sulfated disaccharide is located on the membrane cells and support their differentiation process. However, desulfation of aforementioned disaccharide in these embryonic stem cells could inhibit the cells differentiation [12].

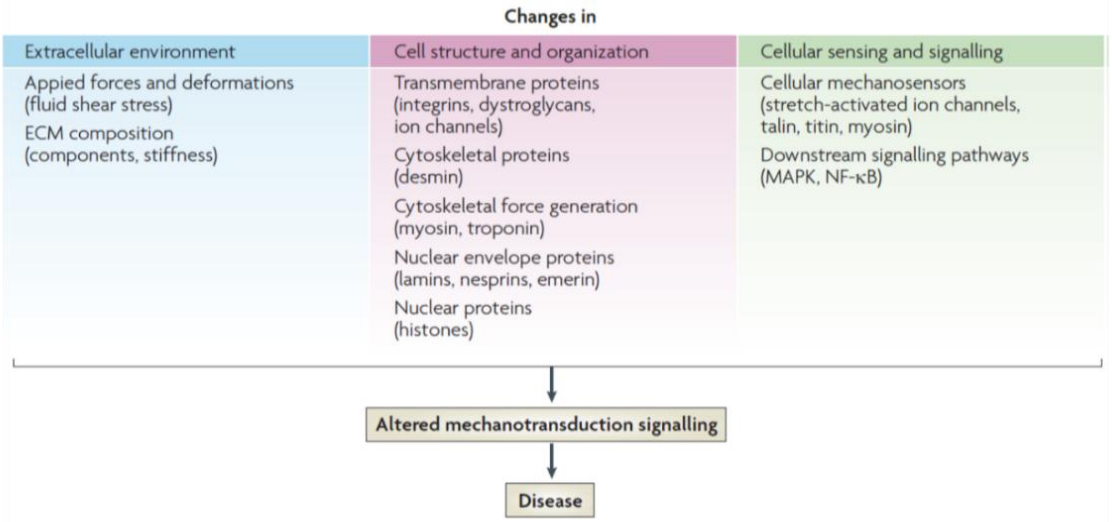

Figure 10. Changes in extracellular environment, cell structure and organization and cellular sensing and signaling are able to alter mechanotransduction signaling and can cause a disease (adopted from [11).

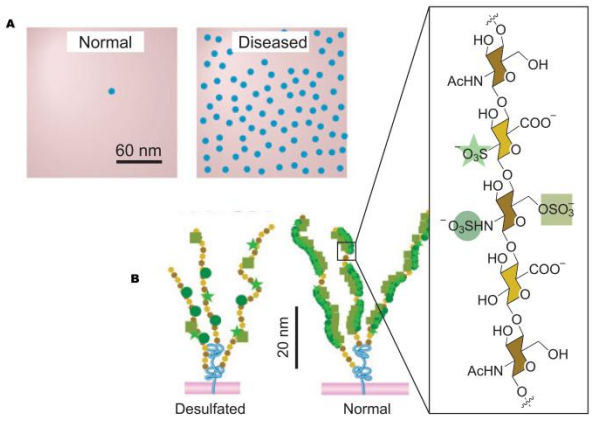

Figure 11. Profile of cell surface features: (A) Alteration of membrane molecule profile on normal and diseased cell (breast cancer cells), where HER2 proteins in breast cancer cells are overexpressed and cover more than 15% of surface cell; (B) Carbohydrate profile on cell surface regulate cell behavior. Desulfation of disaccharide chains on any protein/lipid membrane cell is able to prevent embryonic stem cells from undergoing differentiation (modified from [12]).

As explained before, cell transformation can also be associated with changes in cell metabolism which leads to alterations of extracellular states such as in cancer cells. In a cancer cell, there is any change in metabolism, the process of glycolysis activity is raised so that to maintain cell homeostasis and activity of ion transport, cancer cells increase ions concentration outside the cell (figure 12). It causes changes in potential membrane and cell junctions impairment but at the same time cells become anchorage-independent [13].

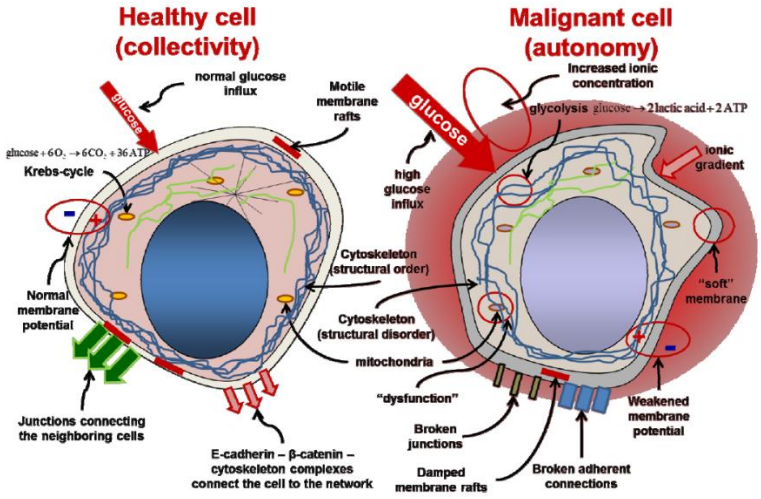

Figure 12. Biophysical differences between the healthy and malignant cells. Malignant cells increase metabolism activity which increase ionic concentration on the surrounding of the cells and disrupt cytoskeleton and junction organization (adopted from [13]).

Abnormalities can also occur in extracellular molecule profiles, for example, it is obvious in cardiac infarction. In myocardial infarction, there are any alterations in the extracellular components, where number and activity of MMP (Matrix metalloproteinase) and cytokine produced by macrophages increase in the extracellular matrix. The activity of macrophages and MMPs in this myocardium extracellular furthermore modifies connective tissue properties and cause moreover myocardial infarction [14].

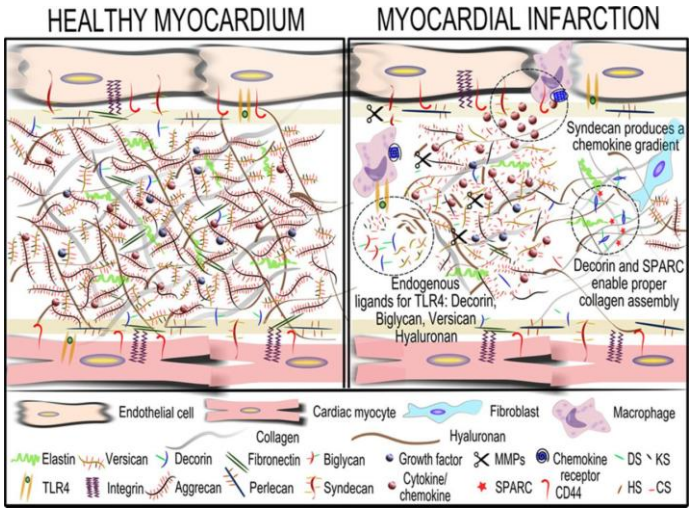

Figure 13. Alteration of architectural arrangement of cardiac ECM (extracellular matrix) in myocardial infarct (Adopted from [14]).

3. Theraphy based on cellular and molecular profile

According to the description above, the condition of genetic and epigenetic of the cell may affect other conditions in omics level such as transcriptomic, proteomic, metabolomic, phenomic characteristics which differentiate by a particular unique molecular profile (figure 14) [15]. In the genomic level we can use specific DNA sequence profile as marker or target for curing a disease such as polymorphism profile (Single nucleotide polymorphism/SNP), LOH (loss of heterozygosity) profile in the chromosomes. In the epigenetic level we can use such methylation or acetylation profile of DNA or histone protein as marker or target for disease therapy. In transcriptomic or proteomic level, specific gene expression profile or miRNA for example can be regulated as targeted therapy or utilized for diagnosis purposes, whereas in metabolomics level, therapy is based on the metabolite level produced in a person. Due to specific molecules profile and certain molecules level in each omics level, it is possible to develop a strategy using these specific molecules for diagnostic and targeted therapy for example by using radiotherapy or chemotherapy.

Cancer treatment can be conducted using chemicals, especially one or more anti-cancer drugs (chemotherapy agents) which can block the activity of certain molecules from any level of omics. Chemotherapy may be applied with therapeutic intent, or it may aim to prolong life or to relieve symptoms (palliative chemotherapy). Chemotherapy is usually delivered in combination with other cancer treatments, such as radiation therapy, surgery, and / or hyperthermia therapy.

Radiation therapy or radiotherapy is a therapy using ionizing radiation, often as part of cancer treatment to control or kill malignant cells. Radiation therapy might be a curative therapy for some types of cancer if they are localized to one area of the body. It can also be applied as part of adjuvant therapy to prevent recurrence of the tumor after surgery to remove the primary malignant tumors (e.g. early stage breast cancer). Radiation therapy is synergistic with chemotherapy and has been used before, during, and after chemotherapy in cancer prone. Radiation therapy is generally administered to the cancerous tumor because of its ability to control cell growth. Ionizing Radiation operates by damaging the DNA of the cancerous tissues that causes cell death.

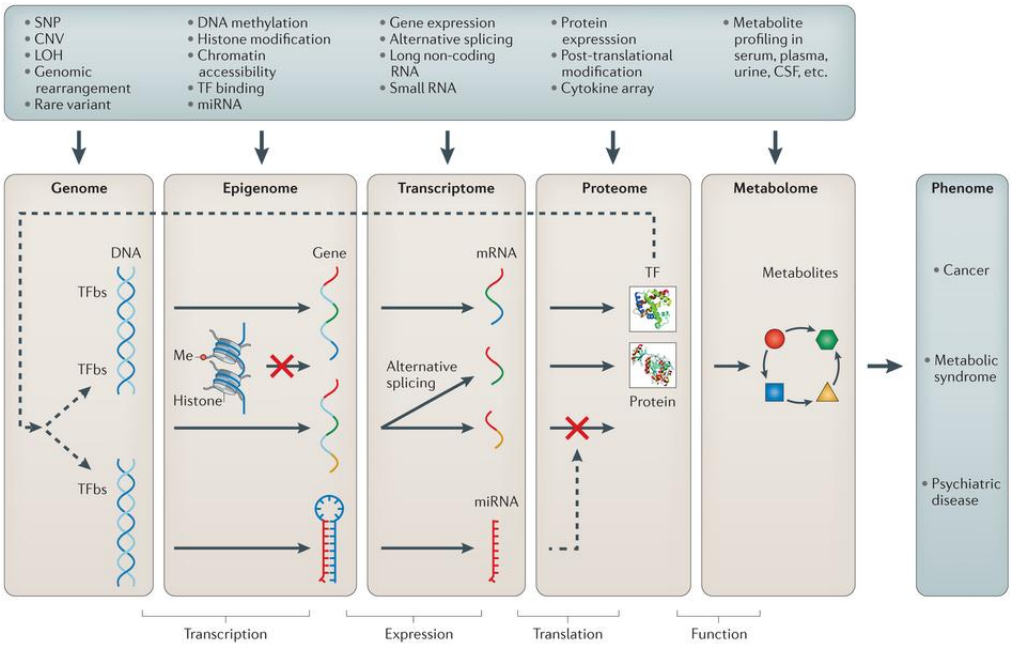

Figure 14. Variety Omics level which can be utilized for diagnostic purposes and therapy namely using specific molecules from each level (adopted from [15]).

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