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The Mechanism of Cell Migration

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Abstract**—** *The assumption that a cell is always fixed at a particular tissue should be avoided. If there is no Immune cell immigration, our body will be attacked by antigen and will not be able to support life. Cancer cell's immigration informs of signs of danger imposed on our body. Cell migration must have a dedicated pathway. If the pathway is found, a new treatment can be sought. In the near future, a nano robot will be able to track down the cell migration pathway and protect our body from diseases. If the migration of useful cells including an immune cell is facilitated and that of harmful cells such as cancer cells is inhibited, a disease free world will not be just a dream.*

Keywords**—** *Cell migration, cell motility, Tumour-infiltrating lymphocytes.*

I. INTRODUCTION

All living things are made of cells, and cells are the smallest units that can be alive. Prokaryotic cells (the bacteria) are smaller and simpler than eukaryotic cells, and do not have a nucleus. Eukaryotic cell possesses a nucleus, a small membrane-bounded compartment that contains the genetic material of the cell [1]. Cells that lack a nucleus are called prokaryotic cells or prokaryotes [1]. Cell Motility means spontaneous, self-generated movement of a biological system [1].

We, as human beings, are made of a collection of cells, which are most commonly considered as the elementary building blocks of all living forms on earth [1]. All cells are small membrane bounded compartments that are capable of homeostasis, metabolism, response to their environment, growth, reproduction, adaptation through evolution and, at the cellular as well as multicellular level, organization.

A. Basic Concept in Cell Motility

Cell motility means wider range movement than cell migration, cell motility include undirected movement of cells [3]. However, cell migration means going to another location from original position, in other words, the translation of cells from one location to another. Unregulated cell migration along a surface or through a tissue gives damage to animals like human beings, regulated cell migration gives benefits to them [3]. In pathology, production of abnormal migratory signals may induce the migration of the wrong cell type to the wrong place, which may have catastrophic effects on tissue homeostasis and overall health [6]. Motility is the nature of cell in prokaryotic cells and the event of cell in eukaryotic cells. Because prokaryotic cell with no movement to the host should be death. The majority of protists are motile, but different types of protists have evolved varied modes of movement [5]. Protists such as euglena have one or more flagella, which they rotate or whip to generate movement. Paramecia are covered in rows of tiny cilia that they beat to swim through liquids [5]. Cell motility in prokaryotic cells is always normal, cell motility in eukaryotic cells may be abnormal events. In human body, cell migration with a specific direction is desirable for the purpose of metabolic activity, but, cell migration with no direction is dangerous. In adult organisms, movements of single cells in search of foreign organisms are integral to the host's defences against infection; on the other hand, uncontrolled cell migration is an ominous sign of a cancerous cell [4]. There are different modes of cell migration depending on the cell type and the context in which it is migrating [6].

B. Why Cells Move

Cell migration is indeed crucially involved for example in embryonic development (where individual as well as collective motions of cells underly morphogenesis), wound healing and recovery from injuries (where cellular migration is essential for tissue repair and regeneration), as well as immune response and most of disease progressions [6]. In animals like human beings, cell motility is at the basis of most - if not all - essential processes participating in their lifetime, from their development, maintenance, to eventual death [1]. Most cells in the body are stationary, but many of these exhibit dramatic changes in their morphology — the contraction of muscle cells, the elongation of nerve axons, the formation of cell-surface protrusions, the constriction of a dividing cell during mitosis [3]. Recent advances in molecular biology and biochemistry have enabled the discovery of the basic underlying molecular mechanisms by which cells are able to feel their environment, exert forces and move in a directed way in search for nutrients or any other task they need to perform [3]. Tremendous advances in the past two decades on both physical micro-manipulation and fluorescence microscopy techniques have enabled the characterization of the processes on cell motility involved with minute details [3].

Most cells in human body that is consist of cells are stationary, but, cell migration is fundamental to the morphogenesis of embryos in human development. Consequently, failure of embryo cells to migrate, or inappropriate migratory movements of embryo cell can result in severe malformed infant after birth or fetal death. A human cannot be born without cell motility in embryonic development. In adult body, cell motility regulated leads to consecutive life, but, cell motility occurred incidentally means risky signal in health and abnormal movements. Eggs (ova) and sperm have half the number of chromosomes of normal body cells. Eggs and sperm are called gametes or sex cells. Egg has a large cytoplasm which contains the nutrients and mitochondria needed for mitosis (cell division) after

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fertilisation. And each egg has a special cell membrane which only allows one sperm to fertilise it. Each sperm has a tail (for motility) which propels it through the cervix, uterus and fallopian tube towards the egg. And each one has many mitochondria (where respiration occurs) to release the energy needed for its journey. Sperm cells also have special enzymes, called acrosomes, which allow them to break through the cell membrane of the egg.

C. Abnormal Cell Migrations

Motility defects of the animal cells themselves can lead to a variety of inherited health problems, including male infertility, deafness and chronic inflammatory diseases [6]. The regulation of cell migration is a complex process involving hundreds of molecules. So, there are risks of a serious malfunction that cause abnormal event in cell migration. A molecule such as a tumor suppressor protein to inhibit tumor cell migration is likely to be an important feature in tumor suppressor activity [7]. Unactivity of the molecule in time results in allowing tumor cell migration. Immune cells has a clear target, the place occupied by foreign antigen, but, infiltration of immune cells into inappropriate place can cause massive damage to normal tissues. Once these cells localize to their abnormal target tissues, they become activated and can cause progressive deterioration of the tissue. Immune cell migration is also critically important for the delivery of protective immune responses to distant target tissues [8].

Thus, In the future, it will be to identify the trafficking molecules that will most specifically inhibit the key subsets of cells that drive disease processes without affecting the migration and function of leukocytes required for protective immunity [8]. Natural killer (NK) cells are lymphocytes that play an important role in defence against infections and cancer [9]. They directly kill tumor-transformed or virally infected cells via the formation of a cytolytic synapse that facilitates polarisation and subsequent secretion of cytotoxic granules directed towards the target cell [9].

NK cell activation is regulated by a balance of activating and inhibitory signals through a multitude that recognise ligands expressed on the surface of other cells [9]. The regulation of NK cell motility is meditated through the balance of activating and inhibitory signals in NK cell, inhibitory receptors was out of order on NK cell cause abnormal migration that inhibitory receptor signalling can reverse the stop signal, allowing NK cells to migrate and resulting in on untarget cells [9].

Cell isolated from the tissue will be dead through necrosis or apoptosis. But, Cancer cell isolated from the tissue never die and migrate random throughout the body. Cancer cells do not stay in the initial site of tumor growth, leave from there without a destination. Cancer cells possess a broad spectrum of migration and invasion mechanisms [10]. It is difficult to prevent cell migration due to the fact that cancer cells can modify their migration mechanisms in response to different conditions [10]. Cancer cells grow and divide in an uncontrolled manner, invading normal tissues and organs and eventually spreading to the body through the process of metastasis formation [11].

Eggs (ova) and sperm have half the number of chromosomes of normal body cells. Eggs and sperm are called gametes or sex cells. Egg has a large cytoplasm which contains the nutrients and mitochondria needed for mitosis (cell division) after fertilisation [12]. And each egg has a special cell membrane which only allows one sperm to fertilise it. Each sperm has a tail (for motility) which propels it through the cervix, uterus and fallopian tube towards the egg, and each one has many mitochondria (where respiration occurs) to release the energy needed for its journey [12]. Sperm cells also have special enzymes, called acrosomes, which allow them to break through the cell membrane of the egg. It needs sane tail and normal acrosomes for a successful movement of sperm cell. The ability of sperm cells to migrate is essential for pregnancy in female. But, sperm cell with abnormal acrosomes is unable to arrive towards the egg, this would result in infertility in women [12].

D. How Cells Move

Cell movement or motility is a highly dynamic phenomenon that is essential to a variety of biological processes such as the development of an organism (morphogenesis), wound healing, cancer metastasis and immune response [13]. Cell migration is an evolutionarily conserved mechanism that underlies the development and functioning of uni- and multicellular organisms and takes place in normal and pathogenic processes, including various events of embryogenesis, wound healing, immune response, cancer metastases, and angiogenesis [6]. Despite the differences in the cell types, all of cell migrations have similar molecular mechanisms which involve intricate cytoskeleton-based molecular machines that can sense the environment, respond to signals, and modulate the entire cell behavior [6]. Advances in fluorescence microscopy, molecular biology and biochemistry have enabled the discovery of the processes underlying motility and the identification of the major proteins behind these processes [13]. Understanding the mechanisms underlying cell migration is also important to emerging areas of biotechnology which focus on cellular transplantation and the manufacture of artificial tissues, as well as for the development of new therapeutic strategies for controlling invasive tumor cells [6]. Cells with ability to migrate have evolved basic mechanisms for generating movement [4]. Cell motility is carefully and precisely orchestrated by the cell with the help of numerous different types of molecular players [3].

Cells have the cytoskeleton, an internal cellular scaffold with kinds of biopolymers, an organized and coherent structure that is formed by connecting these filaments via entanglements, and also crosslinking, bundling, binding, motor and other proteins [13]. These cytoskeletal assemblies then work together as a composite, dynamic material in cell functions such as structural integrity, shape, division, and organelle transport and cell motility [13]. With respect to motility, although the other polymer assemblies in the cell also aid in coordinating movement and powering translocation, the actin cytoskeleton is regarded as the essential engine that drives cell protrusion [13]. During embryonic development, it required for group migration, collective cell migration with the

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ability of groups of cells to move together and simultaneously affect the behavior of one another [14]. Molecular motors with the subset of proteins and macromolecular complexes is essential to migrate cell [15]. They are protein machines whose directed movement along cytoskeletal filaments is driven by ATP hydrolysis [15]. Eukaryotic cells contain motors that help to transport organelles to their correct cellular locations and to establish and alter cellular morphology during cell locomotion and division [15]. Molecular motors can be classified into roughly five categories, namely (1) rotary motors, (2) linear-stepper motors, (3) assembly-disassembly motors, (4) extrusion nozzles, and (5) prestressed springs [1]. Rotary machine usually converts the electrochemical energy stored in proton-concentration gradients, first into mechanical motion, and then back into chemical energy under the form of ATP [1]. In many eukaryotic cells such as sperm, the regular flagellar bending is powered by molecular motors that propel the cell [1]. Cells of all kinds exploit rotary motion, whether in the form of the ATP-synthase machines that generate ATP or the motors that power flagella to propel cells forward [16]. The flagella with molecular rotary motion drive the swimming behavior of bacteria; the motion of bacteria is driven by the rotation of one to ten flagella that are propelled by an exquisite rotary motor [16]. The free energy that drives these motors is provided by protons moving down a transmembrane electrochemical potential gradient. The flagellar motor rotates at 100 turns per second under normal motility speed and can reach a maximal speed of around 300 turns per second, a rate that surpasses the rapid turbine blades of modern jet engines [16]. The bacterial flagellar motor rotates a flagellum using proto n flow through the motor as the energy source, the Fo F1-ATP synthase with two rotary motors is driven by proton flow(Fo motor) and the other by ATP hydrolysis (F1 motor) in sperm cell [17]. The mechanisms of the proton-driven motors, whether flagellar or of ATP synthase are clear interpreted that electrostatic force from moving protons could produce torque if the geometry of proton channels are designed appropriately [17].

E. Efficiency and Accuracy on Cell Migrations

The respiratory epithelium is frequently injured by inhaled toxic agents or by micro-organisms, It begins to operate repair process involved both cell migration and proliferation in the e pithelial wound [18]. Rapid repair is dependent upon the migr ation speed. The ability of cells to move fast is crucial for wou nd healing. During the wound repair, a study showed that cell migration speed (35μm/h-45μm/h) was almost constant during the first 3 days and thereafter dropped down until the wound c losure was completed (after 4 days) [18]. Cells in vivo move t hrough 3D environments. It should be go through 3D extra cel lular matrices (ECM) for cell migration [19]. Tissue consists mostly of cells and extracellular matrix biopolymers such as c ollagen, elastin, laminin, perlecan and other proteins and prote oglycans. Cell migration through 3D extra cellular matrices (E CM) is critical to the normal development of tissues and organ s and in disease processes [19]. Collagen in tissues (ECM) has been traditionally regarded as merely a physical barrier agains t cancer cells migration [21]. Cell migration depends on the ex pression of metalloproteinases (MMPs) to degrade collagen m atrices [19]. There are abundant Type I collagen with high rigi dity in the extra-cellular matrix of tumor tissues, Therefore, ce ll migration speed is modulated by changes in Type I collagen density [19]. The primary migration velocity should be decrea sed with increasing type I collagen density [19]. Immune cells and cancer cells secrete MMPs which are capable of degrading tissues for cell migration [20]. But, immune cells are difficult to go through the extra-cellular matrix of tumor tissues becaus e there are abundant type I collagen with high rigidity. Cancer cells in high rigid tissues are able to avoid attacks by preventin g immune cell migration. However, cancer cells to secrete M MPs easily go through normal tissues and fast migrate toward distant tissues. The expression of matrix metalloproteinase-2 (MMP-2) by cancer cells is implicated in metastasis through ca ncer cell invasion of the basement membranes mediated by a d egradation of collagen IV [29].

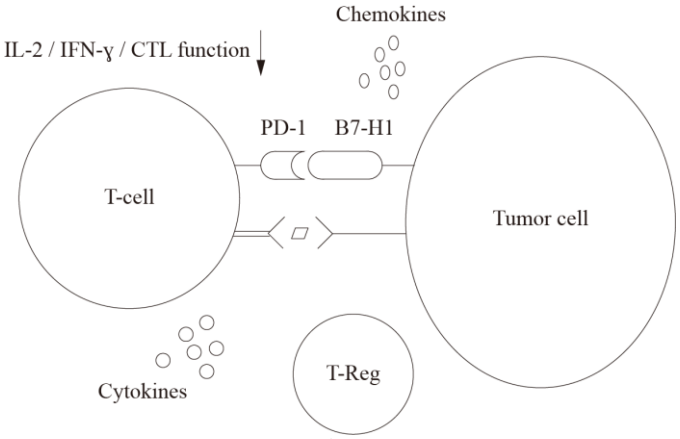

Fig. 1. Tumor cells take advantage of this suppressive mechanism to evade a tumor-directed T cell response.

Alteration of human leukocyte antigen (HLA) expression is one of the mechanisms most frequently used by cancer cells (Figure 2), which arms cancer cells to escape cytotoxic T lymphocyte (CTL) recognition and destruction [24]. Alteration of HLA class I expression enables cancer cells to escape from CD8+ T cell recognition, but also influence the susceptibility of tumor cells to lysis by natural killer (NK) cells, due to the loss of NK cell inhibitory signals triggered by the interaction of HLA class I antigens with NK cell inhibitory receptors [24]. Therefore, upregulation of tolerogenic nonclassical HLA class I molecules such as HLA-F may be an alternative strategy for tumors to acquire protection against both NK and T cells [24]. Chemokines are chemotactic cytokines that control the migratory direction of all immune cells, they serve as critical extracellular mediators of immune migration [22]. Chemokines emerge as “master regulators” in mediating the leukocyte trafficking in resolving infection, play pivotal roles over the rapid recruitment of circulating leukocytes to eliminate the infectious pathogens such as bacteria, virus [23]. During the generation and regulation of adoptive primary and secondary immune responses in the lymphoid system and peripheral nonlymphoid tissue, the chemokine system which are indeed ‘‘maestro” of the movement and localization of

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lymphocyte orchestrates immune cell migration toward target tissue [23]. Cell migration is not a random process. Instead, the cell employs a specialized structure – the lamellipodium – to establish new adhesions at the leading edge and to probe the surroundings for suitable migration directions [25]. Viscosity is a measure of a fluid's resistance or thickness. The less viscous the fluid is the greater the fluidity or ease of movement, Water, for example, has a low viscosity, while honey, being altogether thicker and gloopier, has a higher viscosity. The relationships found were generally valid for various types of fluids including solutions with an elastic microscopic structure (e.g. polymer networks in various solvents) and microscopically rigid systems (e.g. composed of elongated aggregates of molecules - micelles). The fluid viscosity in the cell depends actually not only on the intracellular structure but also on the size of the probe used in viscosity measurement [26]. It is under research a novel method to characterise cell structure such as cancer cell - by measuring the viscosity of the cytoplasm [26]. In the future, scientists can now better estimate the migration time of lymphocyte toward tumor tissue through viscosity factor. The viscosity of ECM (extracellular quality) in tumor tissue (Tumor tissue) viscosity) is higher than normal tissues, So, Lymphocyte is difficult to move to the tumor tissue. It should be lowered the viscosity of the tumor tissue for improving the accuracy of lymphocytes to attack cancer. Hypothermia, controlled or accidental, may significantly compromise host defenses. Hypothermic (30 to 34°C) rabbits have a diminished inflammatory response to an intradermal challenge of bacteria due to the effect of hypothermia on leukocyte migration [27]. Hypothermia may contribute in another way to the decreased leukocyte migration. Under Lowered body temperature, migration speed of lymphocytes decreases, also, the number of circulating lymphocytes does [30]. Cryotherapy is the practice of using ice to aid in recovery, the migration of pro-inflammatory and nerve sensitizing agent to the area is minimized which aids in reducing pain. Muscle damage is an important limiting factor for muscle performance during the days after intense exercise like soccer players, Post-exercise cold water immersion (cryotherapy) is widely used to treat acute traumatic injury and may be appropriate as a recovery strategy after training and competition that cause some level of traumatic injury [31]. Cryotherapy are also thought to reduce the inflammatory response of damaged muscle.

II. Conclusion

Cell migration is not only significant for embryonic development but also in the development of cancer, It also play a role in cancer development, Tumour-infiltrating lymphocytes (TILs) are often found in tumors, presumably reflecting an immune response against the tumor, But. TILs do not take the dynamics of the tumour microenvironment to prevent cancer development, In near future, Biotechnology would develop tools for a deeper understanding of distribution and migratory pattern of immune cells to kill cancer cell. A future study should be designed to improve the effect of TILs on tumors. The nano-robots use an innovative methodology to achieve decentralized control for a distributed collective action in the combat of cancer [32]. A nano-robot can effectively use chemical communication to improve intervention time to identify tumor cells. Nano-robots with sizes comparable to a cell could provide many novel capabilities through their ability to sense and act in microscopic environments. The development of nanorobots may provide remarkable advances for diagnosis and treatment of cancer and for health care. Nanorobots can help with significant improvement on cell therapy techniques, and unprecedented positive results to save lives. Quantitative understanding on regarding cell migrations would shows how normal cells are driven to disease states. Nano robot that can stimulate the cell to migrate inside the body will open a new world free from diseases.

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