



REVIEW: CELLULAR POLARITY AND ITS STRUCTURAL AND FUNCTIONAL ASPECTS

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ABSTRACT

Animal cells exhibit one of the most common features, the polarity, and this feature reflects on the existence of molecular asymmetries in cells. The basic common molecular maneuver involves its establishment and transduction regardless of type of cell and organism. The prime guiding parameters of polarity are polarity cue (signal), cytoskeletal regulations or adaptations, concerned polarity proteins and the efficacy of transduction of information related to polarity. The basic foundational steps of polarity in different types of cells are either similar or have mechanistic parallels. The establishment and maintenance of cell polarity is important to a wide range of biological cellular processes ranging from chemotaxis to embryogenesis. An essential feature of cell polarity is the asymmetric organization of proteins and lipids in the plasma membrane and the cell organelles. In this article, the role of polarity regulators such as, small GTP-binding proteins and phospholipids, spatially and kinetically control vesicular trafficking and membrane organization is reviewed. Further, this presentation is an effort to understand the role of membrane trafficking in cell polarization through delivery of polarity determinants and regulators.

KEYWORDS: Apicobasal-polarity, axis specification, cell polarity signalling, Crumbs complex PAR complex, Rho GTPases, Scribble complex.

Overall, View on biological Material and Role of cellular polarity

Biological material i.e., cell, tissue, organ or an organism, as a whole is a biological material, it has mass and occupies space, consequently, it behaves like a material of course with modified properties. These properties reflect on it being alive or dead. The biological material exhibits an amalgamation of physical, chemical, biochemical features; one can observe adhesion, cohesion, rigidity, elasticity, plasticity, stochastic features and these affect the behavior of biological materials. During embryonic development biological and physical properties are well expressed and even during the normal live state.^[1,2,3] The elasticity of a biological cell/tissue is its ability to regain its original shape/form after the external force or deforming agent is removed. This process involves active role of cytoskeleton, intercellular signalling, volume and morphology of cell and its physiological state.^[1] The cytoskeleton acts as a physical and biochemical interface for the most of cellular processes and plays regulatory role during mechanical and biological activities.^[4] During intra and intercellular signalling, change in its volume, morphology and

physiological state, influences the cellular elasticity.^[1] The cellular plasticity plays an effective role during changes in the cellular phenotype without genetic mutation. A cell responds to its environmental stimuli/cues and stress conditions. Cellular plasticity is very effective during wound healing, fighting infection and cancerous conditions (metastasis).^[2]

Dynamisms is a prominent feature of a living being. It is directional in nature with respect to the stimuli/cues received, analysed, and as per the decision to its response. Each biological cell has a remarkable features like self-assembly and self-organization; these processes are responsible for the formation of all cellular structures that are needed for its functionality. Cellular dynamism involves self-organized molecules and functional structures; their maintenance and interactions towards thermos-regulatory and molecular physiological balance. These molecular interactions are based on genetical regulation.^[5] Another aspect which sustains dynamism of living being is feed-back system, positive and negative both. The stimuli may be physical, chemical, environmental in nature either external or internal. The

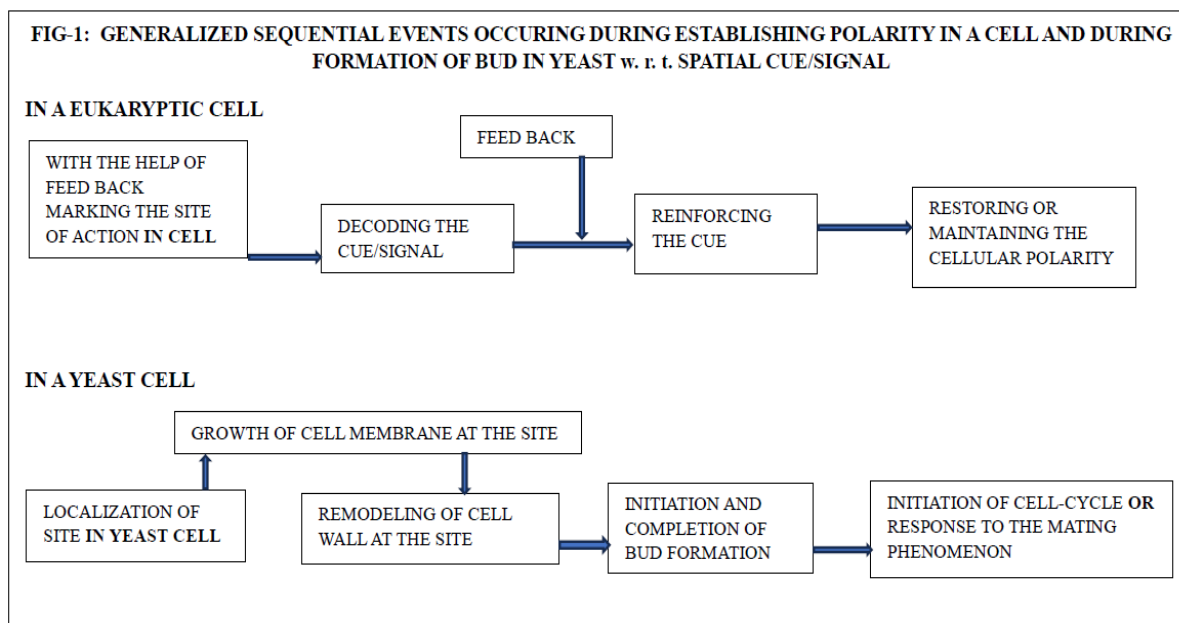
living entity has potential to perceive these stimuli and carryout response which help to maintain its dynamism. The dynamism may result in biophysical, biochemical, structural and functional changes and expressed as a change in shape, structure and function; all these fluctuations are within certain limitation that ensure approximately normal frame work of the living-being. If these alterations go beyond the limits, these may result in cellular dysfunction.

Cellular polarity is the representation of organization of proteins and lipids in a given cell and its components. In a cell, the spatial and kinetic nature of biomolecules like small proteins like GTP binding proteins and phospholipids present in a cell membrane play significant role in establishing its cellular polarity and ensure the wide range of biological processes like from chemotaxis up to vascular trafficking and embryogenesis.^[6] Initially, the prime factor for a cell is establishment of polarized state of a cell which may change subsequently in later stages as per the need. It is of common observation that a cell has an ability to alter its polarity dynamically, i.e., it has an ability to reverse its polarity in response to the extrinsic and intrinsic cues or stimuli. This feature reflects on the concept of controlled mechanism and the process of fluctuations in a cell polarity. There appears to be two stages of cell polarity, broken-polarized and polarized stages. The process of symmetry breaking relates with the loss of symmetry along a particular axis. The symmetry is prerequisite for attainment of cellular complexity.

Polarity, in a biological system represents the distinction of poles along an axis. This type of orientation is the first step for embryonic development to assign dorsal, ventral, anterior and posterior sides, lateral sides of a spherical egg, prokaryote and a eukaryotic metazoan. When a non-

polarized cell undergoes polarization the breaking of symmetry takes place i.e., a process in which uniformity is broken or disturbed or loss of symmetry along a particular axis or function in order to establish polarity. During embryonic development the breaking of symmetry occurs and polarity gets reestablished in an embryonic cell. This reflects on the possible changes in cellular polarity and reorientation in the arrangement of polarity protein molecules. The process of breaking of symmetry is regulated and can takes place spontaneously or instinctively. This process exhibits variation in different types of cells. Generally, its mechanism involves the signalling system based on the conserved G-proteins and uses multiple feedback activity resulting in the asymmetrically allotting on the membrane of cell following 'Turing distribution'; (In biological system, a reaction and diffusion always taking place, under this condition the uniform state changes in to new ordered configuration. This change represents a condition of linear dynamics, in this dynamic process an unstable equilibrium is attained). Thus, in a functioning of a biological system, one can observe a normal physiological stable state changes in to unstable state and this whole process attains the state of unstable equilibrium.

The cell polarization phenomenon exhibits three motifs, namely positive feedback, mutual inhibition and/or the combination of these processes.^[5] There is a possibility of incorporation of negative feedback also. Since, living cell is always in a dynamic state, it essentiate to understand the concept of dynamic equilibrium in any life process. The eukaryotes like migrating neutrophils, amoeba, and melanoma cells (Melanocytes are the pigment containing skin cell undergoing cancerous condition) have shown variety of changing patterns.



The technique 'chimera-geneses of chimera, proteins are encoded using homologous chimera-DNA (c-DNA), appears to be suitable mode of investigation and manipulation of c-DNA sequences. Basically, this resembles closely the corresponding natural process. This reflects on the applications of such technique as 'tool-kit of chimera proteins' to understand the mechanism of cellular polarity.^[7] Further, yeast cells are suitable for such investigations. It is practical to consider phosphatidylinositol triphosphate (2,4,5, PIP₃) a chimeric molecule, as its synthesis and degradation are useful in such studies.^[8] Cellular dynamic processes such as cellular functionality, cell types, genetic makeup, environmental impacts, migration, of neutrophils, protozoan, and movements of other cells within body fluid are under the influence of the cellular polarity. The changes occurring in a cell and its specific environment release some signals and these affect the cellular polarity. These signals/cues may be directional or non-directional.^[9,10,11] A living cell is effectively responsive to its internal and ambient environment. This cellular feature reflects on its ability to receive and behave accordingly to any change, stimuli or cues in its self and the surroundings. These are internal and external cues and function in gradient manner. Broadly, the external signals or molecules reach target cells, this is termed as 'chemotaxis'; the internal signal or molecules that induce response and is known as 'chemotropism'. These direct the target cell to the origin of signals/cues. There is a controlled cytoskeleton dynamics occurring during cellular migration within the internal cellular environment and plays a significant role during cellular migration with the body of an individual. The specific protein control and autocatalytic mechanism within a cell membrane, control this cytoskeleton mechanism. Both these are dependent on the gradient caused during cellular moving in uphill direction. The specific biological control prevents any discrepancy arising due to the gradient sensing between the competition among the internal and external cues and this also likely to affect the process of polarizing due to self-amplification and gradient sensing. The internal cues play a significant role during guiding the pattern of division and tracing sexual pheromone gradient that helps in locating the potential sexual partner.^[12] When the signal of chemo-attractants is less intense or absent in comparison to the spatial concentration gradient, cell polarity reverses in neutrophils. There may be some non-directional cues that induce such polarity reversal. The mechanism of such behavior is unknown.^[8]

The improper arrangement of constituent biomolecules of cell organelles and participating in cellular mechanics result in loss of symmetry and inability of cell to perform its designated functions.^[13] There are some of the key molecular-players that primarily come under the influence of PAR proteins. These proteins are encoded because of *par-gene*, and these are concerned with cytoplasmic partitioning and/or formation of scaffoldings. These proteins are present asymmetrically

and interact among themselves and form physical complexes.^[13]

Tight junctions being intracellular elements and mediate adhesion among the epithelial cells also participate in cell functionality. Specifically, tight junctions regulate permeability across these cells and act as barrier to check the intramembrane diffusion of molecules through the domains of apical and basolateral membranes. Recent investigations reflect on the role of tight junctions in establishing and maintain apico-basal polarity. Proteins playing role in polarization of epithelial cells constitute a multiprotein complex at the site of tight junctions. These protein- complexes play a regulatory role during the polarization process occurring in epithelial cells. Investigation on these proteins as regulatory components may assist to understand the mechanism involved during polarization.^[14]

Cellular polarity is a specific feature that correlates with cell morphology, intra and intercellular normal and specialized activities. This feature also relates with basoapical, unidirectional, anteroposterior and left-right orientation of a cell. These orientations are present in unicellular and multicellular organisms.^[15] Further, cellular polarity is functionally essential in migrating cells within the body of organism, stationary (fixed cells) like epithelial, nervous cells, gametogenesis, fertilization, post fertilizational movements, embryonic development and specific movements within embryo. It is also essential for a cell to response to negative and positive feed-back system. The key molecular participating in cellular polarity are *par* proteins (PAR) as *par genes* express the members of such proteins (PAR-3, PAR-6, a-PKC-a typical protein kinase).^[13,15]

All cells have polarity which acts as bases for some specific shape and functional asymmetry like apico-basal or front-back (anterior-posterior) is one of the common types. Formation of tissue is the result of coordinated integration of such individual cells in the form of multicellular entity like epithelial tube or epithelial lining of tubular organ. Prime core complexes such as 'PAR', 'Crumbs' and 'Scribble complexes' regulate and establish polarity in a cell. Extracellular matrix plays a major role in establishment, orientation and maintaining the tissue-polarity. This tissue-polarity is further controlled because of the specific mechanisms resulting in luminal components in the cases of tubular epithelia. In an organism, 'epithelio-mesenchymal transition' and 'mesenchyme-epithelial transitions' are two primary processes that cause conversion between two types of cell polarity. During cell adhesion transcription factors, extracellular matrix and polarity coordinate in this process.^[16,20]

Molecular basis of cellular polarity

In case of metazoan species, a large number of molecules which help and regulate cellular polarity are preserved in variety of cells at the specific site. Golgi apparatus is the

prime site of protein synthesis and the polarity proteins are no exception. Even the cytoplasmic proteins and the cell membrane proteins are recruited in this process. The polarized vesicles transport the synthesized proteins at the Golgi apparatus to the site of requirement like either for storing or for preserving cellular polarity. Some of the common protein complexes participating in cellular polarity are PAR complex, Crumbs complex and Scribble complex. The PAR complex includes PAR3/ASIP, PAR6, Cdc42 and atypical protein kinase-C. The proteins like Crb, PALS, PATJ and Lin7 come under Crumbs complex. Proteins such as Scrib, Dig, and Lgl are the members of Scribble complex.^[17,18,19,20] These polarity complexes are present on the cell membrane facing cytoplasm within a cell. Generally, in case of epithelial cells, complexes like PAR and Crumbs are present on the cytoplasmic side of apical wall while Scribble complex is on the lateral cell-wall facing cytoplasm.^[19] There are some common signalling molecules such as Rho GTPases, that help in the functioning of controlling vesicle transport as well as the location of cytoplasmic proteins. This is attained adopting regulated phosphorylation; in this process the phospholipids are involved and results in the formation of phosphoinositide. The 'phosphoinositide' act like docking sites for cell membrane proteins and these molecules after phosphorylation help to find appropriate binding protein.^[6]

Initiation and Establishment of cellular polarity

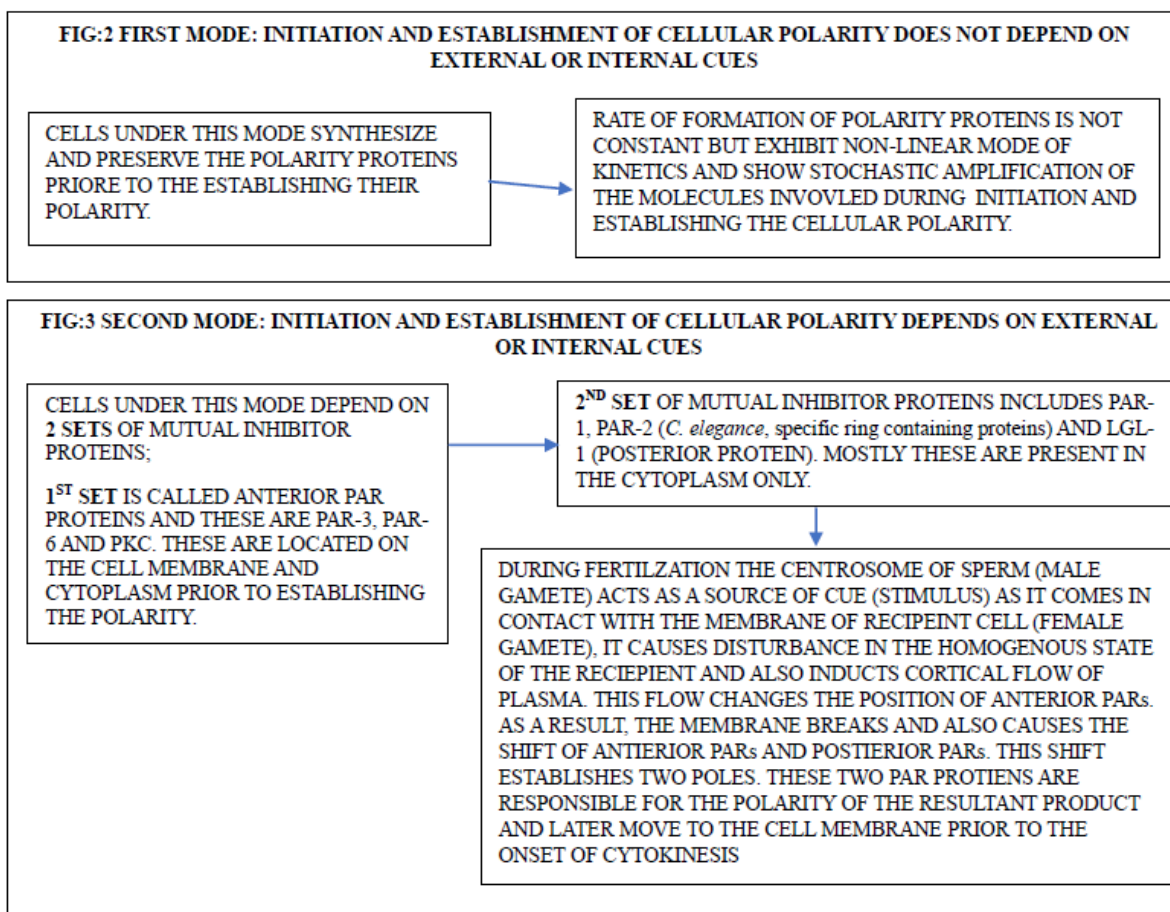
A morphogen (signalling factor) is a signalling biochemical molecule which stimulates a cell and enables it to respond to form a particular pattern; its effectiveness is directly proportional to its local concentration.^[21] Morphogens relate with gradation (successive changes) and help in interpretation of gradation. These are responsible for the signalling network and feedback processes during morphogenesis, help in regulating growth in daughter cells and embryonic development.^[22] Some of the morphogens have been identified and these are Hedgehog (Hh), bone morphogenetic protein (BMP), Decapentaplegic (Dpp), Bicoid Dorsal (Drosophila), sonic Hedgehog (SHH), fibroblast growth factor (FGF) and Nodal (vertebrates). Generally, the morphogens are transported via diffusion, ferry with the help of proteins, using exosomes and exovesicles, or transported with help of cellular projection called cytonemes.^[22,23]

There appears to be some similarity between the mechanisms of formation of pattern in a multi-cellular system and intracellular pattern.^[24] Such interaction network involves two or more chemicals and follow some type of kinetics and differential diffusion, and changes in stochastic concentrations. These help to attain the large-scale stable pattern and this process results in spanning a molecular length scale up to cellular scale or tissue scale.^[24] The morphogens-a system of molecules, interact among themselves and diffuse from

the tissue; these processes pave a way for completion of morphogenesis.

Initially, the concentration gradient of morphogens is homogenous, in due course of time it tends to exhibit unstable homogenous equilibrium. The process of diffusion and random disturbances result in the formation of some pattern. The diffusion and the process of interaction, both processes together may be represented as 'isolated ring-of cells', it becomes convenient to understand mathematically while biological system become unusual and complicated. The suitable examples are arrangement of tentacles of Hydra, whorled leaves on plants, or spherical cells arrangement in pre-embryonic stages like blastula, gastrula. This phenomenon appears to be a conglomeration of principles of physics, biology and mathematics.^[25] Establishment of some specific spatial pattern is prerequisite for the onset of morphogenesis. This establishment of spatial pattern initiates from homogenous precursors. This process depends on short-range-activation, long-range-inhibition, well differentiated concentrations of inhibitors and activators along with their densities of their respective sources. The source density declines as the cell differentiation proceeds even the activators and inhibitors density can also change due to fast diffusion or being exhausted or degraded. During this cellular functionality primary pattern gets established. During these biomolecular activities morphogens set the specific cellular polarity prior to the pattern establishment.^[24]

Primarily, there are two main modes of initiation and establishment of cellular polarity. One type/group of cells that develop polarity spontaneously on their own. The other group of cells develop and establish cell polarity with respect to the cues from their ambient environment or as an inborn capability.^[26] The polarity proteins are synthesized, and preserved in a cell prior to the process of establishment of its polarity. One may say that this feature is the basic and prerequisite for the initiation and establishing cellular polarity. The process of formation of polarity proteins does not show a constant rate of change i.e., the formation of polarity proteins cannot be represented by a single straight line when plotted in a graph. Hence, the formation of polarity proteins exhibits non-linear mode of chemical kinetics and involves the amplification of stochastic fluctuations of the molecule involved (Fig-2).



The second mode of establishment of polarity depends on either extracellular or intracellular cues. Two sets of mutual inhibitors proteins play main role in maintaining polarity, one set includes PAR-3, PAR-6 and PKC, (these are termed as anterior PAR proteins). These are present on plasma membrane and cytoplasm before disturbing cellular symmetry. The second set includes PAR-1, PAR-2 (*C. elegans*-specific ring-containing protein), and LGL-1 (posterior PAR proteins), mostly, these are present in cytoplasm only. During fertilization the centrosome present in male gamete furnishes a cue (stimulus) that disturbs the homogenous state of the morphogen, this involves the induction of cortical flow that affects the allocation of anterior PARs which in turn results in breaking the membrane. Further, these changes, transfers or shifts the anterior PARs to one side towards posterior or another pole. These two PAR proteins retain the polarity and later these are mutually displaced from their position on cell membrane. This exclusion is attained prior to the on-set of cytokinesis (Fig:3).^[27,28]

The mechanism of switching of signal-induced polarity complex pertaining to proteins, is explored on mathematical model. This switching process is accomplished in four general classes of switching mechanisms and these are qualitatively expressed in distinct behaviours. These classes are transient oscillator switch, reset switch, prime release switch and the push

switch. Basically, these mechanisms function like the principles of 'spatial toggle switch' but their non-linear and stochastic dynamics exhibit different characteristics.^[8]

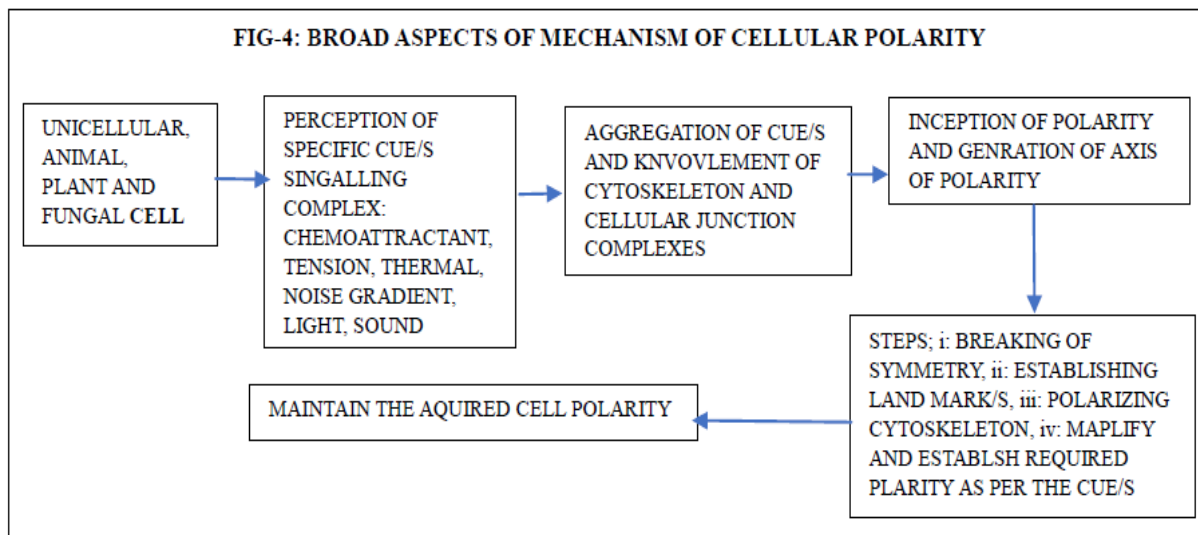
Mechanical disturbances have potential effects on the symmetry breaking process. During polymerization of actin-network the internal tension gets disturbed and causes impulsive destabilized state in a cell. This also affects the cytoskeletal set-up which facilitates the intracellular transportation. The reorientation of actin cytoskeleton, during this process impacts the organization of microtubules, orientation of spindle along the axis of cell polarity, transport of vesicles and their docking. The process of reorientation of actin cytoskeleton also causes local growth of membrane at the site of land-mark. These molecular eventualities cause asymmetry in shape, the cell polarity and enhance distribution of anisotropic mechanical stress that may result in mechanical feed-back process and eventually reinforce the polarity of the cell under consideration.^[29]

Basic insight into the mechanism of cellular polarity

Cellular polarity is an established phenomenon. It is accomplished in four phases, namely, breaking symmetry, establish a land mark or landmarks, polarizing of cytoskeleton and to amplify and maintain the polarized state. Cells exhibit structural and functional diversity but the basic mechanism of cellular polarity

seems to be effectively conserved in both unicellular as well as multicellular systems including animals, plants and fungi. The cellular perception of specific signalling complex initiates a series of activities along with in marking of the 'land-mark' very close to cell membrane; the GTPase family biomolecules belonging to Rho-family assemble at the land-mark. (Such land marks can be seen as bud scar in budding yeast cell, among epithelial cells site of cell-cell adhesion, in plant cells

apex of pollen tube and progressing mycelium or hyphae). The signalling complex can arise from a chemoattractant or a tension or noise gradient. These cues aggregate and involve the cytoskeleton and junctional complexes, specifically, in case of epithelial cells among animals. These activities affiliate the process of inception of polarity cue that generates the axis of polarity all through the cell (Fig-4).^[29]



Basically, how 'cell polarity' initially becomes polarized in symmetrical manner and how it is maintained in a cell, seems to be a prime question. Subsequently, these cells change the polarity in response to the external and internal cues and control their functionality. The hunt is for a reliable mechanism that explains the switching of cellular polarity.^[30] The process of polarization plays a major role in breaking the cellular polarity in cases of budding yeast, epithelial cells, even angular continuous symmetry and discrete symmetry in rod-shaped bacterial cells.^[31,32] Symmetry can also be disrupted spontaneously,^[33] and it can be regulated due to upstream guiding cues and noise.^[34,35,36] There is a possibility that different organisms exhibit different molecular mechanisms of cell polarization but basically incorporate conserved G-protein based signalling system depending on feed-back interactions. This mode explains asymmetric distribution on the cell membrane following 'Turing instability'.^[37] 'Turing instability' deals with the formation of pattern in a reaction-diffusion system, specifically, when the reaction and diffusion cause opposite impacts on the stability of the uniform state. When diffusion is introduced in a stable system (having no diffusion) result in the formation of systemized configurations similar to spots or stripes).

Growth and migration are among the prime functionalities of a living cell. During these functions a 'dynamic front' or more appropriately 'polarity site' develops and is capable of changing direction. During the formation and establishing of polarity site, there is an

aggregation of polarity regulators such as conserved Rho-family GTPase Cdc42; this process is autocatalytic in nature. The mechanism involved during this process of polarity reorientation is not very well understood.

While investigation using yeast, *Saccharomyces cerevisiae*, as model, the polarity reorientation is observed in two potential mating yeast cells partners and active role of polymerized actin, is an important player. The process of polarity reorientation associates with 'actin-mediated vesicle traffic' and reaching the polarity site. Debraj and Daneil, 2020.^[38] investigated this process involving mechanistic computational model in combination with 'polarity protein interactions' and 'vesicle trafficking'. They observed tight spatial focusing of exocytosis elevate the directional persistent movement and this itself associates with Cdc42- directed GTPase activating proteins. The increased secreted vesicle in relation to the distance travelled. Further, the corelation between varied rates of exocytosis and polarity site movement help to understand the complexity of cellular polarity under different functionality; generally, this phenomenon follows simple 'Poisson dynamics' *in vivo* investigations.^[38] (Simple 'Poisson dynamics' provides description related to mass density distribution relationship corresponding to gravitational force or electrostatic field or force).

Cell polarity is vectorial phenomenon and corelates with cellular asymmetry and any type of suitable cue. This concept is applicable to unicellular organisms also. In the

cases of multicellular organisms, the cellular polarity of stem cells (cell signalling dependent) and pre-pattern of polarity plays significant role during embryonic development. The embryonic processes like, cleavage, blastulation, gastrulation, organogenesis and activities of tissues depend on the cellular polarity. The direction of migration is another parameter that relates with cellular polarity. The fate of cell and during cell division the cues concerning asymmetry of intrinsic polarity plays decisive role. Thus, cell polarity exhibits sense of direction and an evolutionary aspect.^[39]

Cellular movements and cellular polarity

Generally, for successful and purposeful movements of cells, some type of cue or stimulus is prerequisite. These stimuli (cues) are external, inter and intracellular in nature. A biological cell has an ability to detect most types of cues, receive, analyse and deliver the suitable response. Further, the environmental cues may be thermal, light, sound, mechanical, chemical, and physical in nature. There are chances that some changes in the cellular polarity, at least in sensory cells on reception of stimuli take place. The common chemicals that influence the orientation of the receptor cell and the causes of chemotaxis. This cellular reorientation or /disturbance affects the cellular polarity; some biomolecules that act as chemical stimuli are cyclic-AMP (c-AMP), N-formyl-methionyl-leucyl-phenylalanine (f-MLP). Cells are very sensitive, even to very dilute chemical gradient of around 2% can induce macroscopic intracellular changes and its polarity. The chemotactic procedure in biological cells also involves some principles of physics, specifically, during the molecular association and dissociation (binding and unbinding of molecules). These are stochastic functions and are sensitive to respective interactions, even processes like subsequent recognition of gradients, internal pathways occurring, can be readily addressed statistically in physical terms. Even the concomitant cellular polarization is better expressed and analysed as the extended non-linear interactive diffusion models.^[40]

Since, a biological cell exhibits cellular elasticity depending on its shape, adhesive ability and physiological state, there are ample chances of its polarity being affected. More so during its directional migration; during directional migration the forces develop which influence the cellular elasticity and the cellular polarity.^[3,41,42] Cell migrating in body fluid or fixed forming a tissue face biochemical and organismic cues/stimuli and the cell itself exhibits chemotactic behavior. This cellular physiological manoeuvring affects cellular polarity.^[41,42] The body fluid works on the basic principles of fluidics-microfluidics *in vitro* and *in vivo*. These principles of microfluidics impact cellular chemotactic behavior. [Microfluidics involves flow of fluids in microchannels (tens to hundreds of micrometers) and laminar flow, large surface to volume ratio, heat and mass transfer rate and the faster rates of reactions. Microfluidics have two systems: micro-

channel systems, scale of vessels range: around tenth of a μL ; and micro-vessel systems, scale of vessels range: maximum width 300 μm). The relative influence of forces like Reynolds (Re), Peclet (Pe), Capillary (Ca) and Weber (We) numbers; the characteristics flow pattern etc.].^[43]

Plasma membrane and its tension influences the cell migration and cellular polarity. The role of membrane tension with respect to controlling of assembly of actin needs better understanding. The 'Formin Bending Protein-17' (FBP-17) is a membrane bending protein (FBP-17) and member proteins of Wiskott-Aldrich Syndrome protein (WASP) play active regulatory role in inducing tension and bending of plasma membrane. The Wiskott-Aldrich Syndrome protein activate Arp2/3 complex (actin related proteins) regulates polymerization, organization and recycling of actin-filament net-work; it also activates nucleation of new actin filament. Both the membrane bending protein and nucleation of actin nucleation enhance the plasma membrane tension. This membrane tension brings about the formation of leading edge in the migrating cell. The membrane tension declines at the rear end of the migrating cell as the membrane tension increases at the leading edge of the migrating cell. As the tension decline on the plasma membrane FBP 17 spread in random manner throughout the cell and there is a loss of assembly of polarized actin. There arises a need of actin protrusive force due to polarized accumulation. This interaction suggests that FBP-17 is required for activation of WASP during the formation of tension on the plasma membrane. It has been seen that there exists a correlation between the activity of FBP-17 and the membrane tension and it is dependent on the tension on liposomal membrane tension.^[44,45,46] During the migration of neutrophils, the signals are confined to the leading edge and membrane tension ensures this feature. It is postulated that there exists a 'constant rate of production of molecules in a given volume per unit time' and it functions following 'first-order degradation rate'. The physical parameters like shape, stretched or severed state do not influence these interactions. The molecules formed are in unpolarized state and are within the cytosol. In a migrating (moving cell) rate of polarization varies in leading half and the dragged half of the cell. The molecules in the cell can move in these two compartments. One may assume that molecules exchange between these two halves (compartments) of cell based on Ehrenfest model of diffusion. This intracellular molecular movement follows the dumbbell shape geometry.^[47]

There is a correlation between spontaneous breaking of symmetry and the induction of actin-based mobility. In case of epithelial cells of fish (the keratocytes) in stationary state the actin-net-work moves inwards and show radial symmetry. Keratocytes are the basal epidermal cells of fish; these cells are suitable to investigate cellular migration; These cells acquire

stereotyped shape and show large fan-shaped lamellipodium and the remaining cell appears to very much like a spherical body. These cells move in the direction of injury and while doing so these adopt two-dimensional confinement while these are between outer epidermal cell layer and the basement membrane. While undergoing migration these cells exhibit 'front to back axis.' As result in a lamellipodial ruffling (47a-Labus et al., 2023). On the on-set of directional cellular movements in these cells, the rate of flow of 'actin-network' elevates in the back half (rear-half) and the orientation remains concentrated at the perinuclear zone of the cell. This interaction takes place in the alignment to the anticipated axis of the direction of cellular movements. The fluctuations in the flow of actin-network can be seen only after the completion of polarization in the cell under study. The inhibited action of myosin-II or Rho kinase disrupts the orientation of the said net-work, flow in the perinuclear zone and reduces the rate of motility initiation in the cells under study. The elevated rate of activities of myosin-II along with calyculin-A increase as the rate of initiation of frequency of motility. When the stationary cells are treated with calyculin-A, one can observe the induced directional mobility starts away from the site of application (stimulation) calyculin-A. Thus, it is seen that there is a reorganization of large-scale- actin-myosin-network and shrinkage in the rear-half of the cell suddenly initiates breaking of symmetry motility due to the polarization in these epithelial cell understudy.^[48]

Mechanical cues developed due to the flow of fluid, fluid flow caused using micropipette or forces induced due to cadherins or electric field or cell migration under wound healing process affect the cell polarity. Generally, when cells get mechanically stimulated their polarity changes and this change prevents the cellular actin polymerization. The rate of cellular polymerization at the front region and the powerful gradient of the chemoattractant cyclic-AMP plays important role to bring about reorientation in the cell.^[49] When the cells undergo collective migration there is a need of adhesive contacts among the cells, coordinated protrusion among polarized cells, and development of propulsive traction forces. It has been seen that the degree of mechanical force used locally to C-cadherins is strong enough to cause protrusion in concerned polarized cells and persistent collective migration of the cells. The mechanoresponsive cadherin-keratin complex of the cell plays a significant role in polarized protrusive response and also promotes collective cell migration.^[50] When moving cells experience field of electric current get reorient and move along the direction of the electric current; this cellular response is known as 'galvanotaxis'. The cells seem to follow a hypothesis that relates with redistribution of the molecular components of the membrane in accordance to the electric field and this process is called 'electrophoretic redistribution'. This molecular redistribution of the membrane is in response to the electric field the cells encounter. Under these

conditions, the intracellular signalling mechanisms transduces the molecular polarization in the membrane and this sets up canonical induce chemotaxis which directs the cells to migrate in specific direction.^[51] The migrating cells exhibit 'durotaxis', a change in migrating behavior due to the hardness of substrate. The cells either retract or turn around on reaching the boundary of the substrate; the polarized cells make an effort to shift mechanical strains towards the front (progressing phase) from the rear (drag phase) while manipulating flexible substrate during migration. This feature reflects on the possibility of some correlation between cellular polarity, rigidity and strain of the tissue (concerned) while cell is performing normal and any pathological or immune interactions.^[52,53] In plant cell, having rigid walls, 'auxin' a plant hormone appears to be associated with cellular polarity which in turn plays significant role during cell division, growth and development. Computational models are very useful in elaborating cellular polarity and its role during cytological investigations in normal and pathogenic conditions along with immunological interactions.^[53,54] PAR-kinases are the functional requisite for polarity establishment in cells having diverse types such as epithelial cells arranged laterally. The PAR-1 transduces after binding 14-3-3 proteins in its phosphorylated substrate, its mechanism is not clear. The polar protein complex 'SCRIB' is asymmetrically present in dividing cells. This protein complex decides the fate of cell and mediate growth factor signalling in active satellite dividing cell; this protein complex is very essential in case of muscle regeneration.^[55, 55a]

Cellular polarity in reproductive cells

Testes are the site of production of sperms and also for endocrine functions. Its polarized state is of physiological significance. Earlier, the polarity proteins like PAR (partitioning-defective) based complex consisting of Par-3/Par6/aPKC (atypical protein kinase-C (Cdc42) play a major role in maintaining the polarity of gamete and testis. Later investigation proves that proteins like Scribble/Dlg-1(Disc large-1) Lgl-2 (Lethal giant larva-2), Crb-3 (Crumbs homolog-3)-based complex are also playing significant role in the polarity of testis as hole.^[56]

Sperms are cytological functional products of highly physiologically active testis, from reproduction and endocrine aspects. The structural and functional components of testis are germinal epithelial cells (lining of seminiferous tubules, forming stages of spermatogenesis), Sertoli cell (site of spermatogenesis) and Cells of Leydig (endocrine site). Germinal epithelia of seminiferous tubules are basically dedicated to produce sperms. As the stages of spermatogenesis mature, which move from peripheral zone to central zone but remain in communication with Sertoli cells. There seems to be very close association between the polarity of the developing spermatogonia and the Sertoli cells. This reflects on variations in the polarities of the both these cellular components of testis participating in

spermatogenesis. Functionally, in an adult mammal, there is a polarized alignment between the stages of spermatogenesis i.e., spermatogonia, spermatids and the Sertoli cells. Even the organelles like phagosomes, endocytic vesicles, nuclei, Golgi apparatus and of these cells are also polarized. The polarity of Sertoli cells and epithelia of seminiferous tubules play a significant role in the formation of sperms in large numbers during spermatogenesis. The polarity of these cells ensures epithelial cycle of spermatogenesis within seminiferous tubules.^[57] Among mammals, the sperms undergo capacitation, hyperactivation and acrosomes interactions in order to gain ability to fertilize. The sperm has to go through different physiological environments starting for spermatogenesis until it meets the female gamete in the female genital tract. These changes include fluidity of its membrane, activation of soluble adenylate cyclase, enhanced intracellular pH and Calcium ions and development of ability for its motility. To attain all these features successfully, sperms have higher degree of polarization and also have resting membrane potential around -40 mV. This specific feature ensures their ability to adopt readily to the ionic fluctuations of its membrane during its journey up to female genital tract.^[58] There are strong possibilities that male contraceptives like 'adjudin' can disrupt cellular polarity between spermatids (those becoming elongated) and Sertoli cells.^[56] The attachment of the head of the developing spermatids shifts between 90° to 180° but not at right angle to the Sertoli cell as seen in normal case, i.e., alignment state. This shift can take place within 6 to 12 hours of exposure and the separation of spermatids from Sertoli cells. This indicates that such interactions induce functional disturbance in the degree of adhesion due to the disturbance in polarity between spermatid and the cytoskeleton. The actin microfilament suitably gets organized and acts as a favourable interface between Sertoli cell and the spermatid; their molecular set-up is referred to as apical-ectoplasmic specialization and it is conformed using electron microscopy. Possibly, F-actin appears to be incapable to maintain specific orientation of spermatid and the adhesion of spermatid resulting in untimely release of sperms. Further, there seems to exist an active role of proteins of polarity and the organization of cytoskeleton, at least in mammalian cells.^[56]

Spermatids have single cell-polarity as well as multicellular polarity depending on their developmental stage during spermiogenesis. On the on-set of spermiogenesis, spermatids have rounded shape and encounter condensation which results in closely packed genetic materials in head region leading to formation of nucleus. Along with this process, the formation of acrosome also starts and gets positioned next to nucleus. This follows the formation and elongation of tail and a shift of orientation of spermatid. The planar cellular polarity is not seen during early stages but only during later stages; in rat, IV-V stages of the cycle the planar cellular polarity is seen when polarized spermatid alienates across the seminiferous epithelium. There is a

specific interrelationship between head-tail, apico-basal polarity and planar cellular polarity during the developmental stages of spermiogenesis. In all probabilities the functional PARs, CRB3 and SCRIB based complex may react with planar cellular proteins and help to maintain planar cellular proteins of spermatid.^[59]

The Sertoli cells exhibit many biochemical activities during the spermatogenesis (*including their polarity*). The apicobasal symmetry of Sertoli cells of mammalian testis is under the regulatory control of three molecular complexes, namely, the PAR-3/PAR-6/aPKC complex, the Crumbs (CRB3) complex and the Scribble (SCRIB) complex. The PAR-3/PAR-6/aPKC and the CRB3 complexes are present in the cell junctions and the apical membrane of the cell while SCRIB complex is localized baso-laterally in the cell.^[60,61,62] The Sertoli cells undergo many changes in the expression and positioning of Sertoli-specific proteins which are helpful in their physiological supportive role with reference to the stage of germ cells during spermatogenesis. Some of the main changes include, the activity of anti-Mullerian hormone declines in the matured Sertoli cells, GATA (DNA-binding sequence (A/T) GATA(A/G), which is recognized by the zinc-finger domains common to all family members. GATA is a family of transcription factors and have six members GATA-1 to -GATA-6) are the transcriptional factors that relate with the specific binding proteins; the activities of each member vary during spermatogenesis in the Sertoli cells depending on the specific stage of germ cell within the tubule.^[63] There is a shift of androgen receptor within the Sertoli cell; these are produced in the cytoplasm of interstitial cells and get shifted to nucleus at maturity.^[64]

Apico-basal polarity concept is present in an ovum. The apical membrane faces towards out-side of the body surface or and the basolateral membrane faces away from the lumen of the internal organs. The zone of an oocyte having nucleus is animal pole while other one is vegetal pole. Quite often, the nucleus of ovum is also referred to as germinal vesicle. To start with, prior to the inception of polarity in egg or female gamete, the actomyosin cortex develops uniform contractability. The PAR protein complex (PAR-3, PAR-6 and aPKC (atypical protein kinase) also gets uniformly distributed in the cortical zone of the oocyte (gamete). The centrosome of the interacting potential sperm acts as a cue (signal) and microtubules grow simultaneously. As these grow the actin and non-muscle myosin-2 (NMY-2) starts reducing in the back zone (posterior zone) of the resultant structure. There is a movement of the actomyosin cytoskeleton in the anterior direction and it moves PAR-3 complex in the anterior zone. As the PAR-3 complex shifts the PAR-2 couples with smooth inactive or dormant posterior cortex. Basically, PAR proteins act as a regulatory component during the activities of polarization like cytoplasmic asymmetries,

positioning of mitotic spindle in the posterior region and timing of cell cycle in the daughter cells.^[65]

Generalized mechanism of regulation of cellular polarity

Cellular polarity is an integral cellular phenomenon and is associated with structural and functional aspects of cell. This cellular feature inculcates the ability of a cell to maintain and manifest its biological and functional integrity and identity. Variety of interactions among the various protein-complexes and the cob-web of signaling pathways orchestrate the phenomenon of cellular functionality.

The concept of cellular polarity looks for some basic parameters or agents that cause breaking of symmetry which initiates establishing polarization of cell in different conditions, strength of polarity in different cells like neutrophils, Dictyostelium etc; the adaptability of cellular polarity responding to the cues of broader spectrum of gradient sensing, phototactic, chemotactic, and planar cell polarity among tissues. Unsuitability of the polarity and to adapt new polarity during collective migration, cellular defects and on the onset of pathogenesis and possibly the specific cues that may help to find cures for such phenomena.^[53,66,67,68,69]

The polarity complexes like Crumbs (CRB), Scribble (SCRIB) and partitioning defective complex (PAR) play major roles in almost all aspects of establishment and maintenance of the cellular polarity. The process of regulation of cell polarity appears to be obscure with respect to the relevant molecular working up-stream of these polarity complexes, conscription of these molecules, the parameters that enforce the interactions of these complexes and their agonistic or antagonistic nature. Further, the role of their spatiotemporal characteristics during their interactions under various physiological cellular conditions, such as, directed migration, asymmetrical cell division and immunological interactions.^[70]

The ability of cell to polarize in different functional and physiological conditions is remarkable; but the mechanism involved is quite intrigued. The recent literature reveals the related investigation based on the principles of experimental biology, biochemistry, biophysics, computational biology, and mathematics. A cell is known to respond with respect to chemical, physical, light, electrical stress, ionic influx and pH related cues/stimuli; while doing so its polarity also changes as per the need.

A cell under migration experiences tension on its membrane and this tension acts as a mechanical stimulus. Macrophages are good examples that exhibit migration as these cells act against inflammation and infection involving chemotaxis and phagocytosis. Macrophages form an actin-based membranous 'podosome' while fighting inflammation and actin-based membranous

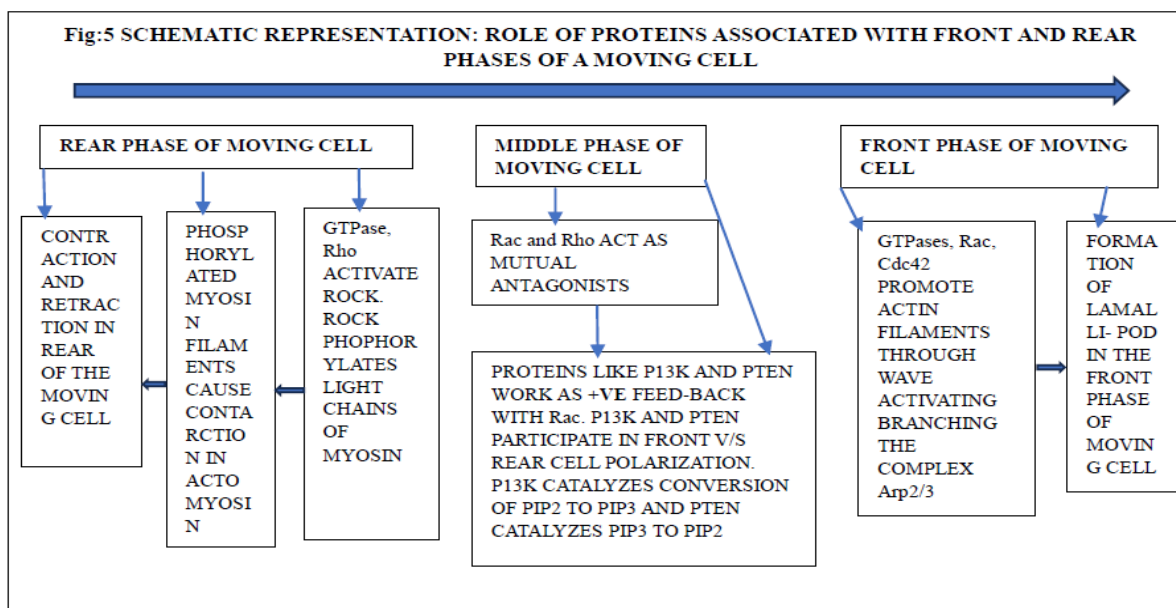
structure the 'phagocytic cup' during phagocytosis for ingestion of foreign bodies. Wiskott-Aldrich syndrome is a X-linked immunodeficient disorder; individuals suffering from this Wiskott-Aldrich syndrome do not have the specific proteins 'Wiskott-Aldrich syndrome proteins (WASP) that facilitates the formation of either 'podosome' or 'phagocytic cup'. The 'Formin-binding proteins-17' (FBP-17) utilizes Wiskott-Aldrich syndrome protein (WASP); the specific protein to Wiskott-Aldrich Protein-interacting protein (WIP) and dynamin-2 participate in the formation of podosomes and phagocytic cup during fighting inflammation and immunodeficient interactions. Thus, FBP-17 (distributed throughout the cell) causes structural changes in the plasma membrane and polymerization of actin, both these processes take place simultaneously; this interaction acts as a step in the formation of podosomes and phagocytic cup. Thus, these molecular changes act as potential contrivance in the WAS deficient individuals which have recurrent infection.^[71]

Whenever tension is exerted on plasma membrane during cellular migration, a membrane-bending protein FBP-17 and stimulator for WASP/N-WASP related actin nucleation is initiated, these also behave like a plasma membrane sensor and play major role in the formation of leading edge of a migrating cell. The FBP-17 is present in higher concentration at the leading edge as compared to the rear edge, thus, its intracellular distribution become non-uniform. When there is no tension on plasma membrane this condition changes and FBP-17 gets distributed throughout the cytoplasm; this condition also results in the loss of polarized actin assembly along the plasma membrane. There is a dependency of FBP-17 as a local stimulator for polymerization of actin and in the presence of tension on plasma membrane inhibits the polymerization. This impact is a part of feed-back system.^[46]

A cell has an ability to establish a vigorous, strong and favourable cellular polarity even when the concentrations and gradient strengths change of chemoattractants.^[72,73] Possibly, the faculty and potential of adaptation to establish a mechanism which ensures the concurrent triggering of activating and inhibitory signals. Further, such mechanism helps a cell to establish cellular polarity even when the activator is local and the inhibitor is functional globally having wide range of gradient criteria. This mechanism related to 'local excitation and global inhibition (LEGI)' appears to have stronger impact on cellular polarity theoretically as well as experimentally.^[74,75] A cell exhibits specific 'cell polarity grids' that works in accordance to localized and fast-spreading components. The active participating proteins forms spread spatially at slower rate in comparison to the fast-spreading participants. This may be because of the structural and functional aspects of membrane or immobile cellular components. The local and global inhibitors move through cytoplasm relatively smoothly. There is a difference in their rates of diffusion of about 2

to 3 times and it is coordinated with their respective molecular weights (Rappel and Edelstein-Keshet, 2017). Broadly, the pattern of cellular polarity follows the principles of 'Turing-type reaction-diffusion system' of partial differential equation.^[76,77,78] Most cells exhibit 'activator-inhibitor model'. The pattern forming process also depends on the tension on its membrane.^[47] The antagonists such as P13K and PTEN or small GTPase (like Cdc42, Rac and Rho) also act as molecular players in cellular-polarity model formation at least in

mammalian and yeast cells.^[79] Rac and Rho act as 'mutual antagonists called front-back organizers and play role in establishing polarity and behavior of a cell. Currently, Rac or Ras, P13K are accepted as 'activators' related to the 'cell edge cytoskeleton' while WASP/WAVE Arp2/3 help in actin branching nucleation and are recognized as "down-stream effectors" (Fig:5). These participate to promote the assembly of actin and protrusion in a moving cell. The participation of P13K appears to be doubtful in case of chemotaxis.^[79,80,81,82]



Polarity status in erythrocytes

Basically, matured red blood cells (erythrocytes; circulating in blood) are devoid of nucleus, ribosomes, and mitochondria, hence, cannot regenerate, synthesize proteins and are unable to consume oxygen for their molecular needs; mostly, these cells rely on anaerobic respiration. Still these cells are highly specialized functional-vital cells that keep tissues of the body well supplied with oxygen and removes carbon-di-oxide. Their precursors are multipotent hematopoietic stem cells. During erythropoietic process, there is a major elimination of cell organelles and remodelling of the cell-membrane. The mechanism involved is still ambiguous. A severe chromatin condensation and institution of the polarity of nucleus occurs in erythrocytes. This complex process incorporates rearrangement of actin cytoskeleton and clathrin-dependent formation of vacuoles at the site of nucleo-cytoplasmic union and results in enucleation process. All these events are the product of interaction between erythroblast and macrophages that are held at erythroblastic island. Mitophagy-a process in which mitochondria get engulfed with the help of double walled autophagosome. The elimination of other cell organelles is still unclear. Any defect in these mechanisms results in varied pathogenic defects like 'myelodysplastic syndrome', 'leukaemia or anaemia'.^[83] Erythrocytes have well-defined glycocalyx and its interaction with glycocalyx of endothelial cells is also known. Impaired

glycocalyx of erythrocytes and endothelial cells is responsible for many pathogenic conditions.^[84a]

The erythroblast has an established cellular polarity and it depends on the restricted microtubule-dependent activation of phosphoinositide 3-kinase (P13K). The erythroblast undergoes enucleation; during this process the nucleus gets displaced sideways and actin remains localized within opposite side. The dynamic cytoplasm contracts causing pressure in that region and this pressure forms a bud, this bud is the result of push of the viscoelastic nucleus sideways and forms constriction. The P13K forms PtdIns-P₂ and PtdIns-P₃ [Phosphatidylinositol (3,4,)-diphosphate and Phosphatidylinositol (3,4,5)-trisphosphate (PtdIns (3,4,5) P₃), this interaction remains within cytoplasmic region of plasma membrane. The depolymerization of microtubules inactivates P13K and damages the cellular polarity impeding the process of enucleation erythroblast.^[84] The erythrocytes are the product of morphological changes in erythroblasts; these precursors of RBCs have well defined cellular polarity and cytoskeleton. Erythrocytes exhibit wide range of elasticity and plasticity; these features enable them to bend and squeeze through the finest blood capillaries in the blood vascular system and ability to regain original shape and size. The degree of elasticity depends on the shape, adhesive ability, and the physiological status.

During this structural exercise the PAR-proteins in RBCs undergo a change as result of senescence and also while these bend and squeeze through fine capillaries. PAR-proteins relate with the cellular polarity.^[83,84a]

Cellular Polarity and Aging

Aging or senescence is a complex process and concerns with the life of every living being. Survey of literature reveals the close association of senescence in an organism with debilitation of telomere, damage of DNA, dysfunctioning of mitochondria, reduction in the nicotinamide adenine dinucleotides, defective macro and micro-autophagy, fatigue and decline of stem cells; decline of protein equilibrium, persistence of inflammation, disturbed nutrient sensing and eating habits, disorganized inter and intracellular communication and imbalanced internal microbiome.^[85]

The role of cellular polarity impacts senescence because this feature plays significant role in cell morphology and physiological functions. Cellular polarity is ubiquitous molecular biological feature and it influences the physiological status of a cell and an organism. Cellular polarity relates with the symmetrical organization, allocation of biomolecules like proteins, mRNAs, lipids, organelles and cytoskeletal components. Yeast cell, *Saccharomyces cerevisiae*, exhibits cellular mechanism that is more or less similar to higher eukaryotes, hence, it is suitable test organism for the related investigations. Investigations using yeast exhibit that the processes of mechanism of cellular polarity seems to be linked with aging and rejuvenation processes in the daughter cells. [The parameters like polar segregation of affected proteins, impact of 'septin-based diffusion barrier' on 'extrachromosomal ribosomal DNA circle (ERCs)'; (septins are GTP-binding proteins expressed in eukaryotic cells except plants; self-replicating circles of DNA that are derived from DNA), asymmetric inheritance of multi-drug resistance proteins and retrograde protein transport can elucidate on the topic]. The mechanisms involved during asymmetric division of germ and stem cells and the mechanism of rejuvenation in the generation need lot of investigations. The gene associated with cellular polarity and aging deserve more attention regards to their respective roles during cellular polarity and aging and rejuvenation.^[86] Investigations on yeast cells related to aging suggest that distinctly the exocytic vesicles move from mother cell to the bud (future daughter yeast cell). During this movement the bud receives a polarized supply of freshly formed membrane, enzymes related to remodelling of cell wall and m-RNA. At the site of neck formation between mother yeast cell and the bud, a ring is formed and this ring consists of GTP-binding proteins- septins. This cortical ring is a regulatory entry port for the 'pro-aging factors' provided by the mother yeast cell. Generally, the damaged proteins due to oxidative stress and carbohydrate proteins are present in mother yeast cell are in higher concentration as compared to the bud. The efficacy of the ring between mother yeast cell and bud declines as a barrier after many cell divisions (around 25

to 30 division), as a result the daughter yeast cells fail to reorient their clock and show decline in their replicative lifespan and this interaction cause breaking of polarity in bud; under this condition the mother yeast cell and daughter yeast cell cannot be differentiated with respect to their size and these exhibit elevated rate of symmetric division. The asymmetric division promotes the increased rate of population in suitable nutrient-rich media; it rejuvenates the daughter yeast cells. This indicates that the rejuvenation is linked with degree of retention of pro-aging factors in mother yeast cell.^[86, 87, 88, 89, 90, 91, 92]

The actin cytoskeleton plays significant regulatory role in the process of aging in yeast. The gene SPC-1 present in yeast inscribe a small protein regulates aging process and it exhibits homology to the SM22/transgelin present in mammals.^[93] If the actin cross-linking gene SCP-1 gets defective or non-functional, then there is an increase in the actin dynamism, ROS formation declines, and there is an extension in the life-span (more than 65%). When there is a reduction in the production of actin and build-up of actin-aggregation, these elevate the formation of ROS. Further, momentary interruption in the actin cytoskeleton disturbs the asymmetric separation of oxidized proteins. The pro-aging factor present in yeast relates with extrachromosomal ribosomal DNA-circles and also influences actin mechanism effectively as the aggregation of damaged proteins do. The extrachromosomal ribosomal DNA-circles result in progressive increase in the size of the nucleolus and its fragmentation. Unfair or insidious genetic functioning elevates the extrachromosomal ribosomal DNA-circles which in turn reduces the replicative duration of life in yeast. When the expression of NAD dependent histone deacetylase SIR-2 is higher and there is a decline in the ribosomal DNA recombination and extrachromosomal ribosomal DNA-circles formation; this heightens the reproductive phase of life but removal of SIR2 reverses the impact. The role of extrachromosomal ribosomal DNA-circles relates with segregation in mother yeast cell in the presence of septin-based diffusion barrier as it controls the movement of extrachromosomal ribosomal DNA-circles already present in the bud. The specific separation of extrachromosomal ribosomal DNA-circles in mother yeast cell concerns with the existence of septin-based diffusion barrier as it regulates the movements of extrachromosomal ribosomal DNA-circles in bud. The role of septin-based diffusion and actin- and formin-interacting proteins correlate with the life-span of the daughter yeast cell (bud).^[86, 94, 95, 96, 97] There is need of more intense investigation in this aspect of cellular polarity and senescence.

Investigations related to senescence in human include experimentation on cultured fibroblasts; these indicate the declined expression and aberrated polar transport-associated components of cytoskeleton, tubulin and actin bundles. RNA-binding proteins have their significant role in transportation of polarity and the polar proteins and related factors. The proteins like HuR/ELAVL-1

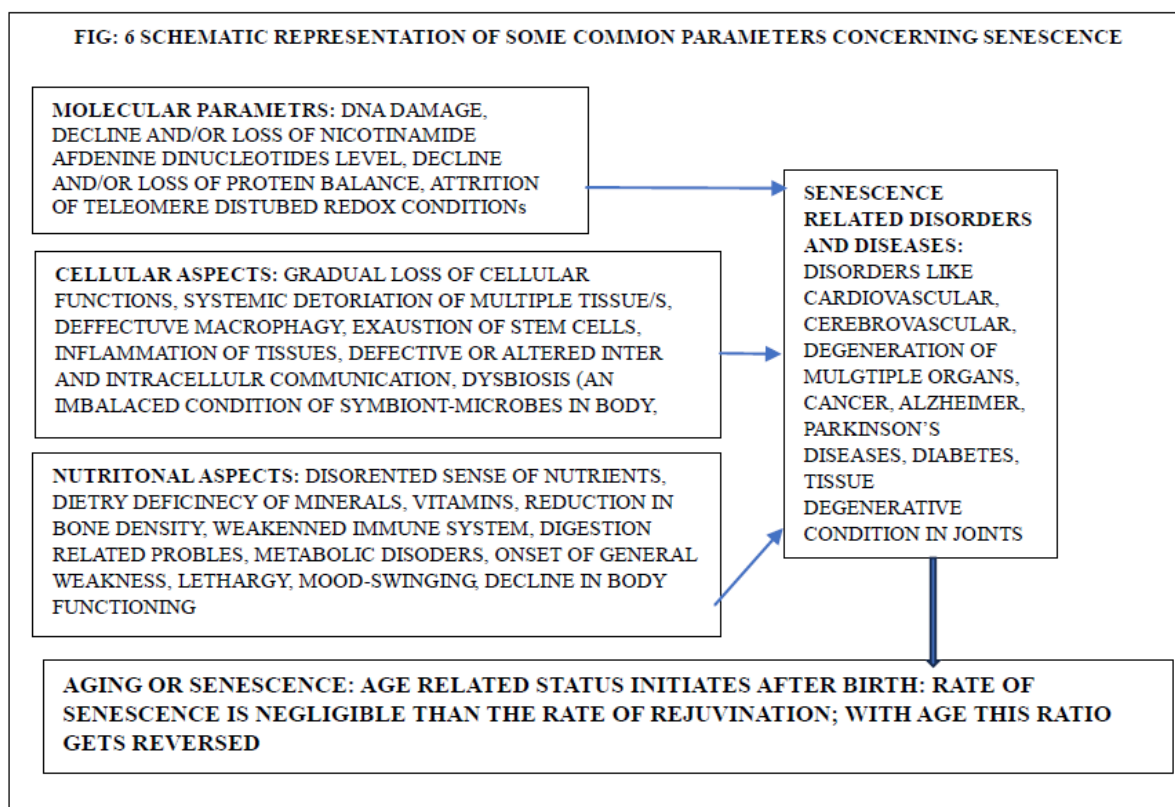
decline in aging fibroblasts. HuR and ELAV-1 come under RNA-binding proteins; HuR- (human Antigen-R); ELAV-1 (Embryonic Lethal Abnormal Vision; Drosophila like-1; these biomolecules increase stability of many LAGs- (lymphocyte activation genes) and anti-inflammatory mediated responses given by the aging fibroblasts.^[85, 98] There appears to be some correlation between the role of RNA binding proteins and the over-expression of Human Antigen-R and ELAV-1 in fibroblasts of older humans and reproductive efficacy.

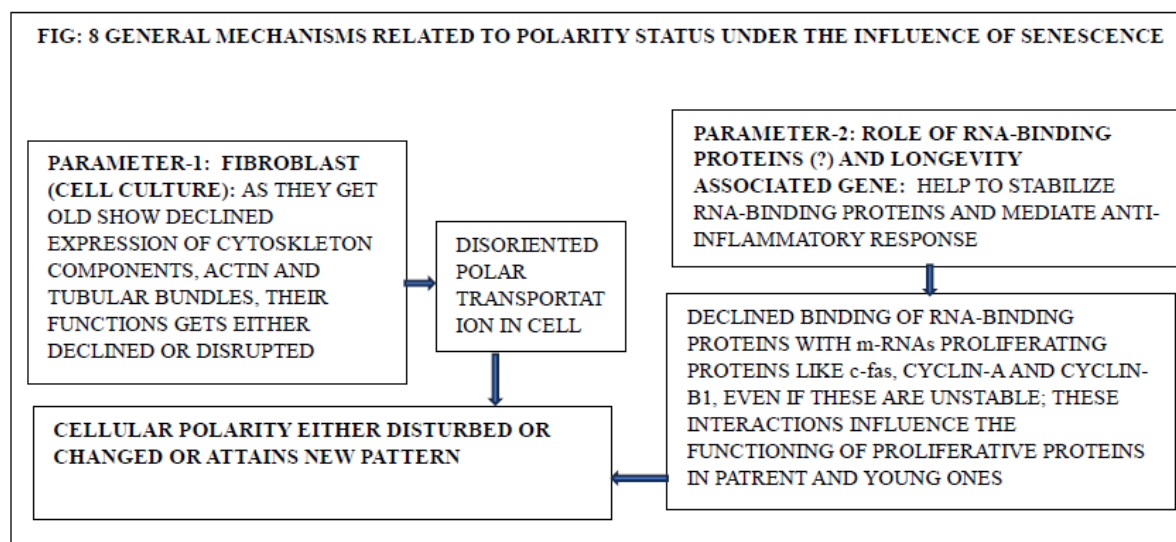
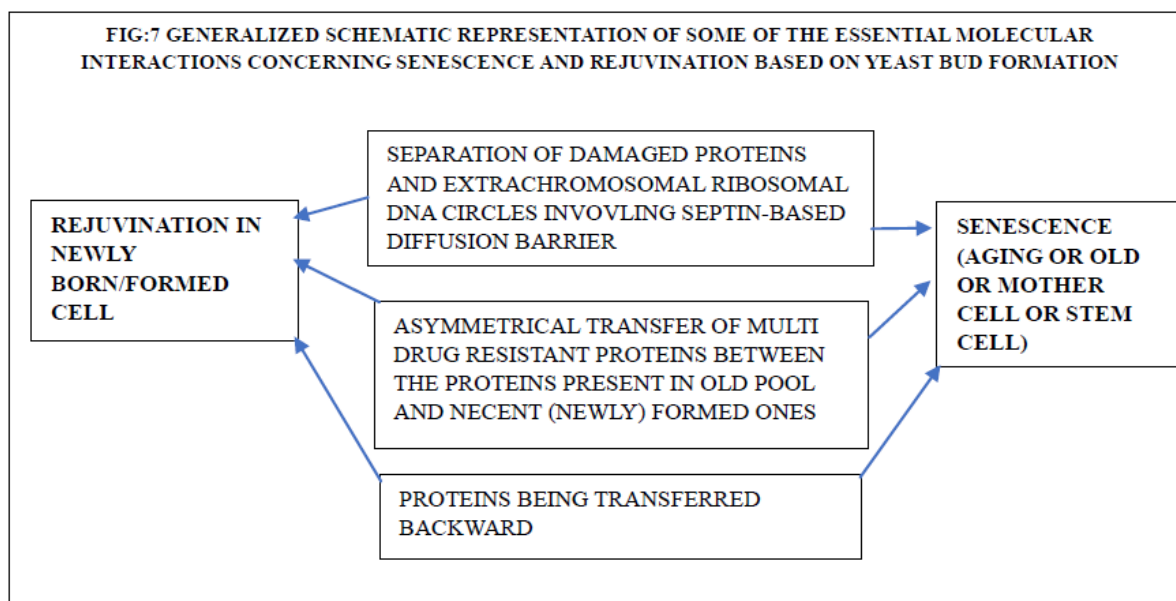
Cellular polarity impacts age-related diseases

There seems to be a common molecular concept regarding senescence and age-related diseases and the cellular polarity plays a significant role in the concerned mechanism. (The common age-related parameters are presented in fig:6.) The cellular polarity gets grossly disturbed or disoriented on the on-set of aging and age-related diseases.^[62,86,99] The role of redox in the maintenance of cell polarity is evident and redox and cellular polarity both contribute grossly in the senescence and concerned pathogenesis. Aging intimately links with 'age-related diseases' (ARDs) and a common molecular correlation. This correlation also facilitates relation with cellular polar status in an individual.^[62,99] There exists a control of markers of cellular aging, p16mRNA is significant which involves RNA binding proteins AUF-1/HNRNPD (this gene concerns with pre-mRNAs within nucleus and affects the process and metabolism of mRNA. There are many genes that are related with aging and senescence related diseases that influence polar expression and segregation. The investigations on

contribution of cellular polarity illustrate its inductive effects on age-related diseases like Alzheimer disease, atherosclerosis,^[100] type-2 diabetes^[101] and various forms of cancers,^[102] like, epithelio-mesenchymal transition (EMT) and loss of primary cilia.^[86, 103, 104,105, 106, 107]

Epithelial tissues are well systematized cytological entity in a multicellular biosystems. Each epithelial cell has apico-basal polarity and maintain structural and functional contact laterally and with the basement membrane. These are dedicated to homeostasis and act as the most effective barrier to the unwanted molecules and organisms that enter in a biological system.^[108] The apico-basal cellular polarity gets disturbed or disorganized in epithelial cancers like breast, lung, prostate and show active participation in the progress of disease. During epithelio-mesenchymal transition there is a loss of intercellular junctions between epithelial cells, disturbances of functioning of their markers and features of mesenchymal cells develop in the affected tissue.^[109] This transition also enhances the chances invasiveness of cancer cells^[110] and stops oncogene-induced cytological senescence resulting in progression of initial development of tumour.^[111] The two signalling pathways concerning the proper functionality of focal adhesion and adhesion junction are active during cell to cell and intracellular signaling processes and play significant role in the working of gene of human longevity network and age-related diseases. These disorders and the signaling systems and epithelio-mesenchymal transition are associated with the cellular polarity of the cells involved.^[112,113]





Investigations using cell culture technique and human fibroblasts as test organism, indicate that as the cells get older there is a dysfunctioning and decline of expression of cytoskeletal components, actin and tubulin bundles; these affect adversely the major polar transport.^[86,107] The other parameter is the probable role of RNA-binding proteins during aging process. There is a decline in the RNA-binding proteins like 'HuR (Human antigen-R)/ELAVL1(ELAV like RNA-binding protein-1); ELAV-Embryonic Lethal Abnormal Visual system). These proteins get stable with the help of 'longevity associated gene' and their combined impact helps to intercede the responses of anti-inflammation. The rate of RNA-binding proteins like 'HuR/ELAVL1' with proliferative proteins like c-fos, cyclin-A and cyclin-B1, declines. As a result, their stability and the level of steady state of the m-RNAs gets disturbed. These interactions are likely to cause ectopic over expression of RNA-binding proteins (HuR) in older human fibroblasts and influencing proliferative status in older and young

ones (Fig; 8).^[86,106] Other option to understand the impact of aging on cellular polarity and/or its expression. The p-16 m-RNA is one of the prime molecular markers for cellular aging; it reflects its regulatory role during interactions of RNA-binding proteins like AUF1(ARE/poly(U)-binding/degeneration factor-1)/HNRNPD (Heterogeneous Nuclear Ribonucleoprotein-D). The gene is related with pre-m-RNA in the nucleus and this gene also affect processing of pre-m-RNA along with the metabolism of m-RNA. Probably, those regions which are responsible for inducing molecular instability are present on p16 mRNA and specifically relate with ARE/poly(U)-binding/degeneration factor-1 (AUF-1); the product is AUF-1-p16-m-RNA complex. The amounts of AUF-1 and AUF-1-p16-m-RNA complex are present in early periods of observation in the culture of fibroblast than the cultured fibroblasts in the later periods. This reflects the impact of aging on the cell under study. These

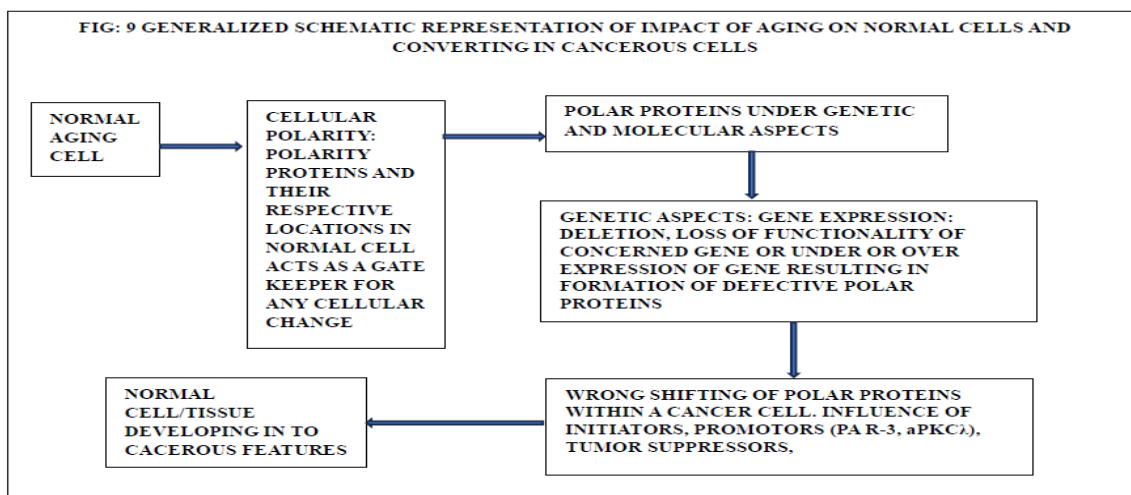
molecular factors affect the expression of polarity and phenotypes.^[86]

Impact of cellular polarity on cancer cells

Cellular polarity is the basis for the cyto-functionality in a living biosystem. In contrast, any change in polarity of cell reflects on its healthy or diseased conditions and cancer is no exception. At the molecular and biochemical levels, the control and out-look of cell polarity is very complex phenomenon and at the same time ambiguous. Cellular polarity is like a gate keeper and any change in its status and components involved are reflection of oncogenic promotion and metagenesis. The mechanism that orchestrates this conversion is still very much unclear in spite of enormous investigations in this direction.^[114] The aPKC- λ 1 (Atypical protein kinase) is recognized as a cause of initiator and progressors of most types of cancers, specifically, epithelial ones. Inactivity of this parameter does not induce tumorigenesis in mice.^[115] Any abnormal shift in cell polarity also acts as an indicator of promotion or suppression of carcinogenesis or tumorigenesis. aPKC λ and PAR-3 act as promoters for papilloma.^[116,117,118] and BCC (basal cell cancer).^[119] while PAK-3 obstructs keratoacanthoma and human SCC (squamous cell carcinoma).^[114,117, 120] Local regulatory cellular mechanism, the rate of basal membrane turnover and local biomechanical status act as indicators for detecting deformation in the tissues due to carcinogenesis. Those changes which relate with initial developing tumors and other cells. It also indicates the inhibition of carcinogenesis during the remedial treatment. The ratio between PARs-3 to aPKC- depends on the control mechanism of cell formation and persistence of mutant papilloma cell.^[114, 116, 117, 118, 121] There exists ambiguity about the tumors and carcinogenicity induction in various types of cancers but investigations of.^[122] evidenced about communication about the cytoskeleton changes to the nucleus that promotes resistance towards the formation tumors in basal cells (BCC tumors). This study supports the probable role of cell polarity and architecture of the affected tissue in case of types of cancer.^[116] The current advancements in mechanical biology, 'intravital imaging,' single-cell technology, and instrumentation enhance better chances of improved mechanistic understanding the intricacies of age dependent changes in cell architecture including cellular polarity in relation to pathogenesis.

In most of the cancerous cells (carcinoma-cells) loss of polarity is of common occurrence and as a result of this loss, the apicobasal polarity shifts to the polarity suitable for cell migration and assailing the neighbouring tissues. This loss of polarity associates with the defective expression of the polarity proteins.^[114, 123, 124] The polarity proteins in case of breast cancer tissue, have been lost and the copying the number of genes that encode for polarity proteins in the heterogenous molecular sub-types of affected breast cancer tissues/cells. The cells with altered polarity proliferate as

cell-clones and the initial stage/pre stages become invasive nature; it highlights the favourable changed polarity in these cell/tissues. It is of common observation that cell triggered, initiated for carcinogenesis and transformed into cancerous cells undergo polarity shift. This shift results in promotion of tissue disruption and tumour or progressive carcinogenesis.^[125,126] The direct involvement of shift of cellular polarity can be questioned but its undeviated participation in triggering, initiating and advancing/progression of cancer in a tissue which appears to have significant molecular function. The shift of polarity may become front-rear polarity, T-cell polarity or any other patterns which suit the cancerous cells.^[126,127] There are many molecular changes in the cells that exhibit carcinogenesis/metastasis. The gene repression involves deletion or/and loss of functionality of genes concerning the mutations and/or irregular and disorganized transcription depending on the type of cancer; for example: role of Liver Kinase-B-1(LKB-1) and Phosphatase and tensin homologue after deletion from chromosome 10 (PTEN-10) act as tumor suppressors and control the signalling pathway of remedial action of rapamycin, specific treatment for gastro-intestinal hamartomatous polyposis (a benign tumor) syndromes. When there is disorganized transcription, the remedial impact gets disordered.^[128] When there is an over expression of related genes due to amplification and/or increased regulatory impact of transcription of lgl-2 (a tumor suppressor); the possible results affecting the receptors for estrogen along with the remedial effects in breast cancer (Fig: 9).^[129,130] In case of mammary (breast cancer).^[130] and prostate tumor formation.^[114,131] There is a change in the protein contents and polarity proteins move to wrong place and cause negative impacts of cellular polarity. These changes in cellular polarity are not a permanent cytological feature but observed in cancer cells and in those cells which circulate along the blood in vascular system.^[114,132] The changes in cellular polarity and polarity proteins act as useful indicators for pre- and post and anti-impacts of different types of tumors.^[114,115]

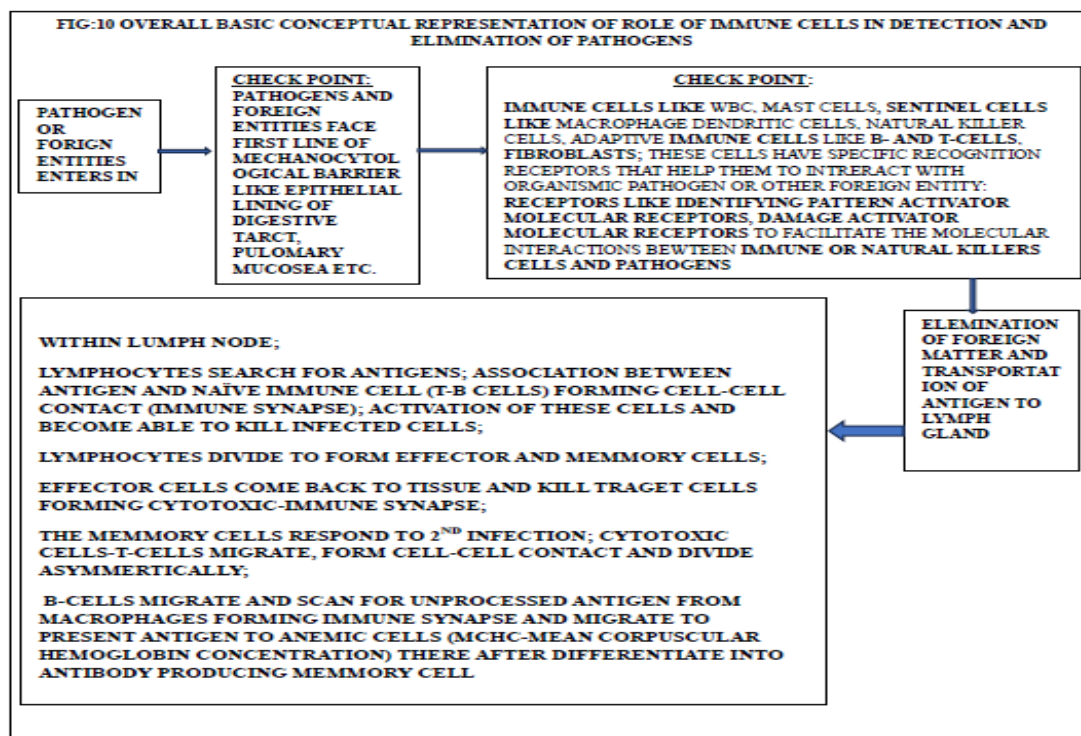


Impacts of cellular polarity on immune cells

Since aging impacts cellular polarity and their coordinated action results in decreased efficacy of immune system. In all probability these two phenomena enhance the chances of immunodeficiency disorders as an individual ages. Age related 'cell-intrinsic parameters,' such as degree of responding to damage of DNA, tendency to produce more reactive oxygen species (ROS), fluctuations in responses with respect to epigenetic aspects, gradual loss of strength and effectiveness of telomere, polarity changes and senescence in stem-cells contribute directly or indirectly and cause decline in the efficacy of immune system.^[133,134] The immune cells detect and eliminate pathogens or any 'foreign molecules' in a biosystem. These cells also communicate with other cells informing

about the potential threat; this threat may be due to organism or any toxic entity.

The immune cells have to proliferate at a relatively faster rate to meet the requirements of efficient immune response. Hence, they undergo asymmetric cell division. Cellular polarity plays significant functional role and facilitate the functionalities of immune cells like scanning the peripheral tissues, recruiting new immune cells, establishing immunological synapse, activating lymphocytes, generating diverse phenotypes and cell types such as memory and effector cells are formed as daughter cells in sufficient numbers. The immune cells, exhibit biological, physiological, biochemical, biophysical perspectives and perform all the mentioned functions.



Immune cells have been assigned the role of detection and elimination of pathogens. This exercise is a complex process and is accomplished in biosystem. The pathogens pass through mechanocytological barriers, scanning by immune cells and finally eliminated (Fig-10).^[136]

A cell is capable to displace or reorient its intracellular molecules and its substructures along a directionally defined axis of symmetry in accordance with its specific biological functionality. The immune cells have to perform three main functions: cell migration, forming cytotoxic and immune synapses, and asymmetric cell division. During cell migration there is a redistribution of the components of cytoskeleton like actin, myosin and adhesion molecules in asymmetrical pattern. This cellular migration involves specific mechanism which may or may not depend on specific adhesion proteins but it utilizes different polarity to accomplish such movements. The immune synapse formation is in congruence with the central combined polarity-axis of lymphocytes and cell-cell contact. This specific polarity axis facilitates the cell division that results in daughter cells with different phenotypes, so to say, this cell division is asymmetrical in nature.^[136]

A cell exhibits specific orientation which is indicative of its external or apical sides and this status is because of the polarity-axis it possesses. This polarity-axis exists as long as the specific state of the cell exists. In case of the migrating or moving cells, specifically, immune cells, the polarity plays significant role during migration, synapses formation and asymmetric cell division to form daughter cells with variable phenotypes. Cellular polarity is fixed and flexibility depends on its specific function. There occurs quick axial disorientation, reorganisation and repolarization of the polarity proteins during the transformation of polarity.^[136] These cells move through vast peripheral zone within the biosystem for scanning pathogens. Their cellular rate of differentiation is low, even the subtle cytomorphological fluctuations occurring in these cells during their phase of asymmetric cell division at least *in vivo*^[137,138,138a,139] make the observation tedious. The roles of some of the specific proteins such as 'Numb and alpha-Adaptin' involved during asymmetrical cell division of hematopoietic stem cells. The daughter cells formed as a result of this type of cell division, some of them are primitive and some are not; this ensures the existence of specific polarity during the asymmetric cell division.^[139,140] In other immune cells like B-cells such behavior is not seen while it is seen in T-cells.^[137,139,141] The T-cell receptors and antigen presenting cells help the T-cells after the processes of polarization and asymmetric segregation of polarity proteins and the fate take place only after the T-cells have been activated with the help of T-cell receptors and antigen-presenting cells. This process of activation results in formation of two varieties of cells namely 'memory T- and effector T-cells'.^[139,142] Of these the memory T-cells further undergo exhibit divide again

asymmetrically and thus the required pool of memory T-cell is maintained. There are different active factors in asymmetric division of T-cells; there are specific receptor like CD3 (also called cytotoxic T-lymphocytes effective against intracellular pathogens like viruses and bacteria) and interferon-gamma receptors on memory cells but their impacts seem to be quite less.^[139,143] Exposure of these cells to the antigen, influences the central memory T-cells to opt for secondary immune response. These cells again undergo asymmetrical cell division forming daughter cells as effector T-cells and central memory cells. CD25 and T-cell transcriptional parameters facilitate control of T-helper cells and also participate in polarization in case of effector T-cells, thereby, the other daughter cells are less in number as memory T-cells. The protein kinase-PKC zeta is important for instituting central memory; its polarization is not same during primary and secondary responses.^[139,143]

The process of polarization of essential proteins control cytomorphology, cellular fate and migration. The a-PKC proteins polarize when T-cells come in contact with antigen on dendritic cells and polar proteins like Par-3 remain in distal location to the dendritic cell. The polarity proteins like 'Scribble and Disc large' (Dlg) form Scribble complex and remain in proximal location. This observation reflects on the significance of polarity for memory T-cell differentiation and also its functional role in antigen presentation in accordance to immune response.^[139,144]

The positioning of a planer cell polarity at right angle to the polar plan in case of endothelial cells has become point of concern among the researchers. It is understood that the planer polarity induces positive impacts while controlling the cardiovascular dysfunctions, ischemic strokes and angiogenesis during pathogenic conditions. The biomechanical forces are able to induce polarity among endothelial cells. Mechanical cues induce polarization in endothelial cells and planer cell polarity is the product of endothelial cells which helps to normalize physiological and biochemical functionalities. The planer cell polarity and the related signaling net-work maintains the appropriate cytomorphological organelles in the endothelial cells. This aspect indicates the potential correlation between planer cell polarity and the vascular dysfunctions.^[145]

CONCLUSION

Cellular polarity is one of the basic structural and functional features of a cell. The components of PAR protein complex are essential requirement during establishing asymmetrical positioning in a cell. Any defective functionality of this composite results in abnormal cellular development and pathogenesis. The gene associated with cellular polarity deserve more attention regarding their respective roles during cellular polarity, aging and rejuvenation. The actin cytoskeleton plays significant regulatory role in the process of aging

in yeast. When there is a reduction in the production of actin and build-up of actin-aggregation, there is an elevation in the formation of ROS. Momentary interruption in the actin cytoskeleton disturbs the asymmetric separation of oxidized proteins. The propagating factor in yeast, relates with extrachromosomal ribosomal DNA-circles and also influences actin mechanism effectively as the aggregation of damaged proteins do. Investigations related to senescence in human include experimentation on cultured fibroblasts; these indicate the declined expression and aberrated polar transport-associated components of cytoskeleton, tubulin and actin bundles. RNA-binding proteins have their significant role in transportation of polarity and the polar proteins and related factors. There seems to be a common molecular concept regarding senescence and age-related diseases and the cellular polarity plays a significant role in the concerned mechanism. The planer cell polarity and the related signaling net-work maintains the appropriate cytomorphological organelles in the endothelial cells. This aspect indicates the potential corelation between planer cell polarity and the vascular dysfunctions here appears to be a greater need to ponder and delve more in the complexities of cellular polarity to understand the mechanism of cellular pathogenesis.

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