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"A Review on Transient receptor potential channel "

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Abstract: Transient receptor potential (TRP) cation channels have been among the most aggressively pursued drug targets over the past few years. Although the initial focus of research was on TRP channels that are expressed by nociceptors, there has been an upsurge in the amount of research that implicates TRP channels in other areas of physiology and pathophysiology, including the skin, bladder and pulmonary systems. In addition, mutations in genes encoding TRP channels are the cause of several inherited diseases that affect a variety of systems including the renal, skeletal and nervous system. This Review focuses on recent developments in the TRP channel-related field, and highlights potential opportunities for therapeutic intervention.

Keywords: TRP Channel, Drosphila, Cation Channel, Brain, Peripheral system.

1.Introduction:

The TRP (transient receptor potential) channel super family is composed of cation channels gated by temperature, light, pressure and chemical stimuli. TRP channels often act as cellular sensors and mediate responses to changes in the extracellular environment. All cells express multiple TRP channel proteins and these channels are involved in numerous critical functions. The present review attempts to summarize our current knowledge of TRP channels in the vascular endothelium and arterial myocytes and their roles in normal vascular function and pathophysiology. TRP channels were initially discovered in the "transient receptor potential" mutant (*trp*mutant) strain of the fruit fly drosophila. TRP channels were found in vertebrates where they are ubiquitously expressed in many cell types and tissues. Most TRP channels are composed of 6 membrane spanning helices with intracellular N- and c termini . Mammalian TRP channels are activated and regulated by a wide variety of stimuli and are expressed throughout the body. Transient receptor potential channels (TRP channels) are a group of ion channels located mostly on the plasma membrane of numerous animal cell types. Most of these are grouped into two broad groups: Group 1 includes Trpc ("Cfor canonical),trpv ("V" for vanilloid), trpvl("VL" for vanilloid-like), trpm ("M"for melastatin), trps ("S" for soromelastatin), trpn ("N" for no mechanoreceptor potential C), and trpa("A" for ankyrin). Group 2 consists of trpp("P" for polycystic) and TRPML ("ML" for mucolipin).[1]Other less-well categorized TRP channels exist, including yeast channels and a number of Group 1 and Group 2 channels present in non-animals.[2][3][4] Many of these channels mediate a variety of sensations such as pain, temperature, different kinds of tastes, pressure, and vision. In the body, some TRP channels are thought to behave like microscopic thermometers and used in animals to sense hot or cold.[2]

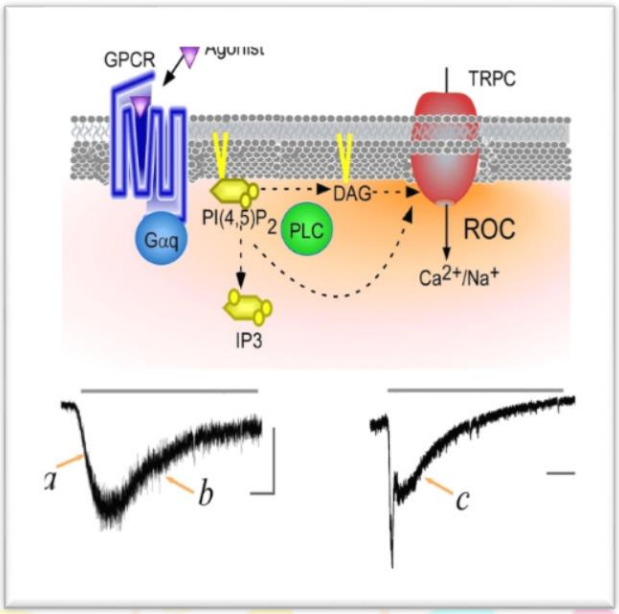


Fig No. 1: Transient Receptor Potential Channel

TRP channels are a class of cationic channels that act as signal transducer by altering membrane potential or intracellular calcium (Ca^{2+}) concentration. The TRP channel era began in 1969 when Cosens and Manning discovered a phenotype in drosophila that exhibited as blindness in the presence of constant bright light. This mutant strain was named *trp*, transient receptor potential, and cloning of the mutated *trp* gene identified the first member of the TRP superfamily[3]This superfamily constitutes a diverse group of polymodal ion channels that are mostly conserved from nematodes to humans. Based on sequence homology the mammalian TRP channel superfamily is classified into six subfamilies. TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPA (Ankyrin), TRPM (Mucolipin and TRPP (Polycystic). The first four subfamilies are categorized as group 1 and the last two constitute group 2. TRP channel activation induces immune modulator effects on multiple levels. This review will focus on the role of TRP channels in immune cells (with a focus on macrophages and T cells) and epithelial cells in general, with an additional special focus on TRPs in intestinal inflammation. Recognizing the large family of TRP channels, this mini-review focuses on TRPA1, TRPM8, TRPV1, and TRPV4 (alphabetical order), which are the most relevant TRP channels in the present context based on published literature until today. Table S1 (available in supplementary material) gives an overview of receptor expression and resulting biological effects in the different cellular compartments.[4]

TRP channels also control the release of immune modulator neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP), the so-called neurogenic inflammation. During recent years, increasing evidence has demonstrated an important role of many TRP channels outside the nervous system in the context of inflammation; findings that extend the role of TRP channels in the regulation of inflammation beyond neuropeptide release. To date, only little is known about the functional role of TRP channels in the immune system. Moreover, recent reports describe a fundamental role of TRP channels in epithelial cells in mediating cytokine/chemokine release as well [5]

TRP channels are important in human physiology, and mutations in TRP genes are associated with at least four diseases. Furthermore, altered expression, function, and/or regulation of TRP channels have been implicated in diseases such as pulmonary hypertension[6]

2.History of drosophila trp channels:

The original TRP-mutant in Drosophila was first described by Cosens and Manning in 1969 as "a mutant strain of D. melanogaster which, though behaving phototactically positive in a T-maze under low ambient light, is visually impaired and behaves as though blind". It also showed an abnormal electroretinogram response of photoreceptor to light which was transient rather than sustained as in the "wild type". It was investigated subsequently by Baruch Minke, a post-doc in the group of William Pak, and named TRP according to its behavior in the ERG. The identity of the mutated protein was unknown until it was cloned by Craig Montell, a post-doctoral researcher in Gerald Rubin's research group, in 1989, who noted its predicted structural relationship to channels known at the time and Roger Hardie and Baruch Minke who provided evidence in 1992 that it is an ion channel that opens in response to light stimulation. The TRPL channel was cloned and characterized in 1992 by the research group of Leonard Kelly.In 2013, Montell and his research group found that the TRPL (TRP-like) cation channel was a direct target for tastants in gustatory receptor neurons and could be reversibly down-regulated.The founding member of the TRP channel superfamily was identified as essential component of Drosophila photo transduction A spontaneous mutation in the trp gene resulted in a transient receptor potential in response to continuous light. Drosophila TRP homologs have been identified in yeast, invertebrates and vertebrates. In mammals, 28 genes are classified as TRP channel subunits that are grouped into six subfamilies: the canonical TRPs (TRPCs), the vanilloid receptor TRPs (TRPVs), the melastatin TRPs (TRPMs), the

mucolipins (TRPMLs), the polycystins (TRPPs), and the ankyrin transmembrane protein 1 (TRPA1)[7] Unlike other ion channels that are classified according to a common ligand, function, or selectivity

3.Structure of Transients receptor potential channel

TRP channels are composed of 6 membrane-spanning helices (S1-S6) with intracellular Mammalian TRP channels are activated and regulated by a wide variety of stimuli including many post-transcriptional mechanisms like phosphorylation G protein receptor potential , legend-gating. The receptors are found in almost all cell types and are largely localized in cell and organelle membranes, modulating ion entry

Most TRP channels form homo- or heterotetramers when completely functional. The ion selectivity filter, pore, is formed by the complex combination of p-loops in the tetrameric protein, which are situated in the extracellular domain between the S5 and S6 transmembrane segments. As with most cation channels, TRP channels have negatively charged residues within the pore to attract the positively charged ions. [8]

3.1Group 1 Characteristics

Each channel in this group is structurally unique, which adds to the diversity of functions that TRP channels possess, however, there are some commonalities that distinguish this group from others. Starting from the intracellular N-terminus there are varying lengths of ankryin repeats (except in TRPM) that aid with membrane anchoring and other protein interactions. Shortly following S6 on the C-terminal end, there is a highly conserved TRP domain (except in TRPA) which is involved with gating modulation and channel multimerization. Other C-terminal modifications such as alpha-kinase domains in TRPM7 and M8 have been seen as well in this group.[9]

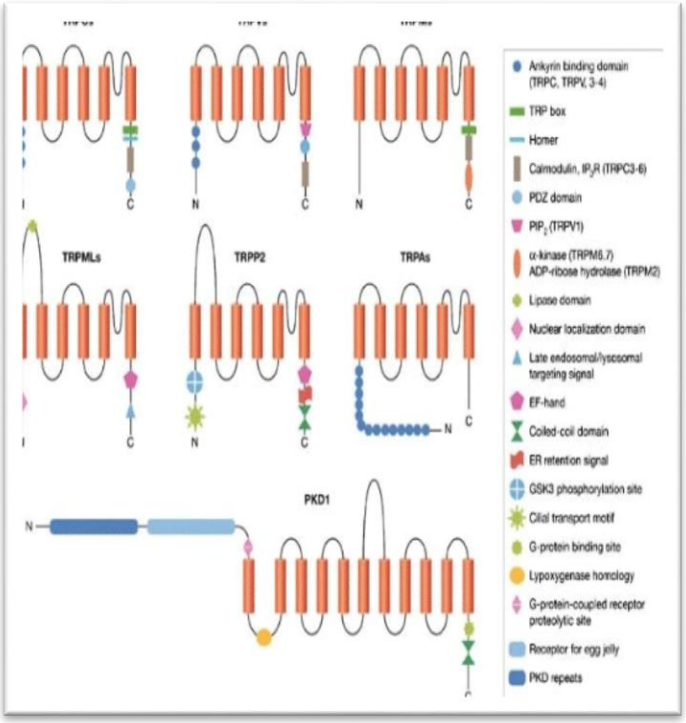


Fig No. 2: Structure of Trpc

3.2 Group 2 Characteristics

Group two most distinguishable trait is the long extracellular span between the S1 and S2 transmembrane segments. Members of group two are also lacking in ankryin repeats and a TRP domain. They have been shown, however, to have endoplasmic reticulum (ER) retention sequences towards on the C-terminal end illustrating possible interactions with the ER.[10][15]

4. 1 functions of Transient receptor potential channel

TRP channels modulate ion entry driving forces and Ca^{2+} and Mg^{2+} transport machinery in the plasma membrane, where most of them are located.[11] TRPs have important interactions with other proteins and often form signaling complexes, the exact pathways of which are unknown. TRP channels were initially discovered in the *trp* mutant strain of the fruit fly drosophila which displayed transient elevation of potential in response to light stimuli and were so named *transient receptor potential* channels. TRPML channels function as intracellular calcium release channels and thus serve an important role in organelle regulation[12] Importantly, many of these channels mediate a variety of sensations like the sensations of pain, temperature, different kinds of tastes, pressure, and vision.[14] In the body,

some TRP channels are thought to behave like microscopic thermometers and are used in animals to sense hot or cold. TRPs act as sensors of osmotic, volume, pressure and vibration. TRPs have been seen to have complex multidimensional roles in sensory signaling.

1. Many TRPs function as intracellular calcium release channels.
    1. Pain and temperature sensation
    2. Taste
    3. Vision
    4. Olfaction
    5. Hearing
    6. Touch
    7. Thermo and osmosensation

4.1.1 Pain and sensation

TRP ion channels convert energy into action potentials in somatic sensory receptor . Thermo-TRP channels have a C-terminal domain that is responsible for thermo sensation and have a specific interchangeable region that allows them to sense temperature stimuli that is tied to ligand regulatory processes.[14]Although most TRP channels are modulated by changes in temperature, some have a crucial role in temperature sensation. There are at least 6 different Thermo-TRP channels and each plays a different role. For instance relates to mechanisms of sensing cold, trpv1and trpm3 contribute to heat and inflammation sensations, and trpa1 facilitates many signaling pathways like sensory transduction, nociception inflammation and oxidative stress[14]

4.1.2 Taste

TRPM5 is involved in taste signaling of sweet, bitter and umami tastes by modulating the signal pathway in type II taste receptor cells.[15] TRPM5 is activated by the sweet glycosides found in the stevia plant.

Several other TRP channels play a significant role in chemosensation through sensory nerve endings in the mouth that are independent from taste buds. TRPA1 responds to mustard oil wasabi, and cinnamon, TRPA1 and TRPV1 responds to garlic TRPV1 responds to chilli pepper TRPM8 is activated by menthol, camphor, peppermint, and cooling agents; TRPV2 is activated by molecules (THC, CBD and CBN) found in marijuana.

4.2 Physiological functions:

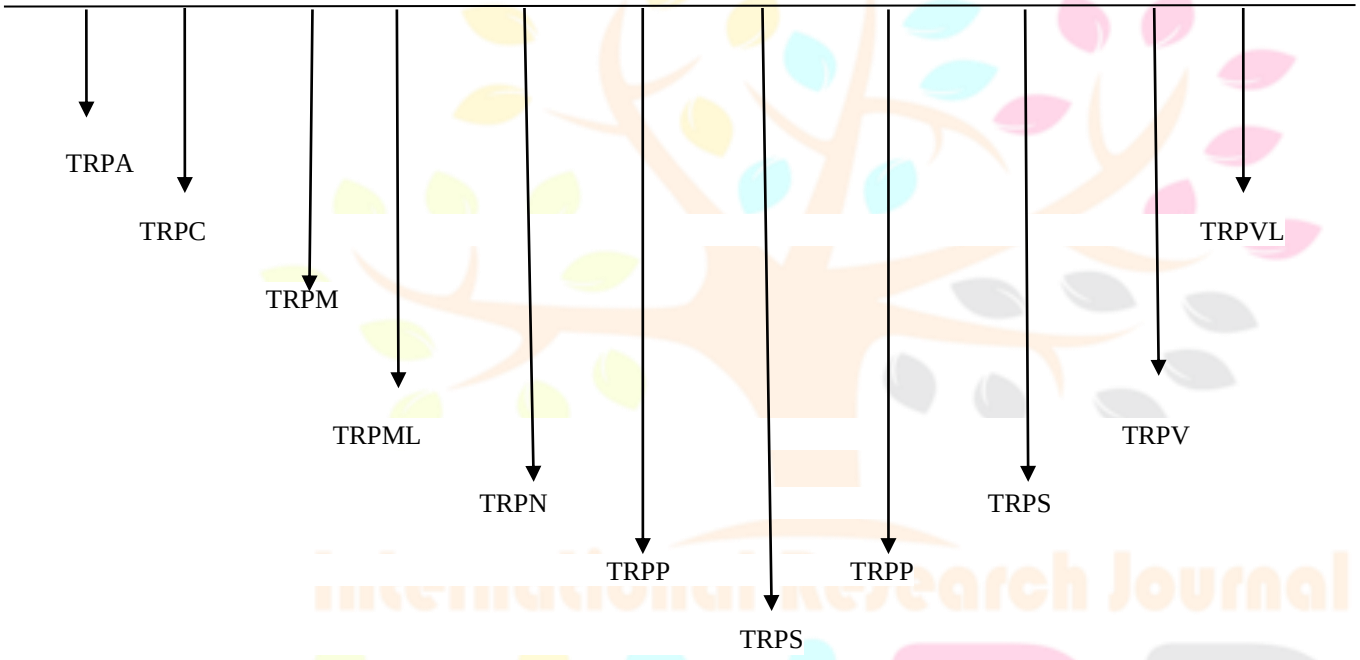
Mouse models and human genetics (see Channelopathies) have revealed diverse functions of TRP channels. Perhaps best characterized is the function of TRPV1 in primary afferent nociceptors. It is essential for the perception of noxious stimuli (heat, capsaicin) and contributes to the development of thermal hyperalgesia following inflammation Other examples for TRPs in somatosensation are TRPM8 that is activated by cooling or pharmacological agents evoking a 'cool' sensation and participates in the thermosensation of cold temperatures. or TRPA1 that is activated by pungent chemicals such as mustard oil (AITC), allicin, and cinnamaldehyde, and many reactive molecules. TRPA1 contributes to nociception TRPC2 is a pseudogene in humans, but in other mammals appears to be an ion channel localized to microvilli of the vomeronasal organ. It is required for normal sexual behavior .Aside from their functions in sensory systems, TRP channels also participate in many more physiological processes for example within the renal, endocrine, cardiovascular, immune, or central nervous system. A comprehensive summary of physiological functions is provided for each channel in the corresponding tables.

5. ACTIVATION MECHANISMS AND PHARMACOLOGY

Most TRP channels can be activated and/or modulated by multiple stimuli including receptor coupled intracellular signaling pathways, physical, and chemical stimuli. It is generally accepted that all TRPCs are activated downstream of G protein-coupled receptors (G_q-linked) and receptor tyrosine kinases, but other TRPs have also been shown to be modulated by phospholipases C (PLC) mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), and production of diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP_3)·$PI(4,5)P_2$ is a common regulator of many ion channels and not specific to TRP channels. The reported effects of $PI(4,5)P_2$ on TRP channels are often complex, occasionally contradictory, and likely to be dependent upon experimental conditions, such as intracellular ATP levels.TRPC channels have frequently been proposed to act as store-operated channels (SOCs) (or components of multimeric complexes that form SOCs), activated by depletion of intracellular calcium stores (reviewed by However, the weight of the evidence is that they are not directly gated by conventional store-operated mechanisms, as is established for Stim-gated Orai channels (also known as CRAC channels).Among the physical stimuli that activate TRP channels, temperature is one of the most remarkable stimuli. Several TRP channels (TRPV1-V4, TRPC5, TRPM3, TRPM5, TRPM8, TRPA1).exhibit temperature sensitivity with high Q10s of gating Defined as the change in the rate of a reaction when temperature is changed by 10°C, the Q10 value provides an estimate for the temperature sensitivity of a protein. While the thermal activation thresholds in thermosensitive TRP channels cover the range of temperatures sensed (from cold to hot), the high Q10s of gating do not necessarily imply a function as a 'hot' or 'cold' sensor. Protein folding is of course temperature sensitive, and thus a change in gating within the narrow temperature range experienced by organisms does not dictate that they are sensors for temperature. For example, many channels with high Q10s are present in the mammalian CNS and other isothermal regions where they are not exposed to temperatures outside a narrow range C-Mechanosensitivity around 37° has also been proposed for several mammalian TRP channels Like temperature, all proteins are sensitive to mechanical forces, but these are only relevant if these forces are in the range experienced by proteins in their native membranes and locations. Those often cited as

mechanosensitive include TRPP1 (PKD2), TRPA1, TRPV4, and TRPV1, but relevant experimental evidence for physiological significance is often lacking or controversial. In contrast, MscL, MscS (bacterial), Piezo1 and 2, and hair cell channels (putatively TMC1/2) are clearly important to physiologically relevant mechanosensing Endogenous and exogenous molecules activate TRP channels. Although progress has been made in uncovering endogenous ligands and signaling pathways that trigger TRP channel activation, it is often still unclear what gates the channels *in vivo*. Among the known endogenous activators or modulators are inorganic ions (mainly Ca^{2+} and Mg^{2+}), bioactive lipids (eicosanoids, diacylglycerol, anandamide), and ADP ribose or ADP ribose-2'-phosphate. Increases in intracellular Ca^{2+} can activate some TRP channels, but will modulate, directly or *via* calmodulin, almost all TRP channels ·Several natural products (*e.g*. capsaicin, menthol, or carvacrol), but also synthesized small molecules have been shown to affect TRP channel gating. However, a selective pharmacology does not yet exist for most TRP channels. Commonly used blockers such as Ruthenium red or 2-APB (2-Aminoethoxydiphenyl borate) are highly nonspecific. More useful tools with high potency and more selectivity have just started to emerge. Examples are the TRPV4 agonist GSK1016790A or its antagonists GSK2193874 and HC-067047, and the TRPA1 antagonist HC-030031·TRPC4 and TRPC5 may be distinguished from other TRP channels by their potentiation by micromolar concentrations of La^{3+}. Natural compounds, usually derived from plants, are ligands that are presumed to have evolved in the natural competition/symbiosis between plants and animals. Capsaicin is the well-known vanilloid in 'hot' peppers and seems to be relatively specific for TRPV1.

6. Classifications and subfamily



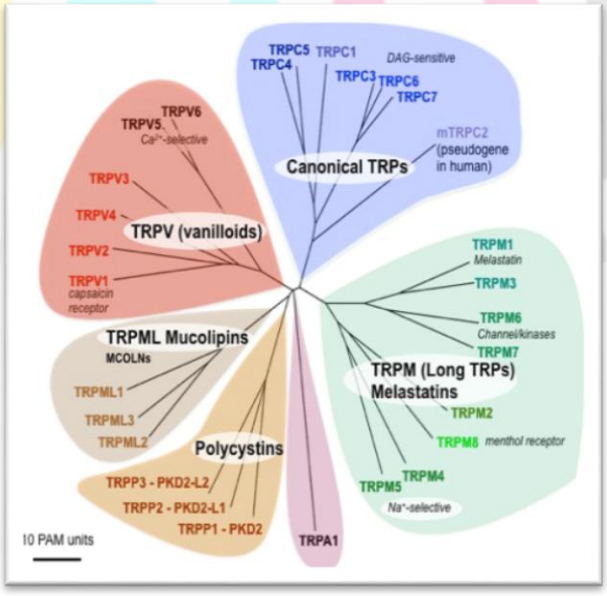


Fig No. 3 classification of trpc

TRP channel classification is currently based only on sequence homology. TRPCs, TRPVs, TRPMs, and TRPA1 have the highest homology to *Drosophila* TRP with TRPCs being the closest homologs. TRPMLs and TRPPs are more distantly related. In the animal TRP superfamily there are currently 9 proposed families split into two groups, each family containing a number of subfamilies.[16] Group one consists of TRPC, TRPV, TRPVL, TRPA, TRPM, TRPS, and TRPN, while group two contains TRPP and TRPML. There is an additional family labeled TRPY that is not always included in either of these groups. All of these sub-families are similar in that they are molecular sensing, non-selective cation channels that have six transmembrane segments, however, each sub-family is very unique and shares little structural homology with one another.[16]

6.1 TRPA

A for "ankyrin", is named for the large amount of ankyrin repeats found near the N-terminus.TRPA is primarily found in afferent nociceptive nerve fibers and is associated with the amplification of pain signaling as well as cold pain hypersensitivity. These channels have been shown to be both mechanical receptors for pain and chemosensors activated by various chemical species, including isothiocyanates (pungent chemicals in substances such as mustard oil and wasabi), cannabinoids, general and local analgesics, and cinnamaldehyde.[17]

While TRPA1 is expressed in a wide variety of animals, a variety of other TRPA channels exist outside of vertebrates. TRPA5, painless, pyrexia, and waterwitch are distinct phylogenetic branches within the TRPA clade, and are only evidenced to be expressed in crustaceans and insects, while HsTRPA arose as a Hymenoptera-specific duplication of waterwitch.Like TRPA1 and other TRP channels, these function as ion channels in a number of sensory systems. TRPA- or TRPA1-like channels also exists in a variety of species as a phylogenetically distinct clade, but these are less well understood.

6.2 TRPC

C for "canonical", is named for being the most closely related to Drosophila TRP, the namesake of TRP channels. The phylogeny of TRPC channels has not been resolved in detail, but they are present across animal taxa. There are actually only six TRPC channels expressed in humans because TRPC2 is found to be expressed solely in mice and is considered a pseudo gene in humans; this is partly due to the role of TRPC2 in detecting pheromones, which mice have an increased ability compared to humans. Mutations in TRPC channels have been associated with respiratory diseases along with focal segmental in the kidney.All TRPC channels are activated either by phospholipase (PLC) or diacyglycerol (DAG)

6.3 TRPM

TRPM, M for "melastatin", was found during a comparative genetic analysis between benign nevi and malignant nevi (melanoma). Mutations within TRPM channels have been associated with hypomagnesemia with secondary hypocalcemia. TRPM channels have also become known for their cold-sensing mechanisms, such is the case with TRPM8. Comparative studies have shown that the functional domains and critical amino acids of TRPM channels are highly conserved across species.

Phylogenetics has shown that TRPM channels are split into two major clades, αTRPM and βTRPM. αTRPMs include vertebrate TRPM1, TRPM3, and the "chanzymes" TRPM6 and TRPM7, as well as the only insect TRPM channel, among others. βTRPMs include, but are not limited to, vertebrate TRPM2, TRPM4, TRPM5, and TRPM8 (the cold and menthol sensor). Two additional major clades have been described: TRPMc, which is present only in a variety of arthropods[18] and a basal clade, which has since been proposed to be a distinct and separate TRP channel family (TRPS).

6.4 TRPML

TRPML, ML for "mucolipin", gets its name from the neurodevelopmental disorder. Mucolipidosis IV was first discovered in 1974 by E.R. Berman who noticed abnormalities in the eyes of an infant.[20] These abnormalities soon became associated with mutations to the MCOLN1 gene which encodes for the TRPML1 ion channel. TRPML is still not highly characterized. The three known vertebrate copies are restricted to jawed vertebrates, with some exceptions

6.5 TRPN

TRPN was originally described in *Drosophila melanogaster* and *Caenorhabditis elegans* as nompC, a mechanically gated ion channel. Only a single TRPN, N for "no chemoreceptor potential C," or "nompC", is known to be broadly expressed in animals (although some Cnidarians have more), and is notably only a pseudogene in vertebrates.Despite TRPA being named for ankyrin repeats, TRPN channels are thought to have the most of any TRP channel, typically around 28, which are highly conserved across taxa.[19]Since its discovery, *Drosophila* C has been implicated in mechanization (including mechanical stimulation of the cuticle and sound detection) and cold nociception

6.6 TRPP

TRPP P for "polytheistic", is named for polycystic kidney disease which is associated with these channels. These channels are also referred to as PKD (polytheistic kidney disease) ion channels.

PKD2-like genes encode canonical TRP channels. PKD1-like genes encode much larger proteins with 11 trans-membrane segments, which do not have all the features of other TRP channels. However, 6 of the transmigrate segments of PKD1-like proteins have

substantial sequence homology with TRP channels, indicating they may simply have diversified greatly from other closely related proteins.

Insects have a third sub-family of TRPP, called brides, which participate in cold sensing.

6.7 TRPS

TRPS, S for Soromelastatin, was named as it forms a sister group to TRPM. TRPS is broadly present in animals, but notably absent in vertebrates and insects. TRPS has not yet been well described functionally, though it is known that the *C. elegance* TRPS, known as CED-11, is a calcium channel which participates in Apoptosis[20]

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6.10 TRPV

TRPV, V for "vanillin", was originally discovered in Endocarditis elegant, and is named for the vanillin chemicals that activate some of these channels. These channels have been made famous for their association with molecules such as capsaicin. In addition to the 6 known vertebrate analogues, 2 major clade are known outside of the testosterone: nanchung and Iav. Mechanistic studies of these latter clade have been largely restricted to Drosophila, but phylogeny analyses has placed a number of other genes from Placebo, Annelids, Cnidarian, Mollusc, and other arthropods within them. TRPV channels have also been described in protests.

6.11 TRPVL

TRPVL has been proposed to be a sister clade to TRPV, and is limited to the cnidarians nematostella vectansis and the annelid capitella teleta. Little is known concerning these channels.

6.12TRPY

TRPY, Y for "yeast", is highly localized to the yeast vacuole, which is the functional equivalent of a lysosome in a mammalian cell, and acts as a mechanosensor for vacuolar osmotic pressure. Patch clamp techniques and hyperosmotic stimulation have illustrated that TRPY plays a role in intracellular calcium release. Phylogenetic analysis has shown that TRPY1 does not form a part with the other metazoan TRP groups one and two, and is suggested to have evolved after the divergence of metazoans and fungi.Others have indicated that TRPY are more closely related to TRPP[23]

7.Transient receptor potential channel as therapeutic target:

1. Trp channel in the bladder disorders
2. Trp channel in the skin
3. Trp channel in the pulmonary

7.1. Trp channel in the bladder disorders:

Several TRP channels are expressed in the bladder in the urothelium, nerve endings and derisory muscle. Roles of TR channels in bladder functions. The maturation reflex is mediated by transient receptor potential cation channel subfamily V, member 1 (TRPV1)-positive nerves and probably albeit to a lesser degree also by TRP cation channel subfamily M, member 8 (TRPM8)-positive nerves. These same neurons convey nociceptive information to the central nervous system. TRPV4 is a key player in bladder function because it is present in both the urothelium and the detrusor muscle, and it is activated by stretch (bladder distension) and hypo-osmolar urine. The activator of TRPM8 in the bladder remains to be determined. The micturition reflex is under the control of a descending central nervous system pathway; when this pathway is disrupted (for example, as a result of spinal cord injury)

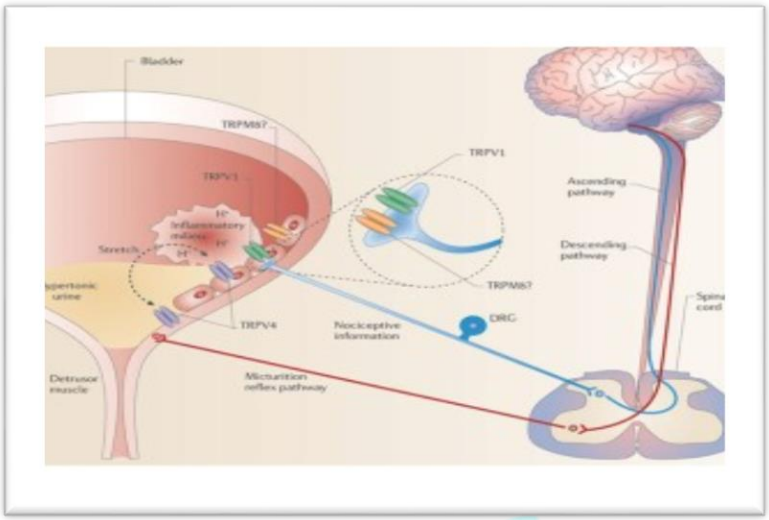

Fig NO.4 trp channel in bladder disease

it becomes autonomous and partly driven by TRPV1. The existence of functional TRPV1 in urothelial cells remains controversial, as evidence for and against the presence of a funtional channel has been presented. Collectively, these findings imply a therapeutic potential of TRPV1 antagonists (or TRPV1 desensitization) and/or TRPM8 agonists as therapies in painful bladder disorders (and in pain induced by benign prostatic hyperplasia) and in an overactive bladder. These findings also suggest that TRPV4 blockers could be useful in the management of an overactive bladder In the skin, they are synthesized by and released from multiple non-neuronal cell types and include histamine, acids, ATP, prostaglandins and pro-inflammatory interleukins. stretch and chemical irritation. Intravesical administration of TRPV1 agonists has been used in the management of the overactive bladder for many years, largely on an empirical basis. The recent recognition of disease state-related changes in the expression of TRP channels has provided a new impetus to investigate the roles of these channels in normal bladder function and dysfunction[24]

7.2 Trp channel in the skin:

Populations of non-neuronal cells within the skin express many different types of TRP channels which are thought to be involved in various key cutaneous functions including skin-derived pruritus, proliferation, differentiation, cancer and inflammatory processes TRPV1 as a key molecule in itch. TRPV1 is involved in the development of skin-derived pruritus, which is thought to occur through itch-specific subpopulations of TRPV1-expressing sensory afferent neurons (also known as pruritoceptive neurons. TRPV1 is also expressed in non-neuronal cell types of human skin74, and its expression is elevated in epidermal keratinocytes of patients with prurigo nodularis75. Certain endogenous signalling molecules that potentiate TRPV1 activity (including acids, ATP, lipoxygenase products, prostaglandins and histamine) are also potent pruritogens. It is probable that on sensory neurons, histamine indirectly activates TRPV1 through histamine H1 receptor-dependent Role of TRPV1 in the control of skin growth, skin cell survival and cutaneous inflammation. It has been suggested that TRPV1 participates in the regulation of cutaneous growth and differentiation. TRPV1-mediated calcium influx in cultured human keratinocytes suppresses proliferation and promotes apoptosis. In addition, activation of TRPV1 by either capsaicin or heat alters the formation of the epidermal permeability barrier in human skin in vivo85. TRPV1 has also been suggested to regulate cutaneous inflammation. Capsaicin-induced activation of TRPV1 on human epidermal and hair follicle-derived keratinocytes in vitro results in the release of several pro-inflammatory cytokines.[25]

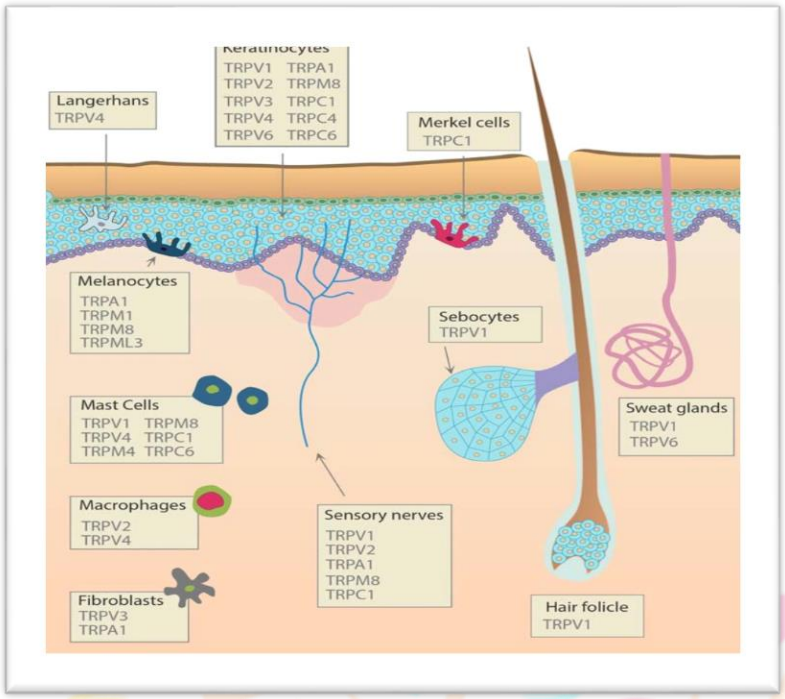

Fig NO.5: trp channel in skin

7.3.trp channel in pulmonary system:

The mammalian respiratory tract is lined with a dense plexus of sensory fibres, including those that express TRPA1 and TRPV1. Activation of this subset of nerve fibres by irritant and/or inflammatory stimuli triggers multiple reflexes such as sneezing, coughing, mucus secretion, bronchospasms and apnoea that limit ventilation and dilute and/or expel foreign materials. Analogous to pain, in which inflammatory mediators produce a hypersensitive response to various stimuli, reflexes such as coughs are proposed to be sensitized by mediators of inflammation and oxidant stress, such that they become triggered by innocuous stimuli. Thus, although a distinct and unusual subpopulation of afferent fibres may be responsible for coughing reflexes airway nocirceptors appear to exert a considerable amount of control over the sensitivity of this reflex.

7.4.trp channel in brain:

TRP channels in the brain Many TRP channels are expressed by brain tissue; some are expressed at high levels (for example, TRPC3 and TRPC5), whereas others are expressed at low levels (for example, TRPV1). The function of these channels remains to be elucidated, but there is evidence that several TRP channels may contribute to neuronal excitability and neurotransmitter-mediated signaling in the brain.[26]

8.Clinical significance:

Mutations in TRPs have been linked to neurogenrative disorders, skeletal dysplasia, kidney disorders and may play an important role in cancer.[27] TRPs may make important therapeutic targets. There is significant clinical significance to TRPV1, TRPV2, TRPV3 and TRPM8's role as thermo receptors, and TRPV4 and TRPA1's role as mechanoreceptors; reduction of chronic pain may be possible by targeting ion channels involved in thermal, chemical, and mechanical sensation to reduce their sensitivity to stimuli. For instance the use of TRPV1 agonists would potentially inhibit nociception at TRPV1,[28] particularly in pancreatic tissue where TRPV1 is highly expressed. The TRPV1 agonist capsaicin, found in chili peppers, has been indicated to relieve neuropathic pain. TRPV1 agonists inhibit nociception at TRPV1

8.1 Role in cancer

Altered expression of TRP proteins often leads to tumor genesis, as reported for TRPV1, TRPV6, TRPC1, TRPC6, TRPM4, TRPM5, and TRPM8 TRPV1 and TRPV2 have been implicated in breast cancer.[29] TRPV1 expression in aggregates found at endoplasmic reticulum or Golgi apparatus and/or surrounding these structures in breast cancer patients confer worse survival. TRPV2 is a potential biomarker and therapeutic target in triple negative breast cancer. TRPM family of ion channels are particularly associated with prostate cancer where TRPM2 (and its long noncoding RNA *TRPM2-AS*), TRPM4, and TRPM8 are over expressed in prostate cancer associated with more aggressive outcomes. TRPM3 has been shown to promote growth and autophagy in clear cell renal cell carcinoma while TRPM5 has ontogeny properties in melanoma.[30]

8.2 Role in inflammatory response

In addition to TLR4 mediated pathways, certain members of the family of the transient receptor potential ion channels recognize LPS LPS-mediated activation of TRPA1 was shown in mice and *Drosophila melanogaster* flies.At higher concentrations, LPS activates other members of the sensory TRP channel family as well, such as TRPV1, TRPM3 and to some extent TRPM8. LPS is recognized by TRPV4 on epithelial cells. TRPV4 activation by LPS was necessary and sufficient to induce nitric oxide production with a bactericidal effect.

9. Different mechanisms of TRP channel modulation by growth factors

9.1. PLC-coupling of RTK and downstream signaling cascades

Stimulation of RTK receptors by GF activates PLC, which in turn generates IP_3 and DAG from PIP_2. This signaling cascade induces a rise in cytosolic Ca^{2+} concentration via two closely coupled components: calcium release via IP_3 receptors from the intracellular Ca^{2+} stores, and Ca^{2+} influx across the plasma membrane. Various TRP channels have been associated with this mode of Ca^{2+} influx in response to GF, whether it is by direct interaction with the RTK receptor or by downstream PLC signaling cascades. The generation of IP_3 and DAG from PIP_2 via GF-induced PLC activation has various consequences for TRP channel activation. First, the effect that PIP_2 exerts on various TRP channels is abolished, thereby altering TRP channel activity. As such, PIP_2 hydrolysis will lead to increased channel activity if PIP_2 was exerting an inhibitory effect. This mode of activation has been suggested for TRPC4 by VEGF signaling and PKD2 by EGf. Alternatively, PIP_2 can activate TRP channels, and hydrolysis could lead to channel inactivity. This is the case for TRPM7, where EGFR signaling results in inhibiting the channel via PIP_2 removal from the channels surroundings. TRPV1 regulation by NGF has been extensively studied, and several different mechanisms for channel sensitization have been suggested. Regarding the effect of PIP_2 on the channel, both inhibiting and activating effects have been reported. Despite these conflicting results, the consensus exists that NGF promotes TRPV1 activation, but rather via other mechanisms than PIP_2 hydrolysis.

9.2. Phosphorylation

Phosphorylation and dephosphorylation are reversible post translation modification able to alter structure and function of ion channels.A certain phosphorylation/dephosphorylation state can give rise to a more active or inactive channel configuration or can promote membrane insertion. Several kinases have been associated with GF signaling and TRP channel activation.
Protein kinase C (PKC) activation can mediate regulatory actions of DAG in response to IGF1 by phosphorylating TRPV1, thereby increasing its membrane expression. This phosphorylation increased TRPV1-mediated current amplitudes, and mutation of the residues acting as PKC substrates abolished this effect.
MAPK/ERK kinases are able to phosphorylate TRPV2 in response to NGF, thereby facilitating neurite outgrowth. As such, neurite length, TRPV2 expression and TRPV2-mediated Ca^{2+} signals were reduced upon mutagenesis of the ERK phosphorylation motifs in TRPV2 . Additionally, TRPV3 phosphorylation by ERK kinases has been observed after EGF signaling in keratinocytes.
The PI3K-dependent Src kinase family is also involved in TRP channel phosphorylation in response to GF signaling. For example,the phosphorylation of C-terminal TRPC4 residues Tyr-959 and 972 following EGFR stimulation, in which the insertion in the membrane was increased. Interestingly, inhibition of the Src family tyrosine kinases reduced Ca^{2+} influx in both COS-7 cells and TRPC4-expressing HEK293 cells. In line with these findings, cells expressing the tyrosine mutants exhibited a reduced EGF response Similarly, phosphorylation of TRPV1 by Src kinases at tyrosine residue Y200 promotes membrane insertion of the channel in response to NGF.
In addition, the TGFβ pathway can regulate TRP channels via phosphorylation as sensitization of TRPV1 was established via phosphorylation of the channel by cyclin depende kinase5 (Cdk5) .

9.3. Reactive oxygen species

The reactive oxygen species (ROS) producing NADP oxidase has been shown to be involved in the signaling pathways of several GF, cytokines, and vasoactive agents. Numerous TRP channels display a sensitivity to redox status changes mediated by ROS, in particular TRPM2. As such, it was demonstrated that VEGF signaling in the context of post-ischemic neovascularization required ROS generation in endothelial cells to activate TRPM2 and induce Ca^{2+} influx . A similar mechanism of activation is described for TGFβ1-mediated activation of TRPV1 in corneal myofibroblasts. Here, phosphorylation of SMAD2 stimulated ROS generation, which directly activated TRPV1.

9.4. RTK-induced protein translocation

Besides altering the activity of TRP channels via RTK signaling pathways, the number of channels residing in the plasma membrane can be modified in response to GF signaling. This translocation can be achieved by vesicular transport of TRP channels along the cellular exocytosis and endocytosis pathways and is mainly regulated by the PI3K pathway .While being a more unconventional activation mechanism for altering channel 'gating', it plays a critical role in the cellular response towards GF signaling.
TRPV2 was first identified as being a GF regulated channel (GRC) In this study, it was shown that IGF-1 stimulation induced Ca^{2+} influx and membrane currents in CHO cells overexpressing TRPV2, most likely via translocation of the channel to the plasma membrane. Moreover, this translocation could be blocked by PI3K inhibitors Wortmannin and LY294002, suggesting that this translocation is mediated by the PI3K pathway. These findings were confirmed in a more recent study, where they demonstrated

increased current density and membrane expression of TRPV2 in a PI3K dependent manner. However, some controversy exists regarding TRPV2 membrane translocation in response to IGF-1, since some groups were not able to reproduce these results. In addition, also PDGF has been shown to increase plasma membrane expression of TRPV2.
The EGF signaling pathway is another major initiator of TRP channel translocation and membrane insertion. As mentioned earlier, TRPC4 translocation to the PM is initiated upon phosphorylation by the Src kinase family. Moreover, both TRPC5 and TRPM6 membrane expression relies on EGF-induced rapid vesicular insertion via the PI3K pathway and Rac1 GTPase .
Finally, NGF can alter membrane expression of the sensory TRP channels TRPM8 and TRPV1 via various pathways. Earlier, we have mentioned the promotion of TRPV1 PM insertion after phosphorylation of the channel in response to NGF. The PI3K pathway plays a crucial role in initiating this translocation, by activating the Src kinases responsible for TRPV1 phosphorylation . Furthermore, TRPM8 PM expression was increased after NGF treatement in a PI3K-dependent manner as well. Additionally, the authors were able to demonstrate that TRPM8 colocalizes with LAMP-2 and suggest that it contributes to the NGF-induced vesicular transport of TRPM8 to the plasma membrane

9.5. Transcription

Another important system controlling TRP channel expression occurs at the level of gene transcription. MAPK/ERK kinases can directly phosphorylate TRP channels to increase their activity or promote their membrane insertion. Moreover, these kinases play a major role in activating the cellular transcriptional machinery, thereby altering gene expression. As such, they are also able to modulate TRP channel expression via the activation of transcription factors (TF) that could bind to the promoter regions of TRP channel genes.
An excellent example of this mechanism is the induction of TRPC6 expression by TGFβ1. TGFβ1 signaling will activate the MAPK pathway via RAS activation. One component of this MAPK pathway is p38 MAPK, which can promote the activity of TF serum response factor (SRF). SRF will bind the promotor region of TRPC6, facilitating its transcription and eventually functional expression[31]
Another GF utilizing the transcriptional machinery to induce TRP channel expression is NGF. In inflammatory conditions, NGF will activate the ras-MAPK pathway to increase TRPV1 mRNA in sensory neurons.
Alternatively, GF can inhibit the expression of TRP channels via transcriptional regulation. TRPA1 was reported as a target of IGF-1/ sirtuin 1 signaling in the mouse heart. IGF-1 normally instructs SIRT1 to occupy the TRPA1 promotor and thereby inhibiting its expression. Interestingly, increased TRPA1 expression was observed in the heart of cardiac-restricted IGF- transgenic mice[31]

10.Conclusion:

The available evidence strongly supports the proposal that TRP channels play important roles in the normal function of vascular ECs and SMCs (Figure 10). TRP channels are implicated in ROC and SOC influx, endoplasmic and sarcoplasmic reticulum Ca2+ release mechanisms, mechanically activated (shear, pressure and stretch) cellular signalling, membrane potential regulation and Mg2+ handling, Additional reports imply that TRP channels are important contributors to the onset, maintenance, progression of or response to vascular pathologies or insults such as hypertension, subarachnoid haemorrhage, vascular hypertrophy, proliferation, ischeamia and oxidative stress. Further studies are needed to elucidate the tissue-specific mechanisms and protein interactions through which TRP channels regulate vascular function in health and disease.

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