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Letter to the Editor

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The Potential of Transient Receptor Potential Channels

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Dear Editor,

Transient Receptor Potential (TRP) family is a class of integral membrane protein described for the first time in 1989 in *Drosophila melanogaster* mutants. A particular phenotype showed photoreceptors characterized by transient voltage response to continuous light exposure. Thanks to sequencing analysis TRP channel proteins have been identified.

These proteins are mostly conserved from nematodes to humans. They are non-selective cation channels unified by homology of their transmembrane domains that act as signal transducer by altering membrane potential or intracellular ions concentration. Based on sequence homology the mammalian TRP channel super family is classified into six subfamilies of about 30 TRP: TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPA (Ankyrin), TRPML (Mucolipin), and TRPP (Polycystic). The major differences between TRP channel subfamilies are found in the N- and C-terminal cytosolic domains, which contain putative protein interaction and regulatory motifs. TRPC channels are considered canonical because they have the closest structure to the TRP channel discovered in *Drosophila*. TRPV channels are termed vanilloid channels because the first discovered channel of this group, TRPV1isactivated by vanilloids, a group of compounds, and structurally related to capsaicin and found in several organic substances. TRPM term derives from melastatin is due to a comparative analysis between benign nevi and malignant nevi. TRPML and TRPP were named after diseases in which their mutations are responsible for the manifestation of this particular disease, such as TRPML1 and mucolipidosis type IV. TRPA that consists of only one channel is named for the large group of ankyrin repeats.

TRP receptors localize to both plasma membranes and internal membranes (such as ER membranes) where this channel mobilizes internal calcium (Ca^{2+}) stores. They are expressed in a wide variety of tissues having several functions, including temperature sensation, nociception, osmoregulation, muscle contraction and vaso-motor control. Moreover, some TRP channels play important roles in the processes of tumorigenesis, migration, and metastasis.

Tumor formation and metastasis are complex processes involving multiple steps. Literature report that many genetic alterations influence TRP channels expression promoting growth, proliferation, and metastasis of tumor cells. Depending on the type of tumor various channels have been involved: TRPC1, TRPC3, TRPC4, TRPC6, TRPM7, and TRPM8 in lung cancer; TRPC1, TRPC3, TRPC6, TRPM7, TRPM8, and TRPV6 in breastcancer; TRPV1, TRPV2, TRPV6, TRPM8, TRPM2, and TRPC6 in prostate cancer; TRPC1, TRPC3, TRPC4, and TRPC6 in ovarian adenocarcinoma; TRPC6, TRPM7, and TRPV6in gastric cancer; TRPC1, TRPC3, TRPC6,

TRPV1, TRPV2, TRPV4, TRPM4, and TRPM7 in liver cancer; TRPM7 and TRPC1 in nasopharyngeal carcinoma; TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, TRPV1, TRPV2, TRPV4, TRPML2, TRPML1, TRPM2, and TRPM8 in glioma; TRPM1, TRPM2, TRPM7, TRPM8 and TRPV2 in melanoma; TRPC6 in esophageal carcinomas; TRPV1, TRPV3, and TRPV6 in colon cancer; TRPC1, TRPC4, TRPC6, and TRPC7 in renal cell carcinoma.

The exact role of all TRP channels in cancer progression is not well understood, although different TRP channels are differently expressed in normal tissues and tumors. This difference may provide a new basis for tumor diagnosis and might be a target to develop a new cancer therapy.

Because TRP channels are permeable for calcium, they are of interest for therapeutic application, for example because of the ability of calcium to induce apoptosis. In fact, malignant transformation of cells, which is facilitated by apoptosis impairment, is often accompanied by alterations in expression or function of these proteins. However, most ion channels have broad expression patterns and thus are not cancer-specific. Therefore, selective targeting is critical to prevent toxicity to normal cells, induced by the pharmacological impact of channel function. Further, it should be considered that most TRP channels that have a role in apoptosis have been also implicated in other cancer-related processes, so their targeting can have several effects.

TRP activation can be also of particular interest to modify the immune response. Indeed, TRP channels are expressed also in immune and epithelial cells with important implications for immunologic response. Evidences indicate that cancer cells cannot be studied alone, but together with the surrounding tumour microenvironment formed by mesenchymal, endothelial and immune cells. Microenvironment strongly contributes to tumour progression as postulated by the 'cancer immune editing theory'. Between cancer cells and immune cells a balance is established leading to elimination, equilibrium or escape of tumor cells. The elimination phase is characterized by the ability of immunity to eradicate tumor cells on the basis of the expression of specific antigens. Engagement of immunoreceptors, such as T-cell and B-cell antigen receptors, causes the release of Ca^{2+} from the endoplasmic reticulum and this TRP-mediated Ca^{2+} influx seems to be important for lymphocyte functions. In this regard, TRPC3 modulates Ca^{2+}-dependent proliferation of primary CD^{4+} T cells. In the equilibrium phase, adaptive immune responses give rise to an immune-selection pressure on tumour cells making survive only cells with reduced immunogenicity. These cells became resistant to killing by the immune system. But the greatest interaction between tumour cells and immune system occurs during the escape phase with the acquired ability of tumor cells to escape and progressively grow developing tumoral mass. Right now key contributor to escape is the development of a complex immune suppressive network in the tumor microenvironment. Growth factors and cytokines derived from both immune and tumour cells contribute to the failure of the immune system in controlling tumour growth. Chronic inflammation in the tumour tissue is able to alter myeloid cells and can convert the mint potent immuno-suppressive cells, called myeloid-derived suppressor cells (MDSCs). The inhibition of this immunosuppressive tumour network in the microenvironment can be dramatically influenced by the function of the ion channels. It has been demonstrated that TRPV1 is able to activate MDSCs, which in turn can inhibit inflammation.

In conclusion, TRP channels may play an important role both in the diagnosis and targeted treatment of tumors. Although there are promising results about TRPs' role in several cancers, the delicate balance of pro- and anti-inflammatory functions of some of them make the development of therapeutic intervention especially challenging.

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