A Comment on Ion Channels as Pharmacological Targets in Oncology

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The recent Perspectives on How to Drug an Ion Channel rightly point out the increasing relevance of ion channels as objects of therapy. We wish to add a few comments about the potential use of channel inhibitors in cancer therapy. During the last decade, different channel types have been found to be overexpressed in a variety of tumors, thus emerging as possible tumoral markers. What is more, ion channels often give manifold contributions to the physiology of the neoplastic cell (Kunzelmann, 2005). A generally recognized mechanism in proliferating cells, originally proposed for T lymphocyte activation, depends on interplay of K^+ and Ca^{2+} channels (DeCoursey et al., 1984). Ca^{2+} fluxes participate in cell cycle control and K^+ channels can modulate Ca^{2+} entry by regulating the resting V_m (membrane potential). Ion channel engagement typically modulates other cellular processes, such as cell volume control and motility, which are implicated in cell division, migration, and invasiveness (e.g., Ransom et al., 2001). Malfunction of these is a hallmark of neoplastic progression and it is increasingly clear that ion channel effects can also be exerted by nonconductive signaling mechanisms (Hegle et al. 2006).

Considering the pharmacological advantages they offer, targeting ion channels would be a blessing for cancer therapy. When a given tumor specifically expresses certain channel types, a possible strategy is local delivering of cytotoxic agents by means of compounds that bind these channels with high specificity, such as monoclonal antibodies or toxins (e.g., Gómez-Varela et al., 2007). However, direct antitumoral effects are also studied intensively, because many channel blockers are well known to inhibit cell proliferation in vitro. Although promising, the application of this strategy in vivo is still in its infancy. Besides the difficulty of finding good lead molecules for medicinal chemistry developments, as discussed in the reviews of the present series, a serious drawback is that channel inhibitors can produce grave side effects. Here, we wish to comment about two issues that may offer ways to circumventing this problem.

The first point arises from the observations of Kaczorowski et al., (2008), who suggest that, even when using compounds that are not specific for channel isoforms, specificity of action can be achieved by exploiting the V_m dynamics of different cell types. For example, neuropathic pain is believed to arise in damaged regions that tend to produce local cell depolarization. Hence, Na^+ channel blockers that tend to bind open and/or inactivated channels would address preferentially depolarized or quickly firing cells. This idea seems suggestive for oncologic applications as well, because the V_m dynamics typical of proliferating cells is very different from that of excitable cells. An example from our field of research is $K_V11.1$ (commonly named ERG1, from *ether-à-go-go* related gene type 1), whose contribution to the cardiac action potential repolarization is well established. In brief, $K_V11.1$ activates/inactivates at depolarized potentials (typically, during the plateau of the cardiac action potential), but the inactivation is rapidly removed on repolarization, which lets ERG1 contribute to shape this phase. In fact, ERG1 inhibitors can produce serious arrhythmias. $K_V11.1$ is often expressed in neoplastic cell lines and primary tumors (Arcangeli, 2005), where it often seems to participate in the promotion of neoplastic progression. Its steady-state activation and inactivation curves crossover around −40 mV (Faravelli et al., 1996), thus producing a significant "window" current in the typical range of quasi-stationary V_m of slowly cycling mammalian cells (between −30 and −50 mV, usually). Therefore, the proportion of channels residing in the different conformational states should be different in excitable and proliferating cells, which we believe encourages to undertake a search for more state-specific compounds, in order to achieve preferential targeting of neoplastic cells. An approach based on a similar reasoning could attempt to target specific cell states. It has in fact been observed in different experimental systems that the K^+ channel's voltage-dependent properties slowly oscillate in phase with the cell cycle stages (to the best of our knowledge, the first direct evidence was provided by Day et al., 1993).

Second, as summarized by Andersen (2008), a drug can affect ion channels in different manners. It may obstruct the channel pore, or produce inhibition through binding of allosteric sites. In addition, an amphiphilic

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compound has several potential ways of altering the channel's conformational states, by interacting with the lipid bilayer. To this list, we would add a further mechanism that, aside from general physiological interest, may also turn out to allow a supplementary pharmacological strategy. Ion channels are increasingly recognized to associate with other membrane proteins to form macromolecular complexes that modulate intracellular pathways. An example with implications for oncology is the interaction between integrin receptors and ion channels. Work dating back to the early nineties (Becchetti et al., 1992; Schwartz, 1993) shows that integrin-mediated cell adhesion to the extracellular matrix is often accompanied by ion channel activation, with ensuing effects on cell differentiation, migration, and other aspects of developmental physiology sensu lato. More recent work indicates that these effects are often mediated by physical association between channel proteins and integrin receptors (e.g., Levite et al., 2000). This association, besides reciprocal regulation between the proteins that form the complex, can recruit a variety of intracellular signaling elements and also feed back on either channel or integrin expression, or both (for review see Arcangeli and Becchetti, 2006). Therefore, we suggest that protein–protein interactions are another possible target for drugs to alter the free energy difference between channel states. Among the extracellular pharmacological treatments (the most useful, in therapy), we deem that this tactic could offer another way to achieve tissue specificity. It may allow to address only those cell types in which certain receptors or accessory proteins are expressed. For instance, in human acute myeloid leukemia cells, hERG1 channels appear to mediate the vascular endothelial growth factor receptor-1–dependent cell migration and invasion, both in vitro and in vivo (Pillozzi et al., 2007). In brief, the neoplastic cell clones expressing hERG1 tend to form a macromolecular complex between the growth factor receptor, the β1 integrin subunit, and the K^+ channel itself. This process considerably increases the malignancy of tumor cell populations. It should then be possible to find molecular strategies to disassemble such a multiprotein complex in malignant cells, which should produce little interference with the physiology of excitable cells. Another suggestive example that may be liable to both the above strategies is offered by voltage-gated Na^+ channels, which mark late stages of breast and prostate cancer and whose accessory β1 subunit behaves as a cell adhesion molecule (Brackenbury et al., 2008).

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