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Role of Voltage-gated Potassium Channels in Cancer

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Abstract. Ion channels are being associated with a growing number of diseases including cancer. This overview summarizes data on voltage-gated potassium channels (VGKCs) that exhibit oncogenic properties: ether-à-go-go type 1 (Eag1). Normally, Eag1 is expressed almost exclusively in tissue of neural origin, but its ectopic expression leads to uncontrolled proliferation, while inhibition of Eag1 expression produces a concomitant reduction in proliferation. Specific monoclonal antibodies against Eag1 recognize an epitope in over 80% of human tumors of diverse origins, endowing it with diagnostic and therapeutic potential. Eag1 also possesses unique electrophysiological properties that simplify its identification. This is particularly important, as specific blockers of Eag1 currents are not available. Molecular imaging of Eag1 in live tumor models has been accomplished with dye-tagged antibodies using 3-D imaging techniques in the near-infrared spectral range.

Key words: Potassium channels — Cell proliferation — Cancer — Near-infrared imaging

Introduction

Ion channels possess several properties that make them an excellent target for drug diagnosis and therapy. They have been implicated in many diseases, either in a primary etiologic role (channelopathies) or as mediators in pathogenesis. Because they are transmembrane proteins, they are accessible from the external environment. This makes it possible to use biological agents such as antibodies or toxins to target them. Another important property of ion channels is that their function can be studied with great accuracy using electrophysiological techniques. Given these features, it is not surprising that roughly one third of all drugs used in modern therapies are ion channel modulators (e.g., Wickenden, 2002).

Pathophysiology of Ion Channels in Cell Proliferation and Cancer

The implications of ion channels in excitable tissue are obvious, given the deep involvement of these molecules in the propagation of signals. The situation is not as clear in the case of non-excitable tissues because we only partly understand the roles of most ion channels in the physiology of non-excitable cells. For voltage-gated channels, this lack of clarity is particularly dramatic, as the effects of changes in membrane potential of non-excitable cells are largely unknown. With regard to cell proliferation and cancer, it is largely accepted that most cell types undergo a transient hyperpolarization at the exit of G1 phase and that tumor cells are, on average, depolarized compared to non-tumor cells. However, this information is essentially all that is known regarding the role of ion channels in non-excitable cells (a detailed review can be found, for example, in Rouzaire-Dubois, Benoit & Dubois, 2002).

It has become widely accepted that voltage-gated potassium channels (VGKCs) are implicated in cell proliferation (*see* Conti, 2004; Pardo, 2004 and references therein for further examples). The main source of evidence for this association is that broad-spectrum blockers of VGKCs inhibit proliferation in many cell types (Table 1). Many publications describe this observation, but make no attempt to describe the mechanistic link between channel block and inhibition of proliferation. There are only a few cases of unambiguous evidence for a direct

Abbreviations: EAG: Ether-à-go-go, VGKCs: voltage-gated potassium channels

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Table 1. Examples of cell types whose proliferation rates have been shown to be diminished by potassium channel blockers

Cell type	Referencess
T-lymphocyte	DeCoursey et al., 1984, Sidell & Schlichter, 1986
Human peripheral lymphocyte	Price, Lee & Deutsch 1989
Monocyte	DeCoursey et al., 1996; Kim, Silver & DeCoursey, 1996
L2 lymphocyte	Lee et al., 1986
Murine B lymphocyte	Amigorena et al., 1990; Arcangeli et al., 1995
Lymphoma	Wang et al., 1992
Human brown fat	Pappone & Ortiz-Miranda, 1993
Human melanoma	Nilius & Wohlrab, 1992; Meyer et al., 1999
Human breast cancer	Woodfork et al., 1995; Pardo et al., 1999
Human cervix	Pardo et al., 1999
Neuroblastoma	Pardo et al., 1999
Rat Schwann	Chiu, & Wilson, 1989; Wilson & Pappone, 1999
Rat glial cells	Puro, Roberge & Chan, 1989; Pappas, Ullrich & Sontheimer, 1994; Pappas & Ritchie, 1998
Neuroblastoma-glioma	Rouzaire-Dubois & Dubois, 1991
Small-cell lung cancer	Pancrazio, Tabbara & Kim, 1993
Human bladder cancer	Monen, Schmidt & wondergem 1998; Wondergem et al., 1998
Neuroendocrine cells	Kayser, Ulrich & Schaller, 1998
Hepatocytes	Liu et al., 1998
Pituitary cells	Vaur et al., 1998
Endothelial cells	Faehling et al., 2001
Keratinocytes	Mauro et al., 1997; Wohlrab & Markwardt, 1999
Corneal epithelium	Roderick et al., 2003
Retinal pigment cells	Hoffman et al., 1998
Chondrocytes	Wohlrab et al., 2002
Myeloblastic leukemia	Wang et al., 1997; Xu, Wilson & Lu, 1996; Xu et al., 1999
Prostate cancer	Skryma et al., 1997
Hepatocarcinoma	Zhou et al., 2003
Mesothelioma	Utermark et al., 2003
Colon cancer cells	Abdul & Hoosein, 2002c; Lastraioli et al, 2004

implication of VGKCs in the process of cell division and/or tumorigenesis although many recombinant channels have been overexpresssed in various cell lines. They derive from the effects on proliferation rates and tumorigenesis of exogenous channel expression in transfected cells. Eag1 (Pardo et al., 1999) and TASKS (Mu et al., 2003), both of whose overexpression favors tumor progression in animal models, can be linked causally to tumor progression.

The main theoretical problem when trying to understand the mechanism of VGKCs' influence on cell division is that both the stimulus that activates these proteins (the membrane potential), and the main response (the efflux of potassium, with a concomitant hyperpolarization) are the same. By comparison, it is as if a single molecule could stimulate all growth factor receptors, and the activated signaling cascade would always be the same. Where then does the need for different channels arise? Why do some VGKCs induce proliferation, and others do not? A more complex mechanism must be at work. The signaling systems may distinguish between membrane potential alterations not only by the fine differences in activation properties of different channels, but also by the location and timing of activation of the channel. To further complicate the issue, most channels form supramolecular complexes with other proteins that can deeply change the properties of the channel alone, as well as influence its location. If the role of VGKCs in cancer were simply due to membrane potential changes induced by potassium currents, then activation of most types of VGKCs would affect proliferation. However, this is not the case.

There are currently two main hypotheses that attempt to explain the effects of VGKCs on proliferation:

Cell Volume. K^+ permeation is required to compensate for the charge of chloride ions flowing out of the cell during volume adaptation in order to maintain transmembrane voltage. Since growth (increase in size) and proliferation (increase in cell number) are closely related processes, control of cell volume may be a possible function exerted by potassium channels. It is unclear whether higher eukaryotic cells have a cell-size checkpoint similar to yeast cells, i.e., whether a certain size needs to be reached before cell division can proceed. This does not appear to be the case in cultured Schwann cells. Neuroblastoma and glioma cells appear to show an optimal cell volume for initiating cell division, although this does not seem to be an absolute requirement for mitosis. The main argument against

the cell-volume hypothesis is that volume control was found not to be related to changes in membrane potential, and is essentially an electroneutral process, arguing against the participation of voltage-gated proteins. In fact, stretch-activated channels would be better candidates for the volume-regulation functions of ion channels.

Membrane Potential: The membrane potential is used by cells to drive the transport of nutrients, and hence it is of primordial importance for rapidly proliferating cells. A negative intracellular potential also facilitates the entry of calcium through calcium channels, which in turn is required for cell replication. Additionally, maintenance of the cellular membrane potential is the best-understood role of voltage-gated channels. This hypothesis suffers a weakness in that a change in resting potential is not always observed when inhibiting cell proliferation through potassium channel blockers (Malhi et al., 2000; Rouzaire-Dubois & Dubois, 1991, Rouzaire-Dubois et al., 2000).

Neither of these two hypotheses satisfactorily explains the role of K^+ channels in cell proliferation. VGKCs are the most diverse family of ion channels, with properties varying over a very broad range, and it is naïve to think that all of them serve just as mere compensation mechanisms for membrane potential depolarizations and/or chloride fluxes. The focus on potassium flux has led much research to neglect the fact that a voltage-gated potassium channel is much more than a voltage-controlled pore for potassium ions. It is also a protein that responds to depolarization with conformational rearrangements, and the opening of a permeation path is only but one of the consequences of this conformational change. Additionally, voltage-gated K channels are a part of supra-molecular complexes in which they act as voltage sensors, but they may also act as a link between the extracellular environment and the cytoplasm. Experiments exploring the roles of VGKCs with a more integrative focus will be needed to clarify this issue.

Defined Ion Channels in Cancer

Several molecularly identified ion channels have been observed to be overexpressed in a number of tumor types. These are Kv1.3, K2p9.1, Kv10.1 (EAG1) and Kv11.1 (HERG).

Of the VGKCs implicated in cell proliferation, Kv1.3 (Stühmer et al., 1989) is probably the best described case (DeCoursey et al., 1984; Cahalan, Wulff & Chandy, 2001, Chandy et al., 2004) since it has been implicated in T lymphocyte activation (DeCoursey et al., 1984; Lee et al., 1986; Gollapudi et al., 1988; Amigorena et al., 1990). The expression of Kv1.3 in tumor tissues and its implication in the proliferation of different tumor types is also well documented (Abdul & Hoosein, 2002a, b; Chittajallu et al., 2002; Abdul, Santo & Hoosein, 2003; Artym & Petty, 2002; Fraser et al., 2003; Preussat et al., 2003).

$K_{2P}9.1$ (TASK-3, KCNK9) (Chapman et al., 2000; Kim, Bang & Kim, 2000; Rajan et al., 2000) is a member of the 4TM2P K^+ channel family, and has been described to be frequently amplified in tumor samples (Mu et al., 2003). $K_{2P}9.1$ was proposed to increase the tumorigenicity of cells in mice models, although it does not induce malignant transformation on its own (Mu et al., 2003).

Of the four molecularly identified potassium channels clearly implicated in tumor proliferation, two belong to the same family, Eag1 (Kv10.1) and HERG (Kv11.1). It is interesting to note that the Eag family is one of the least populous among VGKCs, with only eight members identified in three subfamilies so far. This relatedness implicates a high prevalence of cancer-related VGKCs in this family.

HERG (Kv11.1) was first identified in neuroblastoma cells as responsible for resting-potential variations (Arcangeli et al., 1995, 1997; Faravelli et al., 1996; Smith et al., 2002), but has since been found in other tumor cell lines (Bianchi et al., 1998) and in samples from clinical tumors (Cherubini et al., 2000; Pillozzi et al., 2002; Lastraioli et al., 2004). It has also been proposed that the splice-form distribution of HERG channels is different in normal and tumor tissues (Crociani et al., 2003).

Eag1

Eag1 (Kv10.1) was first described in a mutation screening in *Drosophila melanogaster* as a leg-shaking phenotype (Kaplan & Trout, 1969). Positional cloning mapped the mutation to a sequence similar to already known voltage-gated potassium channels (Warmke, Drysdale & Ganetzky, 1991). All potassium current types in the neuromuscular junction of mutant larvae were shown to be altered, leading to the conclusion that the *eag* locus encodes a voltage-gated potassium channel subunit that contributes to the regulation of multiple currents (Zhong & Wu, 1991). Drosophila *eag* RNA induces the expression of a non-inactivating, voltage-gated potassium current with peculiar selectivity properties (Brüggemann et al., 1993). Screening for homologous genes in mammalian DNA led to the identification of a whole family of genes, with eight different components grouped in three subfamilies, termed eag, eag-like (elk) and eag-related (erg) (Warmke & Ganetzki, 1994). The prototypic member of the third subfamily, cloned from a human library, (HERG), soon attracted large interest after it was identified as the molecular basis of a form of familial LQT syndrome (Sanguinetti et al., 1995; Trudeau et al., 1995). In recent years, interest in HERG channels has increased exponentially, mainly because its

blockage as a side effect, induced by a vast number of drugs, leads to undesirable cardiac complications (e.g., Roy, Dumaine & Brown, 1996; Snyders & Chaudhary, 1996; Spector et al., 1996; Suessbrich et al., 1996). Since then, demonstrating a lack of effect on HERG channels has become a requirement for drug approval by regulatory authorities.

The homologous channel to Eag in plants is AKT1. It is interesting to note that AKT1 is overexpressed in plant tumors, and plants lacking AKT1 did not support tumor growth (Deeken et al., 2003). The human genome has two members of the Eag family, Eag1 (1q32.1-2) (Occhiodoro et al., 1998, Pardo et al., 1999) and Eag2 (14q24.3) (Ju & Wray, 2002; Schönherr et al., 2002). Both proteins form functional VGKCs in heterologous expression systems and both have currents that activate slowly and exhibit no inactivation. The most characteristic electrophysiological property of both channels is a strong dependence of the prepulse potential (Ludwig et al., 1994). When activated from a less negative holding potential (which is still below threshold), the activation kinetics are several times faster than when the prepulse potential is more negative (hyperpolarized). This phenomenon is present in all voltage-gated ion channels and is termed the Cole and Moore shift (Cole & Moore, 1960). However in Eag, the Cole and Moore shift is on the order of tens of milliseconds, whereas it is less than a millisecond in members of VGKCs not belonging to the Eag family. The Cole and Moore shift is also steeper in Eag1 than in Eag2 (Schönherr et al., 2002). In addition, the Cole and Moore shift in Eag channels is enhanced in the presence of elevated extracellular magnesium concentrations but physiological, in the range of a few mM (Terlau et al., 1996). These properties have been used as a fingerprint, indicating the functional expression of Eag channels in cells and ectopic expression systems.

The expression pattern of Eag1 and Eag2 channels is also different. Both of them are abundant and widely distributed in the brain, but their expression levels differ in peripheral tissues. Eag1 has been detected in myoblasts (immediately before fusion) (Occhiodoro et al., 1998), and Northern blot experiments revealed its presence in placenta (Occhiodoro et al., 1998; Pardo et al., 1999), but no message could be detected in other tissues. On the other hand, Eag2 message is found in many organs, such as heart and lung, but is most abundant in brain and skeletal muscle (Ju & Wray, 2002).

The primary structure of Eag channels reveals several conserved domains besides the channel-defining six transmembrane segments and pore domain. The N-terminus contains a domain that has been crystallized and characterized in detail (eag domain) (Cabral et al., 1998). A substantial part of this domain exhibits a structure similar to *Per-Arnt-Sim* (PAS) domains, usually involved in detection of redox reactions. The large C-terminus of EAG contains a conserved cyclic-nucleotide binding domain that may be implicated in trafficking, a site for calmodulin binding (Schönherr, Lober & Heinemann, 2000) (CaCAM has an inhibitory effect on the channel: Stansfeld et al., 1996), a bipartite nuclear targeting signal (whose function is unknown) and a subunit interaction domain (Ludwig, Owen & Pongs, 1997). The latter was the first example of a tetramerizing coiled-coil (TCC) domain found in higher organisms (Jenke et al., 2003). This TCC has the peculiar attribute of determining the specificity of subunit interaction, besides being able to form very stable tetramers. The introduction of the TCC domain of Eag1 into HERG confers to it the ability to associate with Eag1, a heteromerization that does not occur between the native subunits. Sequence analysis has shown that TCC is a frequent association domain in ion channels. These findings have been confirmed for several channels, and mutations have been identified in the respective TCC domains that lead to malfunctions of these ion channels (Dreyer et al., 2004; García-Sanz et al., 2004; Kanki, et al., 2004; Molina et al., 2004; Stocker, 2004, Roncarati, Decimo & Fumagalli, 2005)

Eag1 (and presumably Eag2 as well) carries glycosylation moieties on two extracellular residues located near the pore region of the channel. Interestingly, proper glycosylation of one of the residues (N406) is required not only for the correct processing of the channel protein, but also for the function of the mature channel. Enzymatic de-glycosylation of Eag1 induces a dramatic decrease of current amplitude and slows activation, indicating that the functional properties of the channel are also modulated by the sugar moieties and not merely determined by the protein as such (Napp et al., 2005). This implies that it is possible to modulate the properties of the current carried through Eag channels by changing the composition of sugar components. If this were a common feature of VGKCs, it would add a new level of complexity and variability to the already highly complex VGKCs scenario.

The first indications of a possible function of the EAG1 channel in cell proliferation were found in *Xenopus* oocytes. Oocytes, widely used as a heterologous expression system, are physiologically arrested in the G2 phase of the first meiotic division (a feature often overlooked in expression experiments). In contrast, somatic cells form asynchronous populations with varying proportions of cells in each phase of the cell cycle. The fact that individual somatic cells used as an ectopic expression system are at various cell division stages is also often overlooked in many experiments. Additionally, given that cell adhesion cycles during division, certain stages will be less represented (or even absent) when working with

adherent cell cultures. Individual experimenters might show a bias toward cell stages with particular morphological properties that are a function of cell stage. In oocytes, the cell cycle arrest is removed by a physiological stimulus (progesterone in *Xenopus*). The oocyte then completes the first meiotic division and is again arrested until fertilization. This process is known as maturation, and is often used as a model for the study of mitotic signals. The key molecule triggering this process is mitosis-promoting factor (MPF), a complex between a cyclin-dependent kinase and cyclin B. Activation of MPF in oocytes, or direct injection of exogenous MPF, induces dramatic changes in the electrophysiological properties of Eag1 expressed in oocytes (such as rectification and changes in ion selectivity; Brüggemann, Stühmer & Pardo, 1997). Although the study of this phenomenon is much more complex in somatic cells, a similar cell cycle modulation seems to happen. EAG1 undergoes an increase in selectivity and a decrease in current amplitude occurring during the M phase of the cycle (Pardo et al., 1998). This could be a manifestation of relationships established between Eag1 channels and microtubules, which are extensively re-organized in M phase. Similar electrophysiological modifications occurr after patch excision and application of colchicine or nocodazole, procedures which disrupt microtubule organization (Camacho et al., 2000).

Eag1 in Cancer

Overexpression of Eag1 produces an increase of proliferation in several cell lines, measured by increase in metabolic activity, BrdU incorporation, or cell number. In addition, cells expressing the channel become less dependent on the presence of growth factors in the medium. Cells normally thrive in media supplemented with 10% serum and starve with less than 1%. However, Eag1-transfected cells continue to grow at serum concentration as low as 0.5%. Transfected cells are also able to grow in the absence of a matrix and form foci in agar-containing media, indicating a loss of contact inhibition (Pardo et al., 1999). These properties are typical of transformed (tumor) cells.

A reliable effect of potassium channel blockers is their ability to inhibit cell proliferation. The actual molecular target for these blockers is unknown. Experiments were directed by this laboratory to test whether Eag1 could be a target for some of these drugs. For example, proliferation of MCF-7 cells (a mamma-adenocarcinoma cell line) can be inhibited by various broad-spectrum potassium channel blockers (e.g., quinidine and glibenclamide; Woodfork et al., 1995). While quinidine is a non-specific K channel inhibitor, glibenclamide is usually considered a blocker of ATP-sensitive potassium channels. However, both drugs are able to block currents through Bag channels, an ATP-insensitive channel. The ability of these substances (in terms of concentration) to reduce proliferation matches their ability in reducing Eag currents.

There exist no known specific blockers for Eag1 that can be used to test the effect of current reduction through Eag1 on proliferation. One way to specifically reduce these currents is by reducing the expression of EAG1 protein. When the expression of Eag1 is inhibited by means of anti-sense DMA technology, the proliferation of the affected cells is also reduced, indicating that Eag1 channels promote proliferation under growth conditions used in these experiments.

It is important to note that expression of Eag1 is not an artifact due to cell culture conditions, since it can also be detected in many primary tumors in a clinical environment (*see*, for example, Barajas Farias et al., 2004).

Is Eag1 expression merely an effect of malignant transformation, or is it causally related? When CHO cells expressing Eag1 are injected into immune-depressed (SCID) mice, they give rise to much larger tumors than control cells, supporting the latter. In addition, CHO cells transfected only with the vector, or expressing other VGKCs such as Kv1.4 also grow significantly slower. In the case of NIH3T3 cells the results are even clearer, as these cells only form tumors when expressing Eag1 (Contreras et al., manuscript in preparation).

Targeting tumors that express Eag1 in humans is a promising application of these observations. However, Eag1 channel blockers also block HERG, most with an even higher affinity than Eag1. Therefore, it is important to clearly characterize the mechanism of block of any potential Eag1 blocker. Eag1 can be selectively targeted by exploiting any differences in blocking properties between Eag1 and HERG. This laboratory has characterized the mechanism of block of two relatively specific blockers, the anti-depressant imipramine and the anti-histamine astemizole (García-Ferreiro et al., 2004). Both have been shown to block Eag1 as well as HERG, have been used extensively in clinical settings and both have proven to be relatively safe. Unfortunately, astemizole (which was sold over-the-counter) was withdrawn due to risk-benefit considerations for this common anti-allergic drug. In a limited number of cases, most due to overdosage, astemizole self-administration led to severe cardiac arrhythmia. We have characterized the molecular blocking mechanism of both drugs, and found that they bind to the inner mouth of the open channel, astemizole's apparent affinity being higher than imipramine's. Also the voltage-dependence of block is different, as astemizole shows little or no voltage-dependence, while block by imipramine is voltage-dependent. Both drugs compete with each

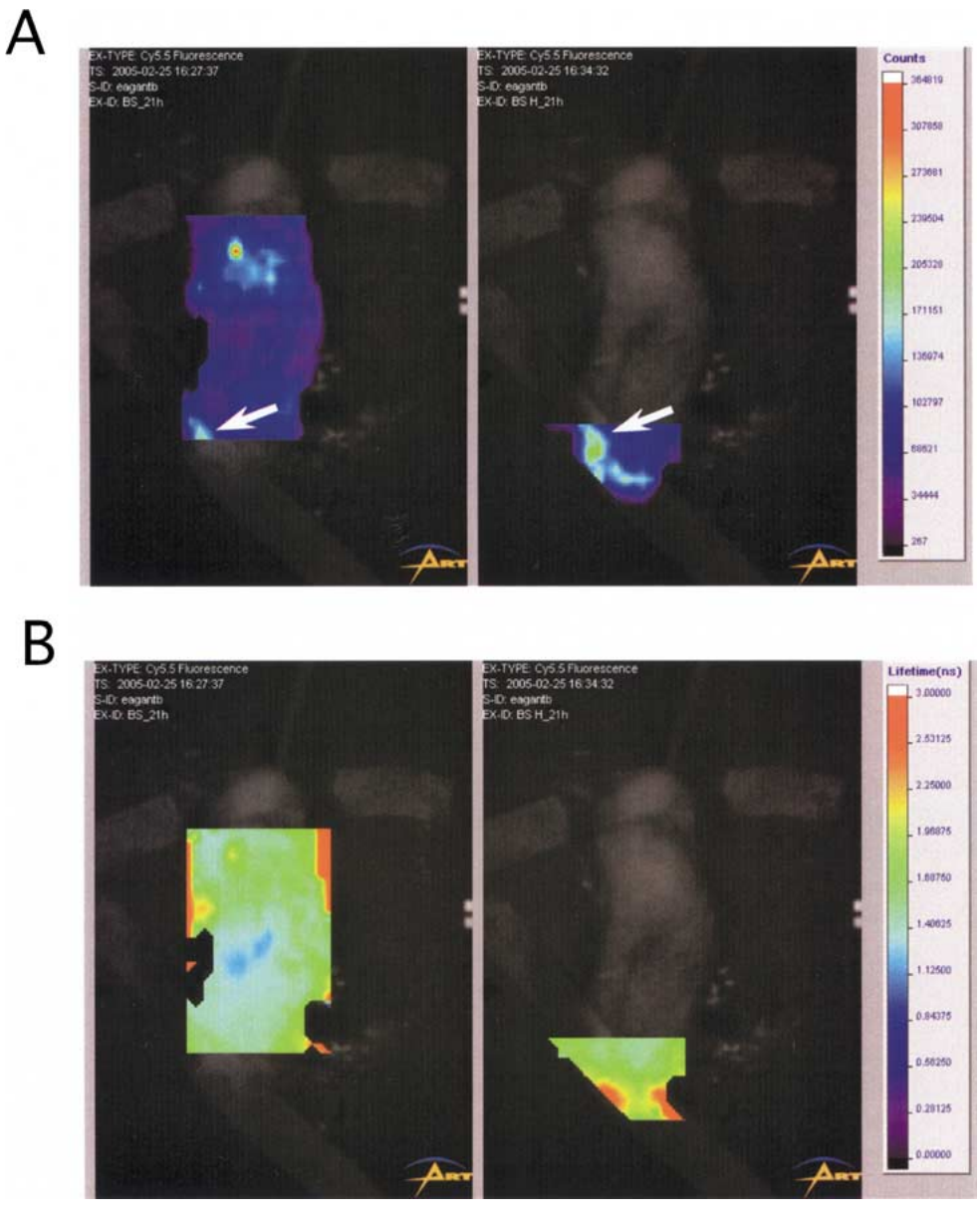

Fig. 1. Pseudo-color image showing near-infrared fluorescence intensity (*A*) and lifetime (*B*) on a mouse carrying an Eag1-expressing tumor after IV injection of specific anti-Eag1 antibody labeled with AlexaFluo 680. The positive lymph node (*arrow*) had not been clinically evident. Measurements of lifetime allow the determination of the specificity of the signal. Only the colored areas were scanned in each case.

other for binding sites, indicating partial overlap among the sites. Any differences in the mechanism of block by these drugs may be exploitable in order to identify compounds that preferentially affect Eag1 and not HERG.

Monoclonal antibodies have the advantage of being potentially very selective. Because Eag1 expression is largely limited to tumor cells, and it is an extracellular epitope, specific antibodies against Eag1 would selectively target tumor cells. Such an antibody would have both diagnostic and therapeutic potentials. As a therapeutic agent, the antibody could modify the activity of Eag1 or it could activate the immune response of the host and thereby target the tumor cells for destruction. A third possibility would be to couple the antibody to a toxic or radioactive agent, in order to concentrate the molecular cargo to the vicinity of the tumor cells and/or induce its internalization. Furthermore, the antibody could be coupled to an enzyme that locally converts a pro-drug into a cytotoxic compound, limiting the toxic activity of the drug to the tumoral environment. A combination of these mechanisms will likely be most effective theraupeutically.

Eag1 as Oncology Target

The specificity and surface expression of the channel can also be used for diagnostic purposes. Recently, a new technique has been developed that allows functional imaging of infrared fluorophores in vivo (*reviewed* in Frangioni, 2003; Shah, 2005). Molecular imaging of fluorescently-labeled antibodies against specific epitopes in vivo shows great possibilities for cancer research. In vitro experiments have already demonstrated decreased proliferation of Eag1-expressing cells by inhibition of the channel, and in vivo experiments following tumor progression under various conditions are underway. This approach not only allows observation of tumor growth and metastasis formation, but also allows the observer to determine whether inhibition of Eag1 leads to a remission. This laboratory has used the explore optix equipment (General Electric Healthcare, London, Canada) to visualize the distribution of Eag1 in an in vivo mouse tumor model. To accomplish this, a monoclonal antibody recognizing an extracellular epitope of Eag1 was labeled with a secondary antibody carrying AlexaFluor680. This IR-fluorescent antibody complex was injected into immuno-suppressed mice carrying previously grafted MDA-MB-435S human mammary carcinoma cells. Figure 1 shows a false-color image of a mouse injected with 100 μg of antibody 24 hours prior to the imaging. The IR fluorescence is concentrated at two spots, the tumor and a sentinel node (arrow) that has not been previously detected by palpation. This pilot experiment demonstrates the potential of in vivo molecular imaging using specific antibody complexes against Eag1 in preclinical cancer research.

In conclusion, a growing body of evidence indicates VGKCs as interesting targets for novel therapeutic and diagnostic approaches in cancer. While VGKCs' function is critical for living organisms, some particular VGKCs become overexpressed in tumor cells, making them good theurapeutic and diagnostic targets.

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