Ion channels: functional expression and therapeutic potential in cancer

Colloquium on Ion Channels and Cancer

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The first colloquium on 'Ion Channels and Cancer' took place between 25 and 28 November 2007, at the Schloss Ringberg in Tegernsee, Germany, and was organized by W. Stühmer and M. Djamgoz.

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decade or so, building on the initial observations that ion channels are involved in both mitogenesis (DeCoursey *et al*, 1984) and malignancy (Pardo *et al*, 1999). A rapidly increasing number of ion-channel types are now known to be expressed in various cancers, and some ion channels are selectively expressed in aggressive cancers and are intimately involved in metastasis (reviewed by Diss *et al*, 2004; Fiske *et al*, 2006; Kaczmarek, 2006; Roger *et al*, 2006; Schönherr, 2005; Villalonga *et al*, 2007).

This two-day colloquium covered the mechanisms behind, and the functional consequences of, the flux of the main ions involved in cellular homeostasis: K⁺, Na⁺, Ca²⁺, H⁺ and Cl⁻. There was also a strong emphasis on linking the function of the ion channels to cellular behaviours that are important during cancer development and progression (Fig 1). The first day focused on ion-channel involvement in cell proliferation, transformation and apoptosis, whereas the second day dealt with cellular behaviours crucial to metastatic cell spread, such as motility and invasion. In addition to the discussions about the ion channels directly implicated in cancer, other talks covered related topics—for example, autoimmune disease, cell activation and vascular permeability—which highlighted mechanisms and pathways potentially relevant to oncology.

One of the important take-home messages touched on by both the speakers and during the discussion periods was the need for the field to make the transition from basic research to the clinic. As ion channels are viable pharmacological targets for many diseases, there was overwhelming confidence that they will have tremendous potential in diagnosis, prognosis and, importantly, therapy. Indeed, this optimism is supported by some recent publications (Fiske *et al*, 2006; Gray & Macdonald, 2006; Hoang *et al*, 2007; Roger *et al*, 2006; Schönherr, 2005; Villalonga *et al*, 2007).

Potassium channels

Various types of K⁺ channel are expressed in non-tumorous cells where they are involved in fundamental cell behaviours such as proliferation and apoptosis (see, for example, Lang *et al*, 2005). K⁺ channels are also expressed in tumours (Pardo *et al*, 2005; Villalonga *et al*, 2007) and therefore there is much interest in understanding their contribution to cancer progression. The group led by H. Ouadid-Ahidouch (Amiens, France) has been studying

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Introduction

The colloquium on 'Ion Channels and Cancer' at the Schloss Ringberg in Tegernsee, Germany, was the first formal meeting to bring together nearly 60 international scientists, oncologists and representatives of the pharmaceutical industry who share a common interest: understanding the role of ion channels in the development and progression of cancer. This field has been growing steadily during the past

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the roles of $K_v10.1$, a voltage-gated potassium channel, and $K_{ca}3.1$, a calcium-activated potassium channel, in breast cancer. Blocking these channels leads to the accumulation of cells in the G1 phase of the cell cycle. Ouadid-Ahidouh proposed that $K_v10.1$ allows entry into G1, and then $K_{ca}3.1$ drives progression through G1 and into S phase. In agreement with this model, growth factors such as insulin-like growth factor 1 (IGF1) increased the expression of both $K_v10.1$ and $K_{ca}3.1$, and induced cell proliferation. The current hypothesis is that $K_{ca}3.1$ activation during G1 results in a strong hyperpolarization of the cell and increases the driving force for Ca^{2+} entry, possibly through the vanilloid receptor-related transient receptor potential channel 6 (TRPV6). For studies on colon cancer, K. Kunzelmann (Regensburg, Germany) used the human T_{84} intestinal epithelial cell model. Among the various K^+ channels expressed, only voltage-gated K^+ channels— $K_v1.5$, $K_v3.4$ and $K_v10.1$ —were involved in proliferation, possibly through the regulation of intracellular pH or Ca^{2+} . After treatment with carcinogens, mouse colon cells showed increased expression of $K_v1.3$, $K_v1.5$, $K_v3.1$ and $K_v10.1$. Indeed, $K_v10.1$ has been detected in human colonic tumours and is associated with a poor prognosis (Ousingsawat *et al*, 2007). In addition, recent experiments using a mouse with a defect in the adenomatosis polyposis coli (APC) tumour suppressor gene—loss of which is an early event during cancer progression—showed increased $K_{ca}1.1$ and $K_v10.1$ expression, which might have clinical implications.

K^+ channels are also important in melanoma. R. Schönherr (Jena, Germany) discussed the importance of $K_{ca}3.1$ and $K_v10.1$ in controlling the proliferation of several human melanoma cell lines. In addition, a microarray comparison between melanocytes and melanoma of 80 different K^+ channel genes revealed a consistent upregulation of $K_{ca}3.1$. Further studies on fresh melanoma tissue revealed the expression of $K_{ca}3.1$ in 80% of the cases and $K_v10.1$ in 50% of the cases. Under hypoxia, which is commonly found in tumours, $K_{ca}3.1$ was upregulated and this might lead to tumour progression. A. Arcangeli (Florence, Italy) provided insight into the significance of the interaction between $\beta1$ integrin and $K_v11.1$ —also known as HERG—which is upregulated in several cancers, including glioma, leukaemia, and stomach and colorectal cancers. This macromolecular complex not only regulates downstream signalling pathways—for example, tyrosine kinases and GTPases—but also leads to signalling through conformational changes rather than ion flux. In acute myeloid leukaemia (AML), in which $K_v11.1$ expression is known to correlate with a poor prognosis, the $K_v11.1$ – $\beta1$ integrin complex associates with the vascular endothelial growth factor (VEGF) receptor 1 to regulate VEGF secretion, cell proliferation and cell migration, resulting in more efficient invasion of the peripheral circulation and extra-medullary sites in immunodeficient mice (Pillozzi *et al*, 2007). Such $K_v11.1$ – $\beta1$ integrin complexes also occur in paediatric acute lymphoblastic leukaemia, in which a block of $K_v11.1$ signalling leads to an increase in apoptosis, indicating that $K_v11.1$ could be a viable therapeutic target.

Transient receptor potential channels

It is becoming increasingly clear that TRP channels are involved in cancer progression (Bödding, 2007; Prevarskaya *et al*, 2007). In relation to prostate cancer, N. Prevarskaya (Villeneuve d'Ascq, France) described the role of classic TRP channels (TRPC), vanilloid TRP channels (TRPV) and melastatin TRP channels (TRPM) in the development of androgen independence. Among other things, androgen independence leads to apoptosis resistance, making the

Fig 1 | A schematic diagram illustrating how the ion channels discussed at the Ringberg Colloquium might be linked with various aspects of the 'six hallmarks of cancer', as originally outlined by Hanahan & Weinberg (2000). TRP, transient receptor potential.

tumour difficult to treat clinically. Prevarskaya's group showed that Ca^{2+} entry on activation of different TRP channels could either stimulate proliferation through TRPC6 and TRPV6, or induce apoptosis through TRPC1/TRPC4 and TRPM8. Interestingly, the expression and subcellular distribution of TRPM8 is regulated by androgens, and is dependent on metastatic potential. Therefore, TRPM8 could lead to Ca^{2+} entry through the plasma membrane or Ca^{2+} release from intracellular stores, and this could contribute to the development of androgen independence (Bidaux *et al*, 2007). D. Bates (Bristol, UK) described the role of TRP channels in vascular permeability and angiogenesis. Both TRPC3 and TRPC6 channels are expressed in rodent microvasculature in which activation by VEGF or diacylglycerol leads to increased intracellular Ca^{2+} and vascular permeability. A dominant negative TRPC6 construct expressed in human microvascular endothelial cells abolished both the increased intracellular Ca^{2+} response to VEGF and cell migration. Such a role implies TRP involvement in the cancer process as angiogenesis is an important aspect of tumour growth and metastasis formation.

Sodium channels

Voltage-gated Na^+ channels (VGSCs) are now known to be upregulated in many types of cancer, including breast, lung—both small-cell and non-small-cell—and prostate cancers, leukaemia (reviewed by Fiske *et al*, 2006; Roger *et al*, 2006) and, more recently, cervical cancer (Diaz *et al*, 2007) and mesothelioma (Fulgenzi *et al*, 2006). Although VGSCs potentiate cell behaviours necessary for the metastatic cascade, the mechanisms through which they act are not well understood. J.-Y. Le Guennec (Tours, France) presented evidence that VGSC ($Na_v1.5$) activity increased the invasiveness of human breast cancer cells through increased cysteine cathepsin activity. Cysteine cathepsins are proteolytic enzymes with many roles in cancer metastasis (Mohamed & Sloane, 2006). Interestingly, analogous results were found for prostate and non-small-cell lung cancers, which also express VGSCs, indicating that the involvement of cysteine cathepsins might be a general mechanism in carcinomas. Also studying breast cancer, S. Fraser (London, UK) reported an increase in $Na_v1.5$ amplitude after acute oestrogen application. Oestrogen is a steroid hormone known to be important during breast cancer progression.

The mechanism by which it increases $\text{Na}_v1.5$ amplitude seems to be through a recently characterized plasma-membrane G-protein-coupled receptor for oestrogen signalling, GPR30, mediated by protein kinase A activation. As the application of oestrogen reduced cell adhesiveness in a VGSC-dependent manner, these findings indicate that the action of oestrogen on VGSCs might be important during breast cancer metastasis. Non-conduction functioning of the VGSC and its possible importance in cancer was discussed by L. Isom (Ann Arbor, MI, USA). VGSCs, which are composed of a central pore-forming α -subunit and auxiliary β ($\beta 1$ – $\beta 4$)-subunits, are part of larger multi-protein complexes that can include components of the cytoskeleton, as well as transport proteins, kinases, phosphatases and extracellular matrix proteins. Therefore, individual components might have different functions and modulation of the complex could contribute to disease conditions, including cancer. For example, $\beta 1$ -null mice suffer many abnormalities, including epilepsy, ataxia, neuronal pathfinding errors and premature death. The exact involvement of the β -subunits might be many and complex, as β -subunits are also known to function independently of the α -subunit. For example, cleavage of the $\beta 2$ -subunit by the β -site of APP cleaving enzyme (BACE1) and γ -secretase results in the release of an intracellular domain of $\beta 2$, and an increase in VGSC ($\text{Na}_v1.1$) mRNA and protein levels in neuroblastoma cells (Kim *et al*, 2007).

Other ion channels and associated mechanisms

J. Pouyssegur (Nice, France) highlighted some of the signalling mechanisms that contribute to tumour resistance and survival in nutrient-depleted and acidic microenvironments. For example, the carbonic anhydrases CAIX and CAXII control internal pH to keep it alkaline, thus promoting cell survival and migration. Hypoxia-inducible factor 1 (HIF1), the expression of which is associated with a poor prognosis, controls the expression of many genes, including BH-3-only proteins BNIP3 and BNIP3L, which influence tumour survival by inducing autophagy (see, for example, Dayan *et al*, 2006). The regulation of voltage-gated Ca^{2+} channels (VGCCs) by growth factors was discussed by E. Fitzgerald (Manchester, UK). Growth factors were found to upregulate VGCCs through Ras/extracellular-signal-regulated kinase (ERK) in dorsal root ganglion (Woodall *et al*, 2008). Both growth factors and the Ras/ERK pathway are extremely important for cancer progression and metastasis although the contribution of VGCCs to the cancer process requires further study. Similarly, L. Kaczmarek (New Haven, CT, USA) described the role of Na^+ -activated K^+ channels, known as *slick* and *slack*, in electrically excitable cells. It has been known for some time that protein synthesis at the synapse is Na^+ -dependent, and the hypothesis being pursued is that changes in conformation of the *slack* channel produced by increased intracellular Na^+ might influence the translation of neuronal mRNAs. Whether such pathways occur during cancer remains to be explored. A. Schwab (Münster, Germany) showed elegantly the involvement of $\text{K}_{\text{Ca}}3.1$ channels in cell migration. Their physiological function in cell migration is to induce localized changes in cell volume at the rear part of motile cells and thereby support the retraction of this cell pole. By using Madin–Darby canine kidney cells transfected with $\text{K}_{\text{Ca}}3.1$ with an extracellular haemagglutinin (HA)-tag, single channels could be detected in the plasma membrane by ‘quantum dot’ labelling (Nechyporuk-Zloy *et al*, 2006, 2008). These experiments showed that the channels move in a diffusive manner and are not ‘trapped’ in the membrane. Such a technique might allow the labelling of any ion channel in the plasma membrane at the single-molecule level.

D. Beech (Leeds, UK) presented work detailing the control of ion-channel expression in smooth muscle cells by repressor element 1-silencing transcription factor (REST). Importantly, REST is known to control the expression of several ion channels—for example, $\text{Na}_v1.2$ —and has been implicated in disease development, including cancer (reviewed by Cheong *et al*, 2006). Vascular smooth muscle cells switch between a quiescent (contractile) and activated (proliferating/migratory) phenotype; crucial to this is the upregulation of $\text{K}_{\text{Ca}}3.1$, which results from the downregulation of REST. Increased $\text{K}_{\text{Ca}}3.1$ leads to membrane hyperpolarization and Ca^{2+} entry through heteromultimeric TRPC1/TRPC5 channels, which are controlled by sphingosine-1-phosphate. However, other ion channels such as $\text{K}_v1.3$ are also important in activated cells and were also found to be regulated by REST. Therefore, REST might have a greater role in the control of ion-channel expression than previously thought. An additional example of the relevance of ion channels in oncology occurs during cancer stem-cell selection in neuroblastoma. E. Wanke (Florence, Italy) reported studies on clonal selection in these tumours and the correlation with changes in electrophysiological properties, so-called ‘electrophysiological clusters of differentiation’ (ECD; Marzi *et al*, 2007). Under hypoxia or in the presence of the antiproliferative etoposide, cell lineages developed with different ECD. These results might help to explain the documented regression of neuroblastoma from a malignant to a benign phenotype, either spontaneously or with antiproliferative treatment. There are further clinical implications because—as long as the cancer stem-cell model holds true—the only possibility of completely eradicating a tumour is by depleting the stem-cell population. Therefore, distinguishing these cells from healthy cells is of pivotal importance.

Clinical potential

E. Stevens (Cambridge, UK) gave an encouraging talk that highlighted the ongoing potential for developing ion-channel modulators as cancer drugs. Particularly relevant are the advances in selective strategies and screening technologies such as automated electrophysiology. The potential of ion-channel inhibitors was ably shown by H. Sontheimer (Birmingham, AL, USA); looking at the role of ion channels in glioma invasion, Sontheimer and colleagues found that a chloride channel (ClC-3) involved in the invasive process is inhibited indirectly, but specifically, by a scorpion toxin, chlorotoxin (Cltx). Importantly, a recently developed, radiolabelled Cltx compound (^{131}I -Cltx) has successfully completed phase I clinical trials for patients with late-stage gliomas (Mamelak *et al*, 2006) and a multi-centre phase II trial is now underway. Similarly, G. Chandy (Irvine, CA, USA) described the selective targeting of a type of voltage-gated K^+ channel (VGPC), $\text{K}_v1.3$, which is expressed in CCR7-CD45RA⁺ effector/memory T cells (T_{EM}) that are involved in inflammatory autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (Beeton *et al*, 2006). By using a modified form of the sea anemone toxin ShK (ShK-186) that shows high selectivity for $\text{K}_v1.3$ compared with other VGPCs, tests in animal models indicated a long-term loss of T_{EM} cells and an improvement in autoimmune disease symptoms. Importantly, ShK-186 spares the CCR7⁺CD45RA⁺ T-cell population that protects against infection and cancers. $\text{K}_v10.1$ was the focus of the presentation by L. Pardo (Göttingen, Germany). Immunohistochemical studies on various types of human tumour revealed $\text{K}_v10.1$ expression in more than 75% of cases but, interestingly, low (or lack of) expression in healthy tissue. Antibodies against $\text{K}_v10.1$, used for *in vivo* imaging in mice, revealed specific labelling of tumours. In addition, the inhibition

of K_v10.1 expression and/or function reduced tumour progression, whereas a specific antibody blocking K_v10.1 activity reduced tumour growth, indicating this could have therapeutic applications.

Concluding remarks

The talks and posters presented at the meeting outlined the remarkable array of processes through which ion channels contribute to the survival of cancer cells, their growth, and progression to the metastatic phase. The topics included the involvement of ion channels in cell proliferation and the development of resistance to apoptosis; their ability to combat the inhospitable surroundings that a cancer cell must endure, including hypoxia and oxidative stress; the various mechanisms involving ion channels that contribute to the metastatic process, including adhesion, motility, invasion, secretion, metabolism and gene expression. Finally, some of the signalling pathways important during carcinogenesis and that have been linked with ion channels—such as growth factors, steroid hormones and protein kinases—were explored. Therefore, although there is much left to understand regarding the involvement of ion channels in the metastatic process, it is encouraging that many of the approaches already adopted have clinical potential in terms of both improved diagnosis/prognosis and therapy.

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