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IP₃ receptor biology and ER calcium dynamics in cancer

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Abstract

Intracellular Ca^{2+} signaling regulates a plethora of cellular functions. A central role in these processes is reserved for the inositol 1,4,5-trisphosphate receptor (IP_3R), an ubiquitously expressed Ca^{2+} -release channel, mainly located in the endoplasmic reticulum (ER). Three IP_3R isoforms ($\text{IP}_3\text{R1}$, $\text{IP}_3\text{R2}$ and $\text{IP}_3\text{R3}$) exist, encoded respectively by *ITPR1*, *ITPR2* and *ITPR3*. The proteins encoded by these genes are each about 2700 amino acids long and assemble into large tetrameric channels, which form the target of many regulatory proteins, including several tumor suppressors and oncogenes. Due to the important role of the IP_3Rs in cell function, their dysregulation is linked to multiple pathologies. In this review, we highlight the complex role of the IP_3R in cancer, as it participates in most of the so-called “hallmarks of cancer”. In particular, the IP_3R directly controls cell death and cell survival decisions *via* the regulation of autophagy and apoptosis. Moreover, the IP_3R impacts cellular proliferation, migration and invasion. Typical examples of the role of the IP_3Rs in these various processes are discussed. The relative levels of the IP_3R isoforms expressed and their subcellular localization, *e.g.* at the ER-mitochondrial interface, is hereby important. Finally, evidence is provided about how the knowledge of the regulation of the IP_3R by tumor suppressors and oncogenes can be exploited to develop novel therapeutic approaches to fight cancer.

Keywords

IP₃ receptor; Ca²⁺ signaling; cancer; migration; invasion; apoptosis; autophagy

Introduction

Ca^{2+} is in all cell types a crucial intracellular messenger, controlling a plethora of cellular functions, including fertilization, differentiation, secretion, muscle contraction, synaptic plasticity and memory formation, gene transcription and metabolism (Berridge, Lipp, and Bootman 2000). Meanwhile it became clear that Ca^{2+} is also controlling cell proliferation (Humeau et al. 2018; Roderick and Cook 2008) and processes as macroautophagy (further named autophagy) and apoptosis (Dubois, Prevarskaya, and Vanden Abeele 2016; Hu, Han, and Jing 2019; La Rovere et al. 2016; Smaili et al. 2013) thereby directly affecting cell death and cell survival decisions. To perform this wide variety of functions, Ca^{2+} is encoded as complex spatio-temporal signals varying in frequency, amplitude, kinetics and subcellular localization which depend on the interplay between the members of the so-called “ Ca^{2+} -signaling toolkit”, a whole set of Ca^{2+} -binding proteins, Ca^{2+} transporters and the modulators of these proteins (Berridge, Lipp, and Bootman 2000; Bootman and Bultynck 2020).

A central tenant hereby is the inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R), a ubiquitously expressed, intracellular Ca^{2+} -release channel mainly localized on the endoplasmic reticulum (ER). This ER Ca^{2+} channel is activated by IP_3 , which is produced from phosphatidylinositol 1,4-bisphosphate by various phospholipase C isoforms after cellular stimulation by *e.g.* hormones, growth factors or neurotransmitters (Foskett et al. 2007; Parys and De Smedt 2012; Parys and Vervliet 2020; Prole and Taylor 2019).

Activation of the IP_3R leads to Ca^{2+} release from the ER into the cytoplasm, setting in motion various cellular signaling cascades. Depending on the cellular situation, the released Ca^{2+} can be funneled to other organelles, transported back into the ER or out of the cell. Meanwhile, the decreased Ca^{2+} load in the ER may lead to the dissociation of Ca^{2+} from the ER Ca^{2+} sensors Stim1/Stim2, leading to their oligomerisation and a rearrangement of their cytosolic domains. This enables the interaction of Stim1 and/or Stim2 with the plasma membrane Orai channels resulting in their opening (Lewis 2019; Zhou et al. 2019). The subsequent Ca^{2+} entry in the cell has a dual role, allowing a more prolonged Ca^{2+} signaling in the cell as well as a replenishment of the ER Ca^{2+} stores. As this form of Ca^{2+} entry primarily depends on the Ca^{2+} -store content, this process is known as store-operated Ca^{2+} entry (SOCE).

IP_3R structure-function relationship

In higher organisms, there are three IP_3R isoforms ($\text{IP}_3\text{R1}$, $\text{IP}_3\text{R2}$, and $\text{IP}_3\text{R3}$), encoded by three different genes (*ITPR1*, *ITPR2* and *ITPR3*) and further diversity is provided at the protein level by

splicing events. The homology among the three isoforms is rather high (around 75% at the amino acid level) and the IP₃Rs form homo- or heterotetrameric complexes with each a total molecular mass of about 1.2 MDa (Foskett et al. 2007; Parys and De Smedt 2012).

Each monomer has a length of about 2700 amino acids and can be divided in three large regions: at its N-terminal extremity the cytosolic ligand-binding region (for IP₃R1: amino acids 1-578), subsequently the large regulatory and coupling region (amino acids 579-2275), and finally the C-terminal part (amino acids 2276-2749) consisting of 6 transmembrane helices forming the ion channel proper, followed by a short cytosolic tail (Sudhof et al. 1991) (Figure 1).

The ligand-binding region can functionally be divided in a suppressor (amino acids 1-225) and an IP₃-binding core (amino acids 226-578). The IP₃-binding core of each of the three IP₃R isoforms forms a cleft with very high affinity for IP₃ (K_d 2 nM), which however is to a variable extent affected by its respective upstream suppressor sequence. The rank order of eventual affinities of the IP₃Rs for IP₃ is therefore IP₃R2 (K_d 14 nM) > IP₃R1 (K_d 50 nM) > IP₃R3 (K_d 163 nM) (Iwai et al. 2007).

IP₃R channel opening needs the binding of IP₃ to each of the four IP₃R monomers (Alzayady et al. 2016). This activation of the channel must be fine-tuned and occurs via a multitude of mechanisms. The regulators can be divided in 3 broad classes, small soluble cytosolic factors (*e.g.* Ca²⁺, ATP, ...) (Foskett et al. 2007; Taylor and Tovey 2010), regulatory proteins (Parys and Vervliet 2020; Prole and Taylor 2016) and post-translational modifications such as phosphorylation/dephosphorylation events (Vanderheyden et al. 2009).

The original analysis of the crystal structure of the N-terminal ligand-binding region (Bosanac et al. 2002; Bosanac et al. 2005), only quite recently extended to the full cytosolic part of the IP₃R (Hamada et al. 2017), has been complemented by high-quality cryo-electron microscopy (Taylor, da Fonseca, and Morris 2004). The latter studies have tremendously increased our knowledge of the structure of the IP₃R.

Presently, the view of the general structure of the IP₃R1 can be summarized as follows. The IP₃R1 has a mushroom-like structure with a height of 19 nm. High-resolution analysis of its closed form (no IP₃, no Ca²⁺ present) allowed the identification of ten domains: β -trefoil domains 1 and 2 (amino acids 1–436), followed by armadillo solenoid folds (ARM1–ARM3, amino acids 437–2192) with an α -helical domain between ARM1 and 2, the intervening lateral domain (amino acids 2193–2272), the transmembrane region with six trans-membrane α -helices (amino acids 2273–2600), a linker domain (amino acids 2601–2680) and the C-terminal domain (amino acids 2681–2731) (Serysheva, Baker, and Fan 2017). The activation mechanism responsible for the channel opening in the presence of IP₃ however remains to be elucidated. Recent studies have provided additional information on the

structure of IP₃R both in the presence and absence of IP₃ and/or Ca²⁺ (Paknejad and Hite 2018) and indicated in the regulatory and coupling region the presence of an auto-inhibitory peptide that can modulate the IP₃-binding site (Azumaya et al. 2020).

Future analysis of the structure of the various IP₃R isoforms under different experimental conditions will allow to better understand the activation and regulation mechanisms of this important class of channels as well as the physiological function of the various isoforms.

Cellular and subcellular localization of the IP₃R

The expression pattern of the various IP₃R isoforms as well as their subcellular localization is strongly tissue-, cell type-, and differentiation stage-dependent (Vermassen, Parys, and Mauger 2004).

Although most cells express more than one IP₃R isoform, IP₃R1 is the most ubiquitous isoform and can be expressed at very high levels in some tissues as *e.g.* Purkinje neurons and oocytes. IP₃R2 has a quite restricted expression pattern and is especially present in hepatocytes, glial cells, cardiomyocytes, various types of secretory cells as well as in some hematological cells (Vervloessem et al. 2015). IP₃R3 levels are generally elevated in rapidly proliferating cells, as well as, together with IP₃R2, in secretory cells (Ivanova et al. 2014).

The fact that IP₃Rs can be expressed at well-determined subcellular localizations strongly affects their function (Alonso and Garcia-Sancho 2011; Hohendanner et al. 2014; La Rovere et al. 2016; Lock, Smith, and Parker 2019). Examples of very specific subcellular localization of IP₃Rs are at the ER-mitochondrial contact sites (Csordas, Thomas, and Hajnoczky 1999; Rizzuto et al. 1993; Szabadkai et al. 2006), in the junctional ER close to the plasma membrane (Okeke et al. 2016; Thillaiappan et al. 2017) as well as at contact sites between ER and lysosomes (Atakpa et al. 2018; Kilpatrick et al. 2013; Lopez-Sanjurjo et al. 2013; Morgan et al. 2013).

Intracellular Ca²⁺ signaling and cancer

As IP₃Rs control a plethora of cellular and physiological functions and processes, IP₃R dysregulation (Berridge 2016) and *ITPR* mutations (Hisatsune and Mikoshiba 2017; Kerkhofs et al. 2018; Terry et al. 2018; Gambardella et al. 2020) have patho(physio)logical consequences. While a number of those defects correlate with one specific disease situation (*e.g.* the occurrence of spinocerebellar ataxia or anhidrosis), this review will demonstrate that the role of the IP₃R in cancer is more complex and so illustrate the multifaceted aspects of IP₃R-mediated Ca²⁺ signaling.

Hanahan and Weinberg (Hanahan and Weinberg 2011) have put forward the concept that tumor formation depends on the acquisition of the so-called “hallmarks of cancer”. These are the sum of the capabilities of the cells to sustain proliferation, evade growth suppressors, resist to cell death, possess replicative immortality, stimulate angiogenesis, invasion and metastasis, reprogram energy metabolism and evade the immune response. Interestingly, in most of these processes, Ca^{2+} can play a role (Monteith, Prevarskaya, and Roberts-Thomson 2017; Prevarskaya, Skryma, and Shuba 2018; Roberts-Thomson, Chalmers, and Monteith 2019; Roderick and Cook 2008), and in various cancers a changed expression pattern was found for members of the Ca^{2+} -signaling toolkit, including the IP_3R , as was recently reviewed (Pierro et al. 2019). Modulation of IP_3R function in cancer cells can be attributed to one or several of the following factors: mutations, change in expression levels, change in subcellular localization or changes in Ca^{2+} -release activity (due to post-translational modifications, interaction with regulatory proteins or protein degradation). Especially noteworthy is that various recognized oncogenes and tumor suppressors directly interact with the IP_3Rs , thereby regulating IP_3R activity or stability (Bittremieux et al. 2016). For all these reasons, members of the Ca^{2+} -signaling toolkit have been proposed as novel therapeutic targets (Bong and Monteith 2018; Cui et al. 2017).

In this review, we will start by explaining the role of IP_3R signaling in autophagy and apoptosis as these processes are critical for cancer development. Next, the complex role that IP_3Rs can play during the various phases of cancer development will be discussed. Finally, we will highlight the interrelation that exist between the IP_3R and a number of tumor suppressors and oncogenes and how these interrelations can be exploited for therapeutic purposes.

The IP_3R as regulator of autophagy

To support cellular homeostasis and to protect themselves from cellular stress, cells make use of a process called autophagy. In this process, long-lived proteins as well as dysfunctional organelles and intracellular pathogens are engulfed by newly formed double-membrane vesicles named autophagosomes. The latter will eventually fuse with lysosomes, forming autolysosomes in which both the autophagosomes and their content are fully degraded, after which the materials can be recycled. Autophagy forms a multi-step process that can be activated by adenosine monophosphate-activated protein kinase (AMPK), inhibited by the mechanistic target of rapamycin complex 1 (mTORC1) and in which over 30 autophagy-related (ATG) proteins play crucial roles (Ravikumar et al. 2010).

As autophagy has essentially a protective function, it can play a dual role in cancer. Initially, by supporting cellular homeostasis and thus antagonizing cellular stress, autophagy will protect cells

from tumorigenicity, but once tumorigenesis has started it similarly will protect the tumoral cells from the harsh conditions in the tumor microenvironment (Eskelinen 2011; Liu and Ryan 2012). Due to the oncosuppressive role of several ATG proteins, including Beclin 1 (Table 1), these are considered as tumor suppressors (Yue et al. 2003).

Although the first effects of Ca^{2+} on autophagy have been described more than 2 decades ago (Gordon et al. 1993), the exact role(s) of Ca^{2+} signaling in the regulation of autophagy is only now slowly emerging. The main reason for this are the various, apparently contradictory results that have been published about the role of Ca^{2+} , as has been reviewed (Decuypere, Bultynck, and Parys 2011; Sun et al. 2016). The reasons for these controversies are multiple, and can be due to cell-type dependent context, the occurrence of various Ca^{2+} -sensitive steps and the use of non-physiological conditions or of drugs with pleiotropic effects in a number of studies (Bootman et al. 2018).

Also the role of the IP_3R itself in autophagy is complex (Parys, Decuypere, and Bultynck 2012). On the one hand, since the IP_3R controls mitochondrial $[\text{Ca}^{2+}]$ and therefore mitochondrial metabolism (*vide infra*), it is clear that when Ca^{2+} transfer from the ER to the mitochondria is suppressed, ATP production drops, the AMP/ATP ratio increases and AMPK is activated. This increase in AMPK activity will lead to autophagy induction (Cardenas et al. 2010). Therefore, in basal conditions, the IP_3R acts as an inhibitor of autophagy. On the other hand, intracellular Ca^{2+} signals occurring in the cytosol can affect autophagy in a different way, whereby IP_3R -mediated Ca^{2+} release stimulates the autophagy process (Hoyer-Hansen et al. 2007; Lam et al. 2008; Liu et al. 2013; Luyten et al. 2017; Wang et al. 2008). At the molecular level, IP_3Rs are directly sensitized by the pro-autophagic protein Beclin 1, driving starvation-induced autophagic flux (Decuypere et al. 2011). Whether Beclin 1 recruitment by IP_3Rs and subsequent IP_3R sensitization also occurs in other autophagy-inducing conditions remains currently not known.

Therefore, the IP_3R , via its actions on autophagy, can also affect cancer cells (Kania et al. 2017). Interestingly, in contrast to other cells, cancer cells appear extremely sensitive to conditions in which the Ca^{2+} transfer to the mitochondria is inhibited. Autophagy induction does not guarantee their survival as the cancer cells, in spite of mitochondrial function decline, do not slow down their proliferation rate and thus undergo a necrotic collapse during cytokinesis (Cardenas et al. 2016).

A specific increase in both $\text{IP}_3\text{R2}$ and $\text{IP}_3\text{R3}$ expression levels in breast tumor tissues relative to the adjacent non-tumoral tissue was observed in patients (Singh, Sharma, et al. 2017). These increased IP_3R expression levels correlated with metabolic changes as a higher rate of glycolysis and an increased glutaminolysis. IP_3R inhibition or siRNA-mediated silencing of $\text{IP}_3\text{R2}$ and -3 in breast cancer cell models affected exactly those same pathways, showing an association between IP_3R levels and

the dysregulated metabolism of cancer cells. Interestingly, and similar to the study by Cardenas et al. mentioned above, the inhibition of IP₃Rs in breast cancer cells induced autophagy but the compromised energetics together with reactive oxygen species (ROS) production led to their demise (Singh, Chagtoo, et al. 2017). Conversely, in clear cell renal cell carcinomas the increased hypoxia-inducible factor 2 α level leads to IP₃R1 overexpression and autophagy induction (Messai et al. 2014). This autophagy induction protects the cancer cells against lysis mediated by natural killer cells.

The IP₃R in apoptosis

An important hallmark of cancer is the avoidance of cell death and cancer cells therefore often have upregulated anti-apoptotic mechanisms. Apoptosis can originate as the consequence of perturbations in the intracellular milieu (intrinsic apoptosis) or due to the presence of extracellular factors (extrinsic apoptosis) (Galluzzi and Vanpouille-Box 2018).

In intrinsic apoptosis, the crucial step is the large structural changes occurring at the level of the mitochondria, called mitochondrial outer membrane permeabilization (MOMP), a process that occurs upon Bax/Bak activation and that is mediated by proteinaceous channel complexes formed by Bax/Bak oligomers (Kale, Osterlund, and Andrews 2018; Singh, Letai, and Sarosiek 2019). MOMP results in the release of pro-apoptotic factors as cytochrome c and second mitochondria-derived activator of caspases (SMAC) from the mitochondrial intermembrane space into the cytosol. Here, cytochrome c forms a complex with apoptotic protease-activating factor 1 (APAF1) forming the apoptosome, leading to subsequent activation of caspase 9 and of the executioner caspases 3 and 7 and thus apoptosis (Galluzzi and Vanpouille-Box 2018). SMAC supports these processes by inhibiting X-linked inhibitor of apoptosis protein (XIAP), a factor that blocks caspase activation.

It is known that IP₃Rs are playing a crucial role in the various processes linked to cellular survival or cell death. These properties are linked to the fact that (a fraction of the) IP₃Rs are localized at ER-mitochondrial contact sites and control therefore the transfer of Ca²⁺ from the ER to the mitochondria (Csordas, Thomas, and Hajnoczky 1999; Giacomello et al. 2010; Rizzuto et al. 1993). If a too high level of Ca²⁺ transfer occurs from the ER to the mitochondria, mitochondrial Ca²⁺ overload follows, which leads to the opening of the mitochondrial permeability transition pore (mPTP) in the inner mitochondrial membrane. The molecular nature of the mPTP is still controversial (Carroll et al. 2019; Urbani et al. 2019) and the link between mitochondrial Ca²⁺ overload and mPTP opening is also not completely understood. The latter can involve Ca²⁺ binding to cardiolipin leading to the disintegration of mitochondrial complex II and a massive production of ROS that triggers mPTP opening (Hwang et al. 2014) and/or a Ca²⁺-mediated conformational change of the F-ATP synthase

which was proposed to form an essential component of the mPTP (Giorgio et al. 2017).

Independently of the exact mechanism, the opening of the mPTP corresponds to the opening of a large, non-specific channel in the inner mitochondrial membrane, and consequently depolarization of the mitochondria, ATP hydrolysis, matrix swelling due to osmotic forces, and ultimately rupture of the outer mitochondrial membrane and the release of the above-mentioned pro-apoptotic factors.

Although originally the idea prevailed that IP₃R3 was particularly expressed at the ER-mitochondria contact sites and therefore most important for triggering Ca²⁺-dependent apoptosis (Blackshaw et al. 2000; Mendes et al. 2005), other evidence also pointed to an important role in these processes for IP₃R1 (Feriod et al. 2017; Szabadkai et al. 2006) or IP₃R2 (Akl et al. 2013), suggesting a cell-type rather than a function-specific isoform distribution. Recent work extended these findings by conclusively demonstrating in cell line models that all three IP₃R isoforms can structurally participate in the ER-mitochondria contacts and that all three can flux Ca²⁺ to the mitochondria (Bartok et al. 2019). IP₃R2 appeared in fact the most effective for this process followed by IP₃R3 and IP₃R1. The latter was however the most effective inducer of SOCE leading to a sustained mitochondrial Ca²⁺ uptake.

The most important factor determining apoptosis sensitivity will therefore rather be the amplitude of the IP₃R-mediated Ca²⁺ transfer between ER and mitochondria than which IP₃R isoform is present at the ER-mitochondria contact sites. Interestingly, it was shown that cytochrome c, which is released from the mitochondria after MOMP, not only induces apoptosome formation, but also interacts with the IP₃R. This interaction antagonizes Ca²⁺-mediated inhibition of the IP₃R and thus amplifies pro-apoptotic Ca²⁺ signaling (Boehning et al. 2003).

Extrinsic apoptosis is initiated by extracellular factors interacting with the so-called death receptors at the plasma membrane as the FAS and TRAIL receptors. Binding of respectively FAS ligand and TRAIL leads to a conformational change that allows for the formation of an intracellular “death-inducing signaling complex” leading eventually to activation of the initiator caspases 8 and 10. These caspases can either directly activate the effector caspases and/or activate them via cleaving the pro-apoptotic protein Bid thus triggering MOMP and apoptosome formation. This shows a convergence of the extrinsic and the intrinsic pathways (Barnhart, Alappat, and Peter 2003; Scaffidi et al. 1998).

Interestingly, it was shown that in some cells, including Jurkat T cells and hepatocytes, both phospholipase C γ 1 and IP₃R1 were needed for Fas-mediated apoptosis (Wozniak et al. 2006).

Moreover, Fas-dependent killing of Jurkat T cells by colon cancer cells depends on IP₃R-mediated Ca²⁺ release, which in turn is amplified by cytochrome c release (Steinmann et al. 2008). Apart from the mitochondrial Ca²⁺ overload that leads to a generalized MOMP and apoptosis, it has been proposed that IP₃R-mediated Ca²⁺ release also stimulates apoptosis by supporting lipidation of various proteins

including the IP₃R itself (Fredericks et al. 2014), various components of the T cell receptor complex and proteins of the Wnt signaling pathway (Chen and Boehning 2017).

The complex role of the IP₃R in tumorigenesis: an integrated view

Tumorigenesis is typically a multi-step process. After oncogenic transformation, a first characteristic of tumor growth is the acquired capacity for quasi-unlimited cellular proliferation. The metastasis of the tumor subsequently depends on the migration capabilities of the cells followed by the invasion of other tissues. As will be discussed below, IP₃Rs actively participate in these key processes of tumorigenesis in various cancer types. The role of the IP₃R has particularly been investigated in breast and colorectal cancer and these cancer types will be discussed in more detail.

Breast cancer

The growth stimulation of the MCF-7 breast cancer cell line by 17 β -estradiol is coupled to an increased expression of IP₃R3 and a corresponding change in intracellular Ca²⁺ signaling (Szatkowski et al. 2010). siRNA-mediated IP₃R3 down-regulation modified ATP-evoked Ca²⁺ signals from sustained to oscillatory and antagonized the growth-promoting effect of 17 β -estradiol, supporting a role for IP₃R3 in proliferation. This latter effect appeared to depend on a direct interaction between ER-localized IP₃R3 and the plasma membrane large conductance Ca²⁺-activated K⁺ (BK_{Ca}) channels (Mound et al. 2013). This coupling allows IP₃R3 to activate the BK_{Ca} channels leading to cellular hyperpolarization. Down-regulation in MCF-7 cells of either IP₃R3 or BK_{Ca} (or of both) led to a decrease in cyclin D1 and in cyclin-dependent kinase 4 levels and to cell cycle arrest in the G0/G1 phase. Furthermore, when comparing the low-migrating MCF-7 and the highly migrating and invasive MDA-MB-231 and MDA-MB-435S cell lines, it appears that specifically a higher expression level of IP₃R3 correlates with a stronger migration capacity that can be reversed by IP₃R3 down-regulation or amplified by IP₃R3 overexpression (Mound et al. 2017). This property could be linked to the fact that the Ca²⁺ signals evoked by IP₃R3 affect the cellular morphology by impacting profilin levels and therefore the actin cytoskeleton (Vautrin-Glabik et al. 2018).

Colorectal cancer

A study performed in 116 patients indicated that while in normal colorectal mucosa only IP₃R1 and IP₃R2 are expressed, in colorectal carcinomas all three IP₃R isoforms are expressed (Shibao et al. 2010). Moreover, not unlike the case of breast cancer, the IP₃R3 expression was especially high in actively invading cancer cells. IP₃R3 levels thus correlated with cancer aggressiveness and poorer

patient survival (Shibao et al. 2010). Noteworthy is the fact that also in Caco-2 colon adenocarcinoma cells IP₃R3 levels inversely correlated with their sensitivity to apoptosis.

The role of IP₃R3 in tumor progression was further highlighted in a colorectal adenocarcinoma cell line DLD1 expressing a single oncogenic K-Ras mutation (G13D) making the protein constitutively active. K-Ras is a small monomeric GTPase and a well-known proto-oncogene. Mutations in the K-Ras isoform occur in 30-40% of colorectal cancers (Arrington et al. 2012). In accordance with the results discussed above (Shibao et al. 2010), IP₃R3 silencing made DLD1 colorectal adenocarcinoma cells more sensitive to apoptosis and decreased their migration capacity (Rezuchova et al. 2019). Moreover, inoculation in nude mice of DLD1 cells with complete IP₃R3 knockout led to smaller tumors than when parental DLD1 cells were inoculated.

Furthermore, comparison of colorectal cancer cell lines (expressing K-Ras^{G13D}) with their isogenic derivatives in which the mutated K-Ras allele was deleted (HKH2 and DKO4 cells), allowed a detailed investigation of the relation between oncogenic Ras and Ca²⁺ handling by the IP₃R (Pierro et al. 2014). In absence of oncogenic Ras, a remodeling occurred towards an increased expression of SERCA2B and of IP₃R3 while IP₃R1 level decreased. This remodeling correlated with an increased ER Ca²⁺ content, a higher level of IP₃-induced Ca²⁺ release (IICR), and subsequently more mitochondrial Ca²⁺ uptake and an increased sensitivity to apoptosis. A follow-up study furthermore indicated that the suppression of the oncogenic K-Ras also led to an increased expression of Stim1 (in the HKH2 cell line) or of Stim2 (in the DKO4 cell line) and a larger SOCE in both cell lines, which can contribute to the larger filling state of the ER (Pierro et al. 2018). Although these results fit in the context that increased IP₃R activity is linked to an increased propensity to apoptosis (*vide supra*) they appear to be in contradiction with the finding mentioned above that higher IP₃R3 levels correlate with increased cancer aggressiveness. Interestingly, the decreased IP₃R activity when oncogenic K-Ras is expressed, is potentially related to the finding that GTP-bound, phosphorylated K-Ras4B forms a trimolecular complex with the IP₃R and the anti-apoptotic protein Bcl-XI (Sung et al. 2013). Under these conditions, the observed pro-survival stimulatory effect of Bcl-XI (White et al. 2005) on the IP₃R is counteracted, leading to a less efficient respiration process, induction of autophagy, and ultimately cell death (Sung et al. 2013).

Other cancers

Also in other cancer types, a relation between IP₃R levels and/or activity has been found with oncogenic progression. Interestingly, in several types of cancer a specific role was found for IP₃R3, though its role appears to differ between the various cancers, as will be further explained below.

In contrast to healthy hepatocytes, IP₃R3 is for example expressed in patients with hepatocellular carcinoma and this independently of the underlying liver disease (Guerra et al. 2019). This *de novo* expression of IP₃R3 appears to be due to a specific demethylation of its promoter. Although further work is needed to unravel the mechanisms, the high expression level of IP₃R3 leads not only to enhanced Ca²⁺ signaling but also to changes in expression of various proteins, including upregulation of the anti-apoptotic, pro-survival transcription factor POUAF1. Such remodeling might explain the lower sensitivity to apoptosis and the poorer patient survival.

In cholangiocarcinoma, the second most important liver malignancy, IP₃R3 levels are increased above normal level in both patient biopsies and in biliary adenocarcinoma cell lines as MzCha1 and HuCCA1 (Ueasilamongkol et al. 2020). Moreover, in MzCha1 cells, the IP₃R3, instead of being concentrated in the subapical ER, was expressed in a more diffuse way, including in close association with the mitochondria. Knockout of IP₃R3 in the cell models led to suppression of mitochondrial Ca²⁺ signaling, arrest of the cells in S-phase, increased cell death, and impaired proliferation and migration.

In clear cell renal cell carcinoma tumors, IP₃R3 mRNA levels were generally increased, while the mRNA levels of IP₃R1 and IP₃R2 appeared unaffected or even downregulated (Rezuchova et al. 2019). In the corresponding RCC4 cell line model, the silencing of either IP₃R1 or IP₃R3 affected cytosolic Ca²⁺ levels, though interestingly IP₃R1 silencing abolished apoptosis while IP₃R3 silencing strongly upregulated it.

In contrast with these various cancer cell types, in the lung adenocarcinoma cell line A549, IP₃R2 appeared the most important for cell migration (Huang et al. 2016). Interestingly, overexpression of the intraluminal ER protein PDIA10 (a.k.a. ERp44) inhibited IICR and decreased migration. It however remains to be elucidated how PDIA10 is affecting in those cells IICR, as it was originally described to uniquely interact with IP₃R1 (Higo et al. 2005).

From the data presented here, it thus clearly appears that IP₃Rs and IICR are involved in various stages of tumorigenesis, but that their role is not fixed. Depending on the IP₃R isoform expressed, their intracellular localization, and the general cellular context, including cell type-specific expression of various other proteins, IICR can drive or regulate different intracellular pathways and consequently exert another physiological function.

IP₃Rs are targeted by oncogenes and tumor suppressors: a therapeutic opportunity?

Several oncogenes and tumor suppressors were found to regulate IP₃R activity or stability and so to modulate their propensity for apoptosis (Bittremieux et al. 2016; Rosa et al. 2020). Generally

speaking, oncogenes promote cell survival and thus tumor formation by suppressing pro-apoptotic Ca^{2+} signaling leading to mitochondrial Ca^{2+} overload, while tumor suppressors will rather stimulate these processes in order to induce apoptosis. Various regulatory proteins derive (part of) their oncogenic or tumor suppressive ability from interfering with the IP_3R -mediated Ca^{2+} signals. As we have reviewed this topic extensively in recent publications (Bittremieux et al. 2016; Parys and Vervliet 2020; Rosa et al. 2020), we have summarized the major properties of these proteins with respect to IP_3R -mediated Ca^{2+} signaling in Table 1 (for the tumor suppressors) and Table 2 (for the oncogenes) as well as their approximate binding sites on the IP_3R in Figure 1. It should be emphasized that those proteins are not necessarily expressed in all cell types, and that their expression patterns and their functional importance can thus be cancer specific (Morciano et al. 2018). A special case concerns the interaction of various proteins of the Bcl-2 family with the IP_3R . With multiple binding sites and with both inhibitory and stimulatory effects described, the situation is quite complex. As a full description of the effects of those proteins on IICR fall outside of the scope of this review, we refer to a recent review for that matter (Ivanova et al. 2020).

To illustrate the potential of the IP_3R in complex with its regulatory proteins to be used as a target for drug development in cancer treatment we would like to highlight some studies in which interfering with IP_3R /Bcl-2 complexes can provoke the death of cancer cells. These translational applications were driven by studies unraveling the molecular determinants underlying IP_3R /Bcl-2 complex formation. In particular, disruption of IP_3R /Bcl-2 complexes can be achieved using peptides containing the interaction site of Bcl-2 in the regulatory and coupling region of the IP_3R 1 (amino acids 1389-1408). The binding of Bcl-2 to this site was demonstrated to inhibit IICR and to have an anti-apoptotic action (Rong et al. 2008). Various cell-permeable forms of this disrupting peptide have been developed, which differ in their stability/efficacy, and these have successfully been used to induce apoptosis via enhanced Ca^{2+} release from the ER in chronic lymphocytic leukemia (Zhong et al. 2011), diffuse large B cell lymphoma (Akl et al. 2013; Bittremieux et al. 2019), multiple myeloma and follicular lymphoma (Lavik et al. 2015) and small cell lung cancer (Greenberg et al. 2015) as well as to enhance the sensitivity of ovarian cancer cells towards cisplatin (Xie et al. 2018). Such peptides can also cooperate with BH3-mimetic drugs currently used in the clinic, including venetoclax (Akl et al. 2015; Greenberg et al. 2015; Lavik et al. 2015; Vervloessem et al. 2017). This clearly demonstrates that insights in the molecular underpinnings of IP_3R regulation by regulatory proteins, including oncogenes and tumor suppressors, can successfully be exploited therapeutically.

Conclusions

The IP₃R is a central player controlling many cellular functions. To that effect, IP₃R activity and stability are controlled by a plethora of mechanisms, often involving interacting proteins. Several of these interacting proteins are known oncogenes and tumor suppressors. As such it comes as no surprise that altered IP₃R signaling is critically altered and contributes to several hallmarks of cancer. This is in large part due to IP₃R localization at the ER-mitochondrial contact sites allowing it to regulate mitochondrial Ca²⁺ levels and subsequently mitochondrial processes including energy production and apoptosis. Interestingly, depending on the cell type under investigation, the various IP₃R isoforms can have different properties and consequently different effects. This can be due to a multitude of reasons, including the presence or absence of regulatory proteins, their subcellular localization and the amplitude of their subsequent Ca²⁺ signals that together will determine which intracellular pathways will be activated. Given the central role of IP₃Rs in most if not all hallmarks of cancer, the IP₃R may have crucial roles in cancer prevention, neoplasia and cancer progression. These insights can be employed to develop novel anti-cancer strategies, as well as providing interesting opportunities for future research and the development of translational applications.

SUMMARY POINTS

- IP₃R receptors control cell death and cell survival decisions critically involved in cancer development
- IP₃R receptors control cellular proliferation, migration and invasion
- IP₃R are targets of oncogenes and tumor suppressors
- Expression of specific IP₃R isoforms may differentially impact cancer progression
- Targeting IP₃R-mediated signaling could provide novel therapeutic avenues to fight cancer

FUTURE ISSUES

- Obtaining detailed structural information about the open and closed states of the various IP₃R isoforms will provide important information about the mode of action of regulatory oncogenes and tumor suppressors
- It is anticipated that not all regulatory proteins acting on the IP₃R in cancer have been identified. Moreover, such proteins likely are highly cancer specific, underlying unique opportunities to target such complexes in different cancers. Further research on this topic is urgently needed
- The possibility for structural and/or functional interactions between various oncogenes and/or tumor suppressors in the regulation of the IP₃R is presently very insufficiently appreciated. It is however crucial to understand how these proteins affect each other in the regulation of the IP₃R
- Development of (isoform) specific IP₃R inhibitors will further increase the understanding of their exact role in cancer
- Targeting the cell-type specific interaction of tumor suppressors and oncogenes with the IP₃R as therapeutic avenue must be further explored and stable peptides and small molecules developed to that effect

ABBREVIATIONS

AMPK	adenosine monophosphate-activated protein kinase
APAF1	apoptotic protease-activating factor 1
ARM	armadillo solenoid fold
ATG	autophagy-related
BK _{Ca} channel	large conductance Ca ²⁺ -activated K ⁺ channel
ER	endoplasmic reticulum
IICR	IP ₃ -induced Ca ²⁺ release
IP ₃	inositol 1,4,5-trisphosphate
IP ₃ R	inositol 1,4,5-trisphosphate receptor
ITPR	inositol 1,4,5-trisphosphate receptor gene
MOMP	mitochondrial outer membrane permeabilization
mPTP	mitochondrial permeability transition pore
mTORC1	mechanistic target of rapamycin complex 1
ROS	reactive oxygen species
SMAC	second mitochondria-derived activator of caspases
SOCE	store-operated Ca ²⁺ entry
XIAP	X-linked inhibitor of apoptosis protein

CONFLICT-OF-INTEREST DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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Tumor Suppressor	Interaction sites	Functional effects
BAP1	N-terminus (IP ₃ R3)	Prevents IP ₃ R3 degradation
Beclin 1	Ligand-binding region (IP ₃ R1 and IP ₃ R3)	Sensitizes IICR
Bok	Regulatory and coupling region (IP ₃ R1 and IP ₃ R2)	Protects IP ₃ R1 and IP ₃ R2 from caspase 3-mediated cleavage
BRCA1	C-terminal part	Increases IICR and sensitivity to apoptosis
PML	Reduces PKB/Akt-mediated phosphorylation (IP ₃ R3)	Stimulates Ca ²⁺ transfer to the mitochondria via IP ₃ R3
PTEN	Ligand-binding region (IP ₃ R3)	Displaces FBXL2 thereby inhibiting IP ₃ R3 degradation
	Inhibits PKB/Akt-mediated phosphorylation	Stimulates IICR

Table 1: List of tumor suppressors interacting with the IP₃R and their effects

Tumor suppressors are alphabetically listed. Interaction sites mention the IP₃R isoform involved when it was specifically described. When more than one interaction site was reported, the functional effects are separately indicated for each one. For the location of known interaction sites, please see Figure 1. IICR: IP₃-induced Ca²⁺ release.

Oncogene	Interaction sites	Functional effects
Bcl-2	Ligand-binding region	Inhibits IICR
	Regulatory and coupling region (all IP ₃ R isoforms)	Inhibits IICR
	C-terminal part (all IP ₃ R isoforms)	Stimulates Ca ²⁺ oscillations
Bcl-2 like 10	Ligand-binding region (IP ₃ R1)	Inhibits IICR
Bcl-X _L	Regulatory and coupling region	Inhibits IICR
	C-terminal part (all IP ₃ R isoforms)	Stimulates Ca ²⁺ oscillations
FBXL2	Ligand-binding region (IP ₃ R3)	Promotes IP ₃ R3 degradation
K-Ras	C-terminal part	Suppresses IICR
Mcl-1	C-terminal part (all IP ₃ R isoforms)	Stimulates Ca ²⁺ oscillations
PKB/Akt	C-terminal part (all IP ₃ R isoforms)	Phosphorylation of the IP ₃ R, leading to IICR inhibition
Stat3	Ligand-binding core/proximal part of the regulatory and coupling region (IP ₃ R3)	Induces IP ₃ R3 degradation

Table 2: List of oncogenes interacting with the IP₃R and their effects

Oncogenes are alphabetically listed. Interaction sites mention the IP₃R isoform involved when it was specifically described. When more than one interaction site was reported, the functional effects are separately indicated for each one. For the location of known interaction sites, please see Figure 1. IICR: IP₃-induced Ca²⁺ release.

Figure legend:

Figure 1: Oncogenes and tumor suppressors interact with and influence IP₃R function.

Linear representation of a generic IP₃R showing the location of the ligand-binding region, the regulatory and coupling region and the C-terminal part. A scale in amino acids is also provided. The oncogenes (top panel) and tumor suppressors (bottom panel) listed in the Tables are depicted at the site of their interaction with the IP₃R. Some of them have multiple interaction sites on the IP₃R, and are therefore depicted multiple times, the same color always denoting the same protein. From only some of those proteins the exact interaction sites are known at the amino acid level. These are (in alphabetical order): Bcl-2 in the regulatory and coupling region (amino acids 1389-1408 of IP₃R1), Bcl-X_L in the C-terminal part (amino acids 2571–2606 and 2690–2732), Bok (amino acids 1895–1903 of IP₃R1), FBXL2 (amino acids 545–566 of IP₃R3), and the PKB/Akt phosphorylation site (S²⁶⁸¹ of IP₃R1). In general, oncogenes stimulate pro-survival Ca²⁺ oscillations while inhibiting pro-apoptotic Ca²⁺ signaling. The latter can occur by direct inhibition of the IP₃R, by inducing post-translational modification of the IP₃R or by stimulating its degradation. Tumor suppressors in contrast will stimulate pro-apoptotic Ca²⁺ signaling by either sensitizing the IP₃R or by preventing its degradation. Of note, there are special situations in which a tumor suppressor may compete with an oncogene for binding to the IP₃R, *e.g.* PTEN and FBXL2, or can reverse post-translational modifications thereby negating the pro-survival effects of the oncogenes. IICR: IP₃-induced Ca²⁺ release.

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