共通の遺伝子変異により発症する．このCAGリピート配列は健常人にも存在する配列(正常約4～35リピート)であるが，PolyQ病患者では約35～40リピートから100リピート以上に異常伸長しており，その閾値は各疾患でおおむね共通している．また，CAGリピート数と疾患の発症年齢・重症度とが強く相関することが知られている．さらに，これらの原因蛋白質はPolyQ鎖以外には相同性を認めず，多くが優性遺伝性で1つの対立遺伝子の変異のみで発症することから，PolyQ病は異常伸長PolyQ鎖自身が原因蛋白質の生理的機能とは無関係に神経毒性を獲得(gain of toxic function)することにより発症すると考えられている．その発症メカニズムとしては，異常伸長したPolyQ鎖を持つ変異蛋白質がミスフォールディング・凝集を生じて封入体として神経細胞内に蓄積し，その結果，細胞レベル・個体レベルでさまざまな機能異常を引き起こし，最終的に神経変性を引き起こすと考えられている[2)3)]．

PolyQ病は上述のように遺伝子異常により定義されており，この点で，歴史的に臨床症状から疾患概念が確立されてきたパーキンソン病や病理学的に定義されてきたアルツハイマー病とは疾患概念の階層性が異なり，より厳密な疾患概念であると言える．PolyQ病のひとつであるハンチントン病は，ヒト遺伝性疾患の中でも人類史上初めてポジショナルクローニングにより原因遺伝子座の決定に成功した疾患であり，その後の爆発的に進展した分子遺伝学的研究の幕開けとして，このことは特筆に値する．その後の神経変性疾患の研究においても，環境要因の寄与が少なく，ほぼ遺伝的要因のみに発症が規定されているというPolyQ病の特徴は，遺伝子異常を基盤とした分子生物学的な病態研究の進展において他疾患をリードしている．さらに，PolyQ鎖長が神経毒性と強く相関することから，晩発性神経変性疾患のモデル化において，より早期に明瞭な表現型を発症する遺伝学的実験モデルの作製に適しており，これらの特徴から異常蛋白質ミスフォールディング・凝集による共通の神経変性メカニズムの解明に大きく貢献している．実際に，ハンチントン病の変異遺伝子を導入した重度の表現型を呈するトランスジェニックマウスがいち早く樹立され，これまで患者脳では見つかっていなかった封入体が発見され[4)]，その後，患者脳の病理学的解析でも確認された[5)]．このように分子遺伝学の進展により，従来の症候学→病理病態学→病因解明という疾患研究の流れが，遺伝学→分子病態学→病理病態学という新しい流れへと大きな変遷を遂げた．

ポリグルタミン病における神経細胞死

神経変性とは，神経細胞(群)の細胞死，脱落を指す．それでは，PolyQ病における神経細胞死はどういう細胞死であろうか？ 細胞死は，形態学的特徴から，能動的なプログラム細胞死であるアポトーシスと，外的要因による受動的な細胞死であるネクローシスに従来分類されてきた．神経変性疾患における細胞死は，明らかに外的要因によるネクローシスとは異なるため，これまでアポトーシスの関与が疑われてきた．実際に培養細胞モデルを用いた研究から，数時間～数日間で生じる細胞死においては，確かにアポトーシス実行因子であるカスパーゼの活性化などが報告されてきた．しかしながら，マウスなどの*in vivo*モデルや患者脳のように，長期間かかって緩徐進行性に生じる神経細胞死においては，典型的なアポトーシス像は認められないことが明らかになった．このように，神経変性疾患における神経細胞死のメカニズムは，まだ十分には解明されていない．

一方，プログラム細胞死にはアポトーシスではなく，むしろネクローシス様の形態を呈するものが知られているが，その詳細は明らかではない．Clarkeが提唱した2型細胞死は，細胞質中に多数のオートファゴソーム様空胞，リソソームの出現を特徴としており[6)]，これは現在ではいわゆるオートファジー性細胞死(autophagic cell death)に相当すると考えられる．ハンチントン病などPolyQ病患者やモデルマウスにおける神経細胞死は，形態的にはアポトーシスの特徴を欠き，エンドソーム，リソソームの蓄積を認めることから，むしろオートファジー性細胞死の関与が示唆されている[7)8)]．アルツハイマー病患者脳でも，多数のリソソーム・オートファゴソーム様空胞を伴う顆粒空胞変性が認められ，パ

ーキンソン病においても病理学的にはアポトーシスに加えてオートファジー性変性が認められる．以上のことから，PolyQ病を含む神経変性疾患においては，カスパーゼ依存的なアポトーシスの関与は少なく，むしろオートファジー性細胞死により緩徐進行性の神経変性・細胞死が引き起こされると考えられている[9]．

ポリグルタミン病における神経機能障害

神経変性疾患における神経症状は，これまでは神経細胞群の変性・脱落の結果，その欠落症状として出現すると考えられていた．しかしながら，PolyQ病患者由来の変異遺伝子を導入したさまざまな遺伝子改変モデルマウスが樹立され，発症前からの経時的な病態解析が可能となった結果，ハンチントン病モデルマウスにおいて神経症状が発症する時点では，著明な神経細胞死は認められないことが明らかになった[4]．さらに驚くべきことに，遺伝子発現誘導システムによるハンチントン病モデルコンディショナルマウスを用いて，発症後からでも異常伸長PolyQ蛋白質の発現を遮断すると神経症状が改善することが示され，PolyQ病の神経症状は神経細胞死よりもむしろ可逆性の神経機能障害に起因すると考えられるようになった[10]（図1）．このことから，従来は発症時には神経細胞死が進行・完成しており難治性と考えられていた神経変性疾患に対し，この神経機能障害を標的とした治療により発症後からでも病態進行を阻止し，症状を改善できる可能性が示唆され，これらの難病の克服へ向けて大きな希望がもたらされた．また，これまで患者死後脳を用いた病理学的解析から「神経変性疾患は神経細胞の脱落・変性に起因する」と定義されていた疾患概念が，部分的にでも覆る可能性が示唆された．このこともまた，分子遺伝学を基盤にした新たな疾患研究の潮流がもたらした賜物であると言えよう．

それでは，PolyQ病における神経機能障害の実体とはどういうものであろうか？ これまでにPolyQ病における神経機能障害として，転写調節障害，ユビキチン・プロテアソーム系やオートファジー・リソソーム系など蛋白質分解システムの障害，細胞内輸送・軸索輸送障害，ミトコンドリア障害，小胞体ストレスなど，さまざまな機能障害が明らかにされている[3]．しかし，これらはすべて細胞内レベルでの機能障害であり，これらが個体レベルでの神経症状にどのようにつながるのかは未解明である．

遺伝子改変技術の発達により，脳部位特異的に異常伸長PolyQ蛋白質を発現する，あるいは脳部位特異的に発現を遮断したハンチントン病モデルコンディショナルマウスが作製された．これらの解析の結果，神経症状は線条体や大脳皮質など個々の神経細胞内での機能障害にのみ起因するのではなく，両者のネットワーク障害の寄与が重要であることが明らかにされた[11][12]．また，グリア特異的に異常伸長PolyQ蛋白質を発現するSCA7モデルマウスを用いて，神経細胞間だけでなく神経－グリア間のネットワーク障害も神経機能障害に関わることが明らかになった[13]．さらに，球脊髄性筋萎縮症や

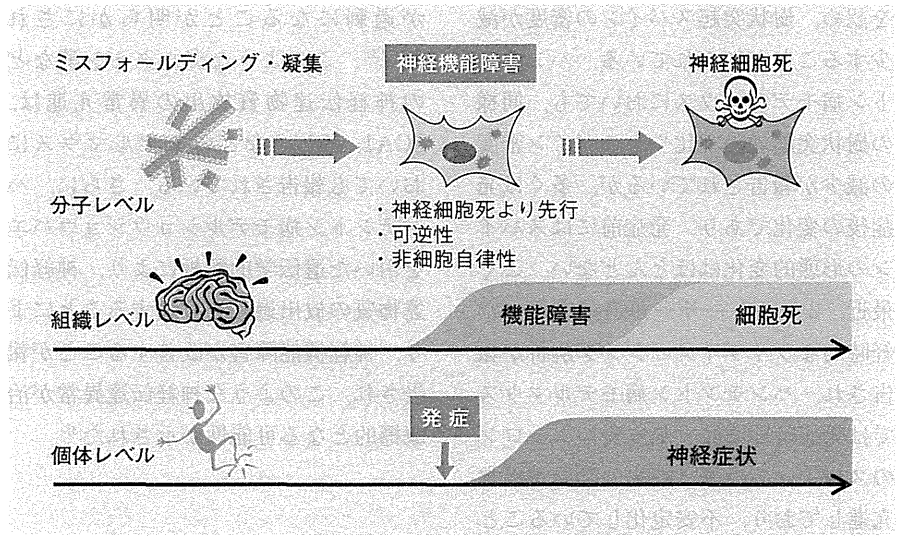

図1　ポリグルタミン病の神経症状は可逆性神経機能障害に起因する

ALSモデルコンディショナルマウスを用いて，筋肉や免疫系細胞など末梢の非神経細胞も病態に深く関わることが示された[14][15]．以上のことから，神経変性疾患における神経機能障害は，単に特定の神経細胞に限局した細胞自律的(cell-autonomous)な障害だけでなく，神経細胞間やグリア，あるいは末梢組織なども含めた非細胞自律的(non-cell-autonomous)なネットワークの機能障害に起因すると考えられるようになった[16]．

ポリグルタミン病におけるシナプス障害

PolyQ病における細胞間ネットワークの障害による非細胞自律的な神経機能障害の原因としては，シナプスを介する神経伝達の障害が想定されている[17][18]．実際に，ハンチントン病患者の剖検脳の病理学的解析から，線条体ニューロン樹状突起の局所的腫脹などを認め，樹状突起スパインの密度が減少することが知られている．ハンチントン病モデルマウスにおいても，同様の樹状突起の狭小化や，スパイン密度の減少が報告されているが，多くは発症後の変化であり，発症前にはスパインの形態的変化はほとんどない．ごく最近，2光子レーザー顕微鏡を用いた経時的なライブイメージング解析が報告され，ハンチントン病モデルマウスでは発症時期頃に大脳皮質ニューロンのスパインの生成・消失の動態が異常亢進しており，不安定化していることが明らかにされた[19]．通常，シナプスの成熟にしたがってスパイン動態は安定化することが知られているが，筆者らもSCA1ノックインマウスにおいて同様の結果を得ており，神経変性疾患における神経機能障害の根底には，シナプス成熟障害が存在することが示唆されている(未発表)．

一方，神経伝達の機能的異常としては，ハンチントン病モデルマウス脳でのマイクロダイアリシス解析により，発症前からグルタミン酸放出が亢進し，グリアによるグルタミン酸取り込み能が低下することが明らかにされている[20]．その分子基盤として，プレシナプスでの代謝型グルタミン酸受容体mGluR2の減少，グリアにおけるグルタミン酸トランスポーターGLT1の低下が報告されている．また，ポストシナプスにおいては，変異型huntingtinによりポストシナプスの足場蛋白質であるPSD95とNMDA受容体NR2Bの結合が促進され，シナプス外におけるNMDA受容体シグナルが過剰になることが明らかにされた[21][22]．このようなグルタミン酸などの神経伝達物質放出の異常亢進は，SCA1，SCA3などのモデルマウスにおいても報告されている．さらに，ハンチントン病モデルショウジョウバエを用いた遺伝学的解析により，神経伝達物質の放出過剰を抑制することにより，神経機能障害が改善することが報告され，このような神経伝達異常が治療標的となる可能性が示された[23]．

おわりに

上述のように，神経変性疾患研究は，分子遺伝学的研究手法の発展を機に爆発的に進み，分子生物学を基盤にした新たな疾患研究の潮流がもたらされた．本稿ではその中でもPolyQ病に着目し，異常蛋白質のミスフォールディング・凝集が引き起こす神経変性メカニズムの研究から明らかにされた最新の知見について概説した．その中で特筆すべきことは，従来の病理学的解析から神経細胞の変性・脱落による欠落症状として理解されていた神経症状は，神経細胞死に至る前の可逆性の神経機能障害に起因する可能性が示されたことである．このことは，発症後からでも病態進行を阻止し，神経症状を改善できる治療法開発へ向けて，大きな福音をもたらした．このような病態研究を通じて，難治性と考えられていた神経変性疾患を克服できる日が来ることを願ってやまない．

●文 献

1) Carrell RW, Lomas DA：Lancet 350：134-138, 1997
2) Nagai Y, Popiel HA：Curr Pharm Des 14：3267-3279, 2008
3) Bauer PO, Nukina N：J Neurochem 110：1737-1765, 2009
4) Davies SW, Turmaine M, Cozens BA et al：Cell 90：537-548, 1997
5) DiFiglia M, Sapp E, Chase KO et al：Science 277：1990-1993, 1997
6) Clarke PG：Anat Embryol (Berl) 181：195-213, 1990
7) Kegel KB, Kim M, Sapp E et al：J Neurosci 20：7268-7278, 2000

8) Yamada M, Tsuji S, Takahashi H : Ann Neurol 52 : 498-503, 2002
9) Rubinsztein DC, DiFiglia M, Heintz N et al : Autophagy 1 : 11-22, 2005
10) Yamamoto A, Lucas JJ, Hen R : Cell 101 : 57-66, 2000
11) Gu X, Li C, Wei W et al : Neuron 46 : 433-444, 2005
12) Wang N, Gray M, Lu XH et al : Nat Med 20 : 536-541, 2014
13) Custer SK, Garden GA, Gill N et al : Nat Neurosci 9 : 1302-1311, 2006
14) Boillee S, Yamanaka K, Lobsiger CS et al : Science 312 : 1389-1392, 2006
15) Cortes CJ, Ling SC, Guo LT et al : Neuron 82 : 295-307, 2014
16) Sambataro F, Pennuto M : Prog Neurobiol 97 : 152-172, 2012
17) Milnerwood AJ, Raymond LA : Trends Neurosci 33 : 513-523, 2010
18) Nithianantharajah J, Hannan AJ : Neuroscience 251 : 66-74, 2013
19) Murmu RP, Li W, Holtmaat A, Li JY : J Neurosci 33 : 12997-13009, 2013
20) Nicniocaill B, Haraldsson B, Hansson O et al : Eur J Neurosci 13 : 206-210, 2001
21) Milnerwood AJ, Gladding CM, Pouladi MA et al : Neuron 65 : 178-190, 2010
22) Okamoto S, Pouladi MA, Talantova M et al : Nat Med 15 : 1407-1413, 2009
23) Romero E, Cha GH, Verstreken P et al : Neuron 57 : 27-40, 2008

Chapter 28
IP_3 Receptors in Neurodegenerative Disorders: Spinocerebellar Ataxias and Huntington's and Alzheimer's Diseases

Masayoshi Tada, Masatoyo Nishizawa and Osamu Onodera

Abstract Modulation of intracellular calcium concentration is a ubiquitous signaling system involved in numerous biological processes in diverse cell types. Alterations of intracellular calcium homeostasis have been implicated in age-related neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and spinocerebellar ataxias (SCAs). Inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs), calcium release channels in the ER membrane, play a key role in regulating intracellular calcium concentration. IP_3R type 1 (IP_3R1), a major neuronal type of IR_3R, is expressed ubiquitously and is involved in diverse biological processes. Cerebellar Purkinje cells are mainly affected by alterations in IP_3R1. Heterozygous deletion or missense mutations in *ITPR1,* the *IP3R1* gene, result in autosomal dominantly inherited ataxias, including SCA type 15 or 29. In addition, mutations in carbonic anhydrase-related protein VIII, which suppresses the binding ability of IP_3 to IP_3R1, cause recessively, inherited ataxia. These results indicate that IP_3R1-mediated calcium signaling has an important role in maintaining the function of Purkinje cells. Moreover, cytosolic calcium overload with excessive IP_3R1 activity has been implicated in pathogenesis of other neurodegenerative diseases, including SCA type 2, SCA type 3, Huntington's disease, and Alzheimer's disease, where dysregulation of IP_3R1-mediated calcium signaling may link to the pathogenesis.

Abbreviations (alphabetical)

AD	Alzheimer's disease
Aβ	Amyloid β

M. Tada · M. Nishizawa
Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan
e-mail: tadamasa@bri.niigata-u.ac.jp

O. Onodera (✉)
Department of Molecular Neuroscience, Center for Bioresources,
Brain Research Institute, Niigata University, Niigata, Japan
e-mail: onodera@bri.niigata-u.ac.jp

N. Weiss and A. Koschak (eds.), *Pathologies of Calcium Channels*,
DOI: 10.1007/978-3-642-40282-1_28,

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATXN2	Ataxin-2
ATXN3	Ataxin-3
CAMRQ3	Cerebellar ataxia and mental retardation with or without quadrupedal locomotion 3
CARP	Carbonic anhydrase-related protein VIII
ER	Endoplasmic reticulum
HAP1	Htt-associated protein1
HD	Huntington's disease
Htt	Huntingtin
mHtt	Mutant huntingtin
IP_3	Inositol 1,4,5-trisphosphate
IP_3R	IP_3 receptor
IP_3R1	Inositol 1,4,5-trisphosphate receptor type 1
LTD	Long-term depression
mGluR	Metabotropic glutamate receptors
MSN	Medium spiny neuron
nAChR	Nicotinic acetylcholine receptor
NCX	Sodium-calcium exchanger
NMDA	*N*-methyl-D-aspartic acid
PMCA	Plasma membrane calcium ATPase
PS	Presenilin
RyR	Ryanodine receptor
SCA	Spinocerebellar ataxia
SERCA	Sarco-/endoplasmic reticulum calcium ATPase
SUMF1	Sulfatase modifying factor 1
VGCC	Voltage-gated calcium channel

28.1 Introduction

Modulation of cytoplasmic free calcium (Ca^{2+}) concentration is a universal intracellular signaling system involved in numerous biological processes, including learning and memory, membrane transport, cell excitability, synaptic transmission, axonal transport, cell division, apoptosis, and cell development, in diverse cell types (Foskett et al. 2007; Bezprozvanny 2010; Finch et al. 2012; Stutzmann and Mattson 2011; Goto and Mikoshiba 2011). Inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs) form a group of Ca^{2+} release channels localized in the endoplasmic reticulum (ER) membrane (Foskett et al. 2007; Bezprozvanny 2005). They function to release Ca^{2+} from ER, the major Ca^{2+} storage organelle, into the cytoplasm in response to IP_3, an intracellular second messenger, which is

generated through hydrolysis of phosphatidyl-inositol 4,5-bisphosphate, a component of the plasma membrane, by phospholipases Cβ and Cγ. This hydrolysis is triggered by the ligand binding to G protein-coupled or tyrosine phosphorylation-coupled receptors followed by the sequential activation of the phospholipases (Fig. 28.1a).

IP_3Rs are ubiquitously expressed in all cell types. Three IP_3R isoforms, IP_3R type 1 (IP_3R1), IP_3R type 2 (IP_3R2), and IP_3R type 3 (IP_3R3), are expressed in mammals including humans (Furuichi et al. 1994; Mikoshiba et al. 1993; Foskett et al. 2007; Taylor et al. 1999; Taylor et al. 2004; Stutzmann and Mattson 2011; Goto and Mikoshiba 2011). The three IP_3R isoforms are 60–70 % identical in sequence (Furuichi et al. 1994; Michikawa et al. 1996). Most tissues express more than one and often all three IP_3R isoforms at different ratios (Taylor et al. 1999; Foskett et al. 2007), and the expression level of each IP_3R isoform can be regulated according to cellular states.

IP_3R1 is the major neuronal form of IP_3R family in the central nervous system (Yamada et al. 1994) and is abundant in the cerebellum, particularly in cerebellar Purkinje cells. It is also expressed in other brain areas, including the cerebral cortex, hippocampus, basal ganglia, and thalamus, as well as in peripheral tissues (Furuichi et al. 1994; Foskett et al. 2007; Nakanishi et al. 1991; Sharp et al. 1999). IP_3R1 is 2,758 residues in length and forms a homotetramer. The primary structure of IP_3R1 consists of three domains, including an IP_3-binding domain near the N terminus, a coupling/regulatory domain in the middle of the molecule, and a transmembrane-spanning domain near the C terminus (Fig. 28.2). In addition, there is at least two consensus protein kinase A phosphorylation sites and at least one consensus ATP-binding site (Nucifora et al. 1995; Foskett et al. 2007). See also Chap. 11 for the details of IP_3R.

Because of the ubiquitous expression of IP_3Rs and their roles in diverse biological processes, it is likely that IP_3R can be implicated in a number of disease conditions. In this chapter, we will discuss the neurological disorders, spinocerebellar ataxia type 15 (SCA15) and 29, caused by alterations in the *IP3R* gene. In addition, we will highlight other neurological disorders, including some SCAs, Huntington's disease (HD), and Alzheimer's disease (AD), where alterations in IP_3R-mediated Ca^{2+} signaling may link to their pathogenesis.

28.2 Dominantly Inherited SCAs Caused by Alteration in *IP3R*

SCA15 (MIM 606658) is an autosomal dominant neurodegenerative disorder characterized by very slowly progressive, pure cerebellar ataxia (Storey et al. 2001; Gardner et al. 2005). A family of Australian origin with SCA15 was the first report on this condition, and the locus was mapped to 3pter-p24.2 (Knight et al. 2003). Then, in two Japanese families with benign SCA, Hara et al. narrowed the

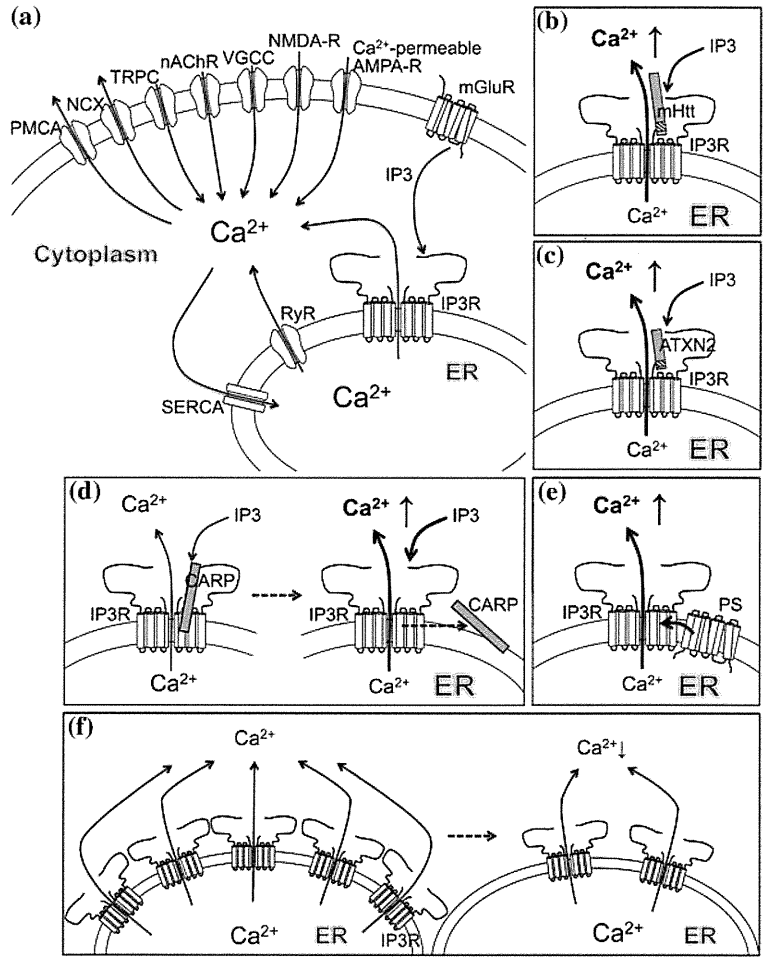

Fig. 28.1 A model of deranged inositol 1,4,5-trisphosphate receptor (IP_3R)-mediated Ca^{2+} signaling in Huntington's disease, spinocerebellar ataxia type 2 (SCA2), type 3 (SCA3), type 15 (SCA15), and type 29 (SCA29), cerebellar ataxia and mental retardation with or without quadrupedal locomotion 3 (CAMRQ3), and Alzheimer's disease. **a** Sources of Ca^{2+} influx are Ca^{2+}-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) glutamate receptors, voltage-gated Ca^{2+} channels (VGCCs), nicotinic acetylcholine receptors (nAChR), and transient receptor potential type C (TRPC) channels. Ca^{2+} release from internal stores is mediated by inositol triphosphate receptors (IP_3R) and ryanodine receptors (RyR). Inositol triphosphate (IP_3) can be generated by metabotropic glutamate receptors (mGluR). Ca^{2+} efflux is mediated by the sodium–calcium exchanger (NCX), the plasma membrane calcium ATPase (PMCA), and the sarco-/endoplasmic reticulum calcium ATPase (SERCA). **b** In HD, mutant huntingtin (mHtt) binds to the C-terminal region of IP_3R and enhances its affinity to IP_3. **c** In AD, presenilins (PSs) can directly increase the activity of IP_3R. ER = endoplasmic reticulum. **d** In healthy individuals, the carbonic anhydrase-related protein VIII (CARP) binds to the modulatory domain of IP_3R and suppresses its affinity to IP_3. In SCA29 or CAMRQ3, CARP cannot bind to IP_3R, resulting in increased affinity of IP_3R to IP_3. **e** In SCA2 or SCA3, mutant ataxin-2 (ATXN2) or ataxin-3 (ATXN3) also binds to the C-terminal region of IP_3R and enhances its affinity to IP_3. **f** In SCA15, the reduced IP_3R levels results in dysregulation of IP_3R-mediated Ca^{2+} signaling

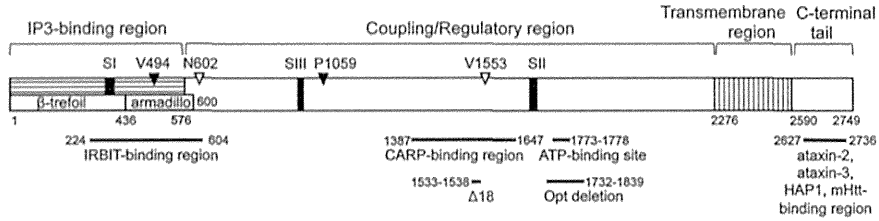

Fig. 28.2 Domain structure of inositol 1,4,5-trisphosphate receptor type 1 (IP_3R1). IP_3R1 consists of three major domains, including the amino-terminal IP_3-binding region, coupling/regulatory region, and transmembrane region. The structural features shown are as follows: alternative splicing sites SI (318–332), SII (1692–1731), and SIII (917/918). β-trefoil domain, armadillo repeat domain, IRBIT-binding region, carbonic anhydrase-related protein VIII (CARP)-binding region, Opt deletion, Δ18 deletion, ATP-binding site, and ataxin-1-, ataxin-2-, HAP1- and mHtt-binding regions

region to 3p26.1-p25.3 (Hara et al. 2004). In a large four-generation Japanese family, initial studies showed a linkage to chromosome 8, and the condition was formally designated SCA16. However, additional studies revealed a linkage to 3pter-p26.2 (Miura et al. 2006). In 2007, heterozygous large deletions (200–400 kb) in genes encoding IP_3R1 and sulfatase modifying factor 1 (SUMF1) were identified in affected members of the Australian and two other British families (van de Leemput et al. 2007). In addition, a heterozygous large deletion only in *ITPR1*, the *IP3R1* gene, as well as a point mutation in *ITPR1* was identified in the Japanese families. These have been reported to link to the same locus, indicating that *ITPR1* is the causative gene for SCA in humans (Hara et al. 2008; Iwaki et al. 2008).

28.2.1 Clinical Features of SCA15

SCA15 is clinically characterized by autosomal dominant inheritance, very slow progression, and pure cerebellar ataxia. Age at onset varies between 7 and 66 years (usually between 30 and 50) (Storey et al. 2001; van de Leemput et al. 2007; Hara et al. 2008; Iwaki et al. 2008). The disease usually begins with gait ataxia. Tremor may begin simultaneously with or even occasionally precede gait ataxia. Deterioration in handwriting, motion-induced instability, and myoclonus were also the initial symptoms in some individuals. Cerebellar signs and symptoms including truncal and limb ataxia, ataxic speech, and gaze-evoked nystagmus are core features in combination with head tremor (titubation), upper limb postural tremor, action tremor, and impaired oculocephalic reflex. Hyperreflexia, but neither Babinski reflex nor spasticity, may be noted as a pyramidal sign. Fatal complications such as severe bulbar palsy do not develop. Cognitive function seems to be intact. There have been no reports describing epilepsy in individuals affected with SCA15.

Brain magnetic resonance imaging (MRI) reveals marked atrophy of the cerebellar vermis with mild atrophy of the cerebellar hemispheres (Hara et al. 2004; Knight et al. 2003; van de Leemput et al. 2007; Novak et al. 2010; Synofzik et al. 2011). Nerve conduction studies are typically normal, but mild slowing of conduction velocities of sural sensory and median motor nerves were shown in affected members of a Japanese family with SCA15 (Hara et al. 2008). Disease progression is notably slow. Most patients with SCA15 can ambulate independently or with a cane 10–40 years after onset (Storey et al. 2001; van de Leemput et al. 2007; Hara et al. 2008; Iwaki et al. 2008). Neuropathological findings are not available in SCA15.

28.2.2 SCA15 Diagnosis

SCA15 is defined by the presence of a pathogenic mutation in *ITPR1*. SCA15 diagnosis should be considered in individuals who exhibit the clinical features of SCA15 and in whom the diagnosis of SCA1, 2, 3, 5, 6, 8, 12, and 14 have been excluded by genetic testing. Most patients with SCA15 are diagnosed by gene dosage analysis for *ITPR1*. Because most *ITPR1* mutations are exonic deletions, genetic testing should begin with gene dosage analysis followed by sequence analysis if a deletion is not identified.

28.2.3 SCA15 Prevalence

In the Australian population, pathogenic *ITPR1* deletions were found in approximately 2.7 % of families with autosomal dominant SCA who were negative for common SCA repeat expansions in coding exons (Ganesamoorthy et al. 2009). In the Caucasian population, an *ITPR1* deletion was found in 1.8 % of 333 families (Marelli et al. 2011). On the other hand, *ITPR1* deletions were found in 8.9 % of 56 central European families negative for common SCA repeat expansions (Synofzik et al. 2011). The precise prevalence of SCA15 is however still obscure, because most previous studies used quantitative PCR for genetic testing of SCA15 and this method cannot detect small deletions, insertions, or nonsense mutations in *ITPR1*. Hara et al. analyzed *ITPR1* deletions using custom high-definition comparative genomic hybridization microarrays covering the entirety of *ITPR1* at an average interval of 200 bp for the probes in 54 Japanese families with undetermined autosomal dominant SCA and did not find *ITPR1* deletions, indicating that SCA15 is a quite rare ataxia in the Japanese population (Hara et al. 2008).

28.2.4 Molecular Genetics of SCA15

28.2.4.1 *ITPR1* Deletions

ITPR1 consists of 58 exons. Heterozygous deletions encompassing exons 1–10, 1–40, and 1–44 of *ITPR1* were identified in three unrelated Australian and British families with SCA15 (van de Leemput et al. 2007), and a heterozygous deletion of entire exons in the gene was found in another Japanese family (Hara et al. 2008). Most patients with SCA15 also have deletions in the adjacent *SUMF1* (van de Leemput et al. 2007; Hara et al. 2008; Ganesamoorthy et al. 2009; Novak et al. 2010; Di Gregorio et al. 2010; Castrioto et al. 2011). Although individuals with homozygous *SUMF1* deletions show mental retardation, seizure, and leukodystrophy, individuals with heterozygous *SUMF1* deletions are healthy (Cosma et al. 2003). These findings suggest that partial *SUMF1* deletion does not contribute to SCA15 pathogenesis. In addition, a heterozygous deletion of exons 1–48 in *ITPR1*, but not in *SUMF1*, was identified in a Japanese family (Iwaki et al. 2008), indicating that the pathogenic mechanism underlying SCA15 is *ITPR1* haploinsufficiency. Although it is expected that micro deletions, insertions, or nonsense mutations cause SCA15, these mutations have not yet been fully identified and evaluated.

28.2.4.2 Missense Mutations in *ITPR1*

Two heterozygous missense mutations, P1059L (c.8581C > T) and V494I (c.1480G > A), have been also identified in Japanese and Australian families with SCA15, respectively (Hara et al. 2008; Ganesamoorthy et al. 2009). Proline at position 1059 in the amino acid sequence is highly conserved in IP_3R1 among species, although it is not the same in human ITPR2 and ITPR3. This residue is located in the coupling domain (Fig. 28.2), whose function remains poorly understood. Valine at position 494 is located in the IP_3-binding domain consisting of β-trefoil and armadillo repeat domains (Ganesamoorthy et al. 2009; Foskett et al. 2007). The proper coordination of both domains is necessary for the binding of IP_3 to IP_3R1. Valine at position 494 is not particularly conserved among species. Although it seems likely that the missense mutations may affect IP_3R1 function, the Ca^{2+} release properties of IP_3R1 with P1059I mutation is largely unaffected (Yamazaki et al. 2011). To show that these missense mutations contribute to disease pathogenesis, it should be clarified how these mutations affect the functional properties or the kinetics of biogenesis and turnover of IP_3R1.

A recent study demonstrated that two other heterozygous missense mutations in *ITPR1*, V1553 M (c.4657G > A) and N602D (c.1804A > G), caused another neurological disease in families with autosomal dominantly inherited congenital nonprogressive ataxia, designated as SCA29 (OMIM 117360) (Huang et al. 2012). Mild and very slow progressive ataxia observed in SCA29 is similar to that in

SCA15. However, these families exhibited several characteristic clinical features, including delayed motor milestones (suggesting the existence of congenital ataxia) and mild intellectual impairment (Dudding et al. 2004, Huang et al. 2012). In addition, the severity of ataxia and intellectual impairment was variable in each affected member even in the same family. Valine at position 1553 is located in the carbonic anhydrase-related protein VIII (CARP)-binding region, and asparagine at position 602 is in the IRBIT-binding region, respectively. Both IRBIT and CARP compete with IP_3 for binding to IP_3R1 and suppress IP_3R1 activity (Hirota et al. 2003; Ando et al. 2006). Interestingly, homozygous mutations in *CA8*, which encodes CARP, cause an autosomal recessive congenital ataxia associated with mild intellectual impairment (Turkmen et al. 2009). Therefore, the two missense mutations in the families might increase the sensitivity of IP_3R1 in response to IP_3 and therefore be a cause of the disease in these families.

28.2.5 Roles of IP_3R1 in SCA15 Pathogenesis

Western blot analysis of IP_3R1 protein levels in immortalized lymphoblasts from affected individuals carrying *ITPR1* deletions revealed remarkable reduction in IP_3R1 protein levels (van de Leemput et al. 2007; Novak et al. 2010). In addition, RT-PCR analysis showed that the mRNA expression levels of *ITPR1* in fibroblasts obtained from an affected individual with SCA15 were half of the levels measured in normal controls (Hara et al. 2008). These findings suggest that SCA15 is caused by *ITPR1* haploinsufficiency and that cerebellar Purkinje cells are particularly vulnerable to the dosage of *ITPR1* (Fig. 28.1b).

How does IP_3R1 haploinsufficiency cause cerebellar ataxia in patients with SCA15? IP_3R1, the major neuronal IP_3R, is expressed ubiquitously in various regions of the central nervous system including CA1, basal ganglia, and the thalamus and particularly in the cerebellar Purkinje cells (Nakanishi et al. 1991; Sharp et al. 1999). Intracellular Ca^{2+} homeostasis is important for maintaining the function of neurons, particularly Purkinje cells (Hartmann and Konnerth 2005; Mikoshiba 2007). As described later, mice homozygous for null *ITPR1* develop ataxia and epilepsy (Matsumoto and Nagata 1999; Matsumoto et al. 1996), whereas mice heterozygous for null *ITPR1* develop only mild motor discoordination (Ogura et al. 2001). Thus, *ITPR1* haploinsufficiency may result in dysfunction restricted to the cerebellar Purkinje cells, whereas complete loss of IP_3R1 results in more severe dysfunction of not only Purkinje cells but also cortical neurons.

Indeed, none of the individuals with SCA15 with heterozygous *ITPR1* deletions had epilepsy or abnormal electroencephalogram, and the clinical phenotype was restricted to pure cerebellar ataxia even in the elderly (Gardner et al. 2005; Hara et al. 2004; Knight et al. 2003; van de Leemput et al. 2007). These findings indicate that Purkinje cells are particularly vulnerable to abnormalities in IP_3R1. The reduced IP_3R1 levels may cause dysregulation of intracellular Ca^{2+} homeostasis, leading to persistent long-standing dysfunction of Purkinje cells and

eventually degeneration of the selective neuronal populations. The neuropathological findings of affected individuals with deletion or missense mutations in *ITPR1* will confirm this speculation.

28.3 IP_3R Mutant/Deficient Mice

28.3.1 ITPR1 Knockout Mice

Homozygous IP_3R1 knockout mice, in which cytosolic IP_3-induced Ca^{2+} release is almost completely deficient, are rarely born alive, indicating that IP_3R1 has some function during embryonic development. Even if they survive, the mice exhibit severe ataxia and tonic or tonic–clonic seizure and die by 3–4 weeks after birth (Matsumoto et al. 1996; Matsumoto and Nagata 1999). Cultured Purkinje cells from the mice shows abnormal dendritic development and enlarged parallel fiber terminals with many vesicles (Hisatsune et al. 2006). IP_3R1 in granule cells, not in Purkinje cells, is crucial for the outgrowth of the Purkinje cell dendrites. Brain-derived neurotrophic factor (BDNF) production in cerebellar granule cells induced by IP_3R1-mediated signaling, modifies the parallel fiber-Purkinje cell synaptic efficacy, resulting in the formation of Purkinje cell dendrites (Hisatsune et al. 2006).

In neurophysiological analysis, long-term depression (LTD) is completely diminished in cerebellar Purkinje cells (Inoue et al. 1998). However, the effect of IP_3R1 on synaptic plasticity in the hippocampus is a little complicated. A classical form of LTD induced by sustained low-frequency stimulation is not affected at the CA3-CA1 synapses (Fujii S et al. 2000), whereas it is diminished at mossy fiber-CA3 synapses (Itoh et al. 2001). In addition, although paring stimulations of pre- and postsynaptic sites in a post - > pre order induces homo- and heterosynaptic LTD at the normal hippocampal CA3-CA1 synapses, the homosynaptic LTD is converted to long-term potentiation (LTP) and heterosynaptic LTD is disappeared (Nishiyama et al. 2000; Nagase et al. 2003). LTP induced by the short tetanus (100 Hz, 10 pulses) is enhanced in CA1 synapses. Moreover, IP_3R1 is indispensable to the induction of depotentiation and suppression of LTP (Fujii et al. 2000). These results indicated that IP_3R1-mediated Ca^{2+} signaling plays an important role for the regulation of synaptic plasticity in different ways in each situation.

28.3.2 Opisthotonus (Opt) Mouse

The *Opt* mouse has a spontaneously generated allele of deletion of exons 43 and 44 in *ITPR1* that results in an in-frame deletion of residues 1732–1839 (107 amino acids) in the regulatory domain (Street et al. 1997). Homozygous *Opt* mice are small at birth, lack their normal mobility, exhibit seizures 2 weeks after birth, and

die by 4 weeks of age. The phenotype of *Opt* mice largely overlaps that of homozygous *ITPR1* knockout mice. The recombinant *Opt* IP_3R1 mice showed reduction in ATP sensitivity compared with wild-type IP_3R1 mice, consistent with the fact that *Opt* deletion involves the ATP-binding site, yet the recombinant *Opt* IP_3R1 remains functional (Tu et al. 2002). A strong Ca^{2+} release from intracellular stores was elicited in the cerebellar Purkinje cells of homozygous *Opt* mice treated with the mGluR agonist quisqualate (Street et al. 1997). Nevertheless, *Opt* IP_3R1 expression levels in the brain tissues of heterozygous *Opt* mice were reduced compared with those of the wild-type mice, and *Opt* IP_3R1 was almost undetectable in the homozygous *Opt* mice (Street et al. 1997; Foskett et al. 2010). Although mechanisms underlying the reduced IP_3R1 levels remain to be elucidated, it is presumed that cellular protein quality control mechanisms may recognize *Opt* IP_3R1 as aberrant and degrade it promptly. Further studies are needed to clarify the precise mechanisms underlying neurological deficits in *Opt* mice.

28.3.3 The Δ18 Mouse

The Δ18 mouse has a spontaneously generated deletion of 18 nucleotides in exon 36 of *ITPR1* that results in an in-frame deletion of six amino acid residues (residues 1533–1538; Glu-Ser-Cys-Ile-Arg-Val) in the regulatory domain (van de Leemput et al. 2007). The homozygous Δ18 mice show severe neurological symptoms, small weight at birth, abnormal mobility, and die by 4 weeks of age. Their phenotype is similar to those of *ITPR1* knockout and *Opt* mice (van de Leemput J et al. 2007; Street et al. 1997; Matsumoto et al. 1996). The functional significance of the six deleted residues, which are not particularly conserved among isoforms and species, remains to be examined. As observed in *Opt* mice, immunostaining of the cerebellar Purkinje cells and western blotting of the whole brain lysates revealed that IP_3R1 expression levels were markedly reduced in the homozygous Δ18 mice (van de Leemput et al. 2007). It is interesting that the recombinant expression of the mutant IP_3R1 proteins produces functional ion channels, including *Opt*, *Δ18*, and P1059L, but appears to cause disease because of reduced IP_3R1 levels, perhaps due to rapid degradation by cellular quality control mechanisms. Thus, it will be interesting, in future studies, to investigate the effects of these mutations not only on ion channel properties but also on the kinetics of channel biogenesis and turnover.

28.4 CARP and Ataxias

Despite the abundant expression of IP_3R1 in Purkinje cells, IP_3R1-mediated Ca^{2+} release in response to IP_3 in these cells is lower than that in other tissues. CARP may, in part, account for this mechanism. CARP binds to the modulatory domain

of IP_3R1 (residues 1387–1647) and suppresses the binding ability of IP_3 to IP_3R1 (Hirota et al. 2003). In addition, CARP is expressed exclusively in the Purkinje cells. These results suggest that CARP regulates IP_3R1-mediated Ca^{2+} signaling particularly in the Purkinje cells. Therefore, it would be speculated that the loss of function of CARP results in an enhanced sensitivity of IP_3 binding to IP_3R1, consequently leading to dysregulation of IP_3R1-mediated Ca^{2+} signaling in the Purkinje cells (Fig. 28.1c).

Interestingly, CARP was identified as the antigen of auto-antibody observed in a patient with paraneoplastic cerebellar degeneration (Bataller et al. 2004). Moreover, Turkmen et al. identified a homozygous missense mutation (S100P, c.298T > G) in *CA8*, which encodes CARP, in affected patients with recessively inherited ataxia (Turkmen et al. 2009). They exhibited mild mental retardation and congenital ataxia with quadrupedal gait. Another homozygous missense mutation, G162R (c.484G > A), was identified in three related Arabian families with ataxia and mild cognitive impairment without quadrupedal gait (Kaya et al. 2011). A whole brain MRI showed varying degrees of cerebellar atrophy. Fluorodeoxyglucose positron emission tomography revealed hypometabolic cerebellar hemispheres, temporal lobes, and mesial cortex. These families are designated as cerebellar ataxia and mental retardation with or without quadrupedal locomotion 3 (CAMRQ3, MIM 613227). The reduced levels of S100P CARP in cell culture experiments suggest that the loss of function of CARP caused ataxia. Indeed, in CAMRQ3, waddles (*wdl*) mice, harboring a spontaneously occurring 19-base pair deletion in *CA8*, exhibited ataxia and appendicular dystonia without pathological abnormalities in the central nervous system (Jiao et al. 2005).

28.5 Deranged IP_3R-Mediated Ca^{2+} Signaling in Ataxias Caused by Expanded Polyglutamine (polyQ) Stretches

SCA type 2 (SCA2) and type 3 (SCA3), polyQ diseases, are autosomal dominantly inherited ataxias caused by the expansion of CAG repeats that encode abnormally expanded polyQ in the ataxin-2 (ATXN2) and ataxin-3 (ATXN3) proteins, respectively (Zoghbi and Orr 2000; Williams and Paulson 2008; La Spada and Taylor 2010; Costa Mdo and Paulson 2012). The diseases are progressive in nature and generally feature degeneration of the cerebellum, brainstem, and spinocerebellar tracts. Mutant polyQ proteins including mutant ATXN2 and ATXN3 are prone to undergo a conformational change that favors β sheet-rich structures and to aggregate in cells, leading to the formation of neuronal inclusion bodies, a prominent pathological hallmark of polyQ diseases (Muchowski and Wacker 2005; Williams and Paulson 2008; Nagai et al. 2007; Paulson et al. 1997). PolyQ expansions usually act in a dominant toxic manner associated with altered interactions with other proteins, resulting in altered cellular processes such as perturbed proteostasis, transcriptional dysregulation, oxidative stress, impaired neurotransmission,

insufficient trophic support, and aberrant cellular excitability (Williams and Paulson 2008; Costa Mdo and Paulson 2012; Takahashi et al. 2010). Increasing evidence suggests that deranged neuronal Ca^{2+} signaling plays a role in the pathogenesis of polyQ diseases (Chen et al. 2008; Liu et al. 2009). Cerebellar Purkinje cells seem to be particularly vulnerable to fluxes in cytosolic Ca^{2+} levels. Several neuronal genes abundantly expressed in Purkinje cells that are involved in Ca^{2+} signaling or homeostasis are downregulated in the cerebellum of SCA1 mutant mice before the occurrence of motor deficits or pathology (Serra et al. 2004; Lin et al. 2000). Unlike SCA15, other SCAs are affected by exaggerated Ca^{2+} flux but not by suppressed cytosolic Ca^{2+} signaling. Among these SCAs, to date, only ATXN2 and ATXN3 have been reported to directly affect IP_3R1 function.

28.5.1 SCA2

SCA2 is clinically characterized by progressive cerebellar ataxia of gait, limbs, and speech associated with slow saccades, early hyporeflexia, severe tremor of postural or action type, peripheral neuropathy, cognitive disorders, and other multisystemic features (Lastres-Becker et al. 2008; Magana et al. 2012). Cerebellar Purkinje cells are predominantly affected in SCA2. The disease-causing protein ATXN2 is expressed ubiquitously. Increasing evidence suggests that ATXN2 is involved in multiple cellular processes including RNA post-transcriptional and translational regulation, stress-granule formation, endocytosis, cytoskeletal reorganization, and Ca^{2+}-mediated signaling (Albrecht et al. 2004; van de Loo et al. 2009; Neuwald and Koonin 1998; Satterfield and Pallanck 2006; Lastres-Becker et al. 2008; Ralser et al. 2005a; Ralser et al. 2005b; Shibata et al. 2000; Kozlov et al. 2010; Ciosk et al. 2004; Satterfield et al. 2002; Liu et al. 2009), although the precise physiological function of ATXN2 is unknown (Pulst et al. 2005). The mechanisms underlying Purkinje cell degeneration in SCA2 are also poorly understood.

The presence of ATXN2 in ER suggests its participation in intracellular Ca^{2+} signaling pathways. Supporting this hypothesis, pull-down and co-immunoprecipitation assays revealed that mutant, but not wild-type, ATXN2 (58Q) specifically binds to the cytosolic C-terminal region (residues 2627–2749) of IP_3R1 (Liu et al. 2009). Association of mutant ATXN2 (58Q) with the receptor increases the sensitivity of IP_3R1 to activation by IP_3 in bilayer reconstitution experiments (Fig. 28.1d). In Ca^{2+} imaging experiments, a significant increase in Ca^{2+} release from ER through IP_3R1 was observed in primary Purkinje cells cultured from SCA2 transgenic mice (58Q), which express human *ATXN2* with 58 CAG repeats under the control of the Purkinje cell-specific promoter (Huynh et al. 2000). Ryanodine or dantrolene, inhibitors of ryanodine receptors (RyR), alleviated the adverse effects of mutant ATXN2 such as excessive Ca^{2+} release and glutamate-induced cell death in 58Q Purkinje cell cultures (Liu et al. 2009). In addition, long-term feeding of SCA2 mice (58Q) with dantrolene ameliorated age-dependent

motor discoordination and loss of Purkinje cells. More recently, long-term suppression of IP_3R1-mediated Ca^{2+} signaling by viral expression of the inositol 1,4,5-phosphatase enzyme in the Purkinje cells of SCA2 transgenic mice (58Q) rescued age-dependent dysfunction in the firing pattern of SCA2 Purkinje cells and motor deficits and cell death in SCA2 mice (Kasumu et al. 2012). These findings support the idea that excitotoxic Ca^{2+} signaling through IP_3R1 plays a key role in SCA2 pathogenesis.

28.5.2 SCA3

SCA type 3 (SCA3), also known as Machado–Joseph disease, is the most common inherited SCA and one of the nine known polyQ diseases (Costa Mdo and Paulson 2012; Tsuji et al. 2008; Paulson 2012). SCA3 is clinically characterized by progressive cerebellar ataxia and variable findings including a dystonic-rigid syndrome, a Parkinsonian syndrome, or a combined syndrome of dystonia and peripheral neuropathy. The most affected brain regions are the dentate and pontine nuclei, internal portion of globus pallidus, substantia nigra, subthalamic nucleus, and spinocerebellar tracts (Stevanin et al. 2000; Yamada et al. 2008; Yamada et al. 2000). The cerebellar cortex is relatively spared in SCA3 compared with other SCAs. The disease-causing protein ATXN3 is ubiquitously expressed and abundant in cerebellar Purkinje cells. ATXN3 is a 43-kDa cytosolic protein containing the amino-terminal Josephin domain and three ubiquitin-interacting motifs and functions as a deubiquitinating enzyme (Costa Mdo and Paulson 2012). Similar to other SCAs, the precise mechanisms of SCA3 remain poorly understood.

In SCA3, deranged Ca^{2+} signaling has also been implicated in pathogenesis (Bezprozvanny 2011). Inhibition of Ca^{2+}-dependent protease calpain suppressed aggregation of mutant ATXN3 in transfected cells (Haacke et al. 2007). In a SCA3 fly model, knockdown of expression of *PICK1*, which is a regulator of traffic of ion channels involved in Ca^{2+} homeostasis (Chung et al. 2000; Hanley 2006; McGurk and Bonini 2012), suppressed external eye degeneration, insoluble aggregations, and inclusions. Mutant, but not wild-type, ATXN3 specifically binds to the cytosolic C-terminal region of IP_3R1 (Chen et al. 2008), as cases in mutant huntingtin (mHtt) and mutant ATXN2 (Fig. 28.1d and e). Association of mutant ATXN3 with the receptor increases the sensitivity of IP_3R1 to activation by IP_3 in bilayer reconstitution and Ca^{2+} imaging experiments. In addition, long-term feeding of SCA3-YAC-84Q transgenic mice with dantrolene ameliorated gae-dependent motor deficits and prevented neuronal cell loss in the pontine nuclei and substantia nigra regions. These findings indicate that deranged IP_3R1-mediated Ca^{2+} signaling may play an important role in SCA3 pathogenesis.

28.6 Deranged IP_3R-Mediated Ca^{2+} Signaling in HD

HD is a dominantly inherited neurodegenerative disorder caused by polyQ expansions in Htt, which primarily results in the selective degeneration of the striatal medium spiny neurons (MSNs) (Bonelli and Beal 2012). The disease is clinically characterized by movement disorders, cognitive decline, and psychiatric symptoms. A pathological hallmark of HD is cytoplasmic and nuclear aggregates containing htt and other proteins. Although the physiological function of wild-type htt is unknown, its amino acid sequence indicates that it possesses HEAT repeats, protein interaction domains, suggesting that it may function as a scaffold protein (Bonelli and Beal 2012). Several lines of evidence indicate that a toxic gain of function of mHtt accounts for HD pathogenesis, although the molecular mechanisms that underlie this pathogenesis and selective neurodegeneration remain unknown.

Deranged Ca^{2+} signaling has also been implicated in HD pathogenesis (Bezprozvanny 2011; Bezprozvanny 2009). mHtt binds specifically to the C-terminal region of IP_3R1 (Tang et al. 2003; Tang et al. 2005). A comprehensive high-throughput screening confirmed binding of mHtt to IP_3R1 (Kaltenbach et al. 2007). Mutant, but not wild-type, Htt sensitizes IP_3R1 activation by IP_3 in planar lipid bilayer experiments and facilitates IP_3R1-mediated intracellular Ca^{2+} release in rat striatal MSNs (Tang et al. 2003) (Fig. 28.1e). The effect of mHtt on IP_3R1 is facilitated when mHtt is associated with Htt-associated protein 1 (HAP1), which has also been shown to interact with IP_3R1 (Tang et al. 2004), suggesting that HAP1 plays an important role in functional interactions between Htt and IP_3R1. Specific inhibitors of IP_3R1, 2-aminoethoxydiphenyl borate and enoxaparin, provided protection in the same model (Tang et al. 2005). Genetic knockdown and chemical inhibition of IP_3R1 also reduced mHtt aggregation in cultured cells (Bauer et al. 2011). Expression of the GFP-fused C-terminal fragment of IP_3R1 in MSNs from HD transgenic mice stabilized exaggerated Ca^{2+} signaling and protected HD MSNs from glutamate excitotoxicity (Tang et al. 2009). Infection of adeno-associated viruses expressing the recombinant IP_3R1 C-terminal fragment in the striatum ameliorated motor deficits and loss of MSNs in a HD mouse model (Tang et al. 2009). In addition, long-term feeding of HD mice with dantrolene, a relevant Ca^{2+} signaling stabilizer, alleviated motor deficits, formation of nuclear inclusion bodies, and loss of MSNs (Chen et al. 2011). Thus, deranged IP_3R1-mediated Ca^{2+} signaling also plays an important role in HD pathogenesis.

ER stress has been implicated in the pathogenesis of numerous neurodegenerative diseases including HD. It was demonstrated that ER stress induced IP_3R1 dysfunction through an impaired interaction of IP_3R1 with an ER chaperone GRP78, which positively regulates IP_3R1 tetrameric assembly in an energy dependent manner (Higo et al. 2010). Stabilizing Ca^{2+} signaling by targeting IP_3R1 appears as an attractive therapeutic strategy for HD.

28.7 Deranged IP_3R-Mediated Ca^{2+} Signaling in AD

AD is the most common form of age-related dementia, clinically characterized by a decline in memory, particularly in short-term and working memory, apathy, depression, impaired judgment, and changes in behavior (Forman et al. 2004; Brookmeyer et al. 2007). The key pathological hallmarks of AD are accumulation of extracellular amyloid β (Aβ) plaques, intracellular neurofibrillary tangles, and neuronal loss accompanied by extensive neurodegeneration of the median temporal lobe, parietal lobe, selective regions of the frontal cortex, and cingulate gyrus (Wenk 2003; Giannakopoulos et al. 2009; Forman et al. 2004). Mutations in presenilins (PS1 and PS2) and amyloid precursor protein (APP) cause most early-onset, autosomal dominant familial cases of AD (Tanzi and Bertram 2005).

Numerous lines of evidence indicate that altered Ca^{2+} signaling also plays an important role in AD pathogenesis. Aβ oligomers can form Ca^{2+}-permeable channels in neuron plasma membranes (Arispe et al. 1993; Lee et al. 2002; Kuchibhotla et al. 2008). Aβ oligomers also perturb neuronal Ca^{2+} homeostasis through modulation of the activities of *N*-methyl-D-aspartic acid receptors (De Felice et al. 2007; Shankar et al. 2007), AMPA receptors (Hsieh et al. 2006), and P/Q-type voltage-gated Ca^{2+} channels (Nimmrich et al. 2008). Another key connection between Ca^{2+} signaling and AD pathogenesis is based on studies demonstrating that mutations in *PSs* found in familial AD cause dysregulation of Ca^{2+} signaling (Ito et al. 1994; Leissring et al. 1999; Stutzmann et al. 2004; Stutzmann et al. 2006; Stutzmann 2005; Yoo et al. 2000; LaFerla 2002). Despite some differences in the proposed mechanisms, most studies have shown that various PS mutations result in exaggerated Ca^{2+} release from ER through IP_3R1 or RyR (Leissring et al. 1999; Cai et al. 2006; Cheung et al. 2008; Stutzmann et al. 2006; Chan et al. 2000; Rybalchenko et al. 2008; Chakroborty et al. 2009; Smith et al. 2005; Berridge 2010; Supnet and Bezprozvanny 2011) (Fig. 28.1f). Exaggerated Ca^{2+} signaling in AD may negatively affect reactive oxygen species generation, mitochondrial function, gene transcription, and Aβ production. Aged neurons are particularly vulnerable to cytosolic Ca^{2+} overload because of their lower capacity of buffering Ca^{2+} (reviewed in Supnet and Bezprozvanny 2011; Berridge 2010; Hermes et al. 2010).

28.8 Future Perspectives

As stated above, increasing evidence indicates that deranged IP_3R1-mediated Ca^{2+} signaling has been implicated in neurological diseases including AD, HD, and SCAs. Despite many advances in understanding disease mechanisms, no preventive treatment exists for these fatal neurological disorders. In SCA15, point mutations as well as large deletion mutations in *ITPR1* cause diseases because of reduced IP_3R1 levels, perhaps due to rapid degradation by cellular quality control

mechanisms. On the other hand, increasing evidence supports the idea that exaggerated Ca^{2+} influx through IP_3R1 plays an important role in pathogenesis of other neurological diseases, such as AD, HD, and some SCAs. Neurons abundantly expressing IP_3R1 are vulnerable to alterations of intracellular Ca^{2+} homeostasis, particularly exaggerated Ca^{2+} signaling. Understanding the molecular mechanisms underlying neurodegeneration caused by reduced IP_3R1 levels or exaggerated IP_3R1-mediated Ca^{2+} signaling will provide new insights into disease pathogenesis and eventually the development of new therapeutic approaches. Modulation of Ca^{2+} signaling by targeting IP_3R1 appears as an attractive therapeutic strategy for these neurological disorders.

Acknowledgments This study was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (C) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a Grant-in-Aid for the Research Committee for Ataxic Diseases from the Ministry of Health, Labor and Welfare, Japan.

References

Albrecht M, Golatta M, Wullner U, Lengauer T (2004) Structural and functional analysis of ataxin-2 and ataxin-3. Eur J Biochem 271:3155–3170

Ando H, Mizutani A, Kiefer H, Tsuzurugi D, Michikawa T, Mikoshiba K (2006) IRBIT suppresses IP3 receptor activity by competing with IP3 for the common binding site on the IP3 receptor. Mol Cell 22:795–806

Arispe N, Rojas E, Pollard HB (1993) Alzheimer disease amyloid beta protein forms calcium channels in bilayer membranes: blockade by tromethamine and aluminum. Proc Natl Acad Sci U S A 90:567–571

Bataller L, Sabater L, Saiz A, Serra C, Claramonte B, Graus F (2004) Carbonic anhydrase-related protein VIII: autoantigen in paraneoplastic cerebellar degeneration. Ann Neurol 56:575–579

Bauer PO, Hudec R, Ozaki S, Okuno M, Ebisui E, Mikoshiba K, Nukina N (2011) Genetic ablation and chemical inhibition of IP3R1 reduce mutant huntingtin aggregation. Biochem Biophys Res Commun 416:13–17

Berridge MJ (2010) Calcium hypothesis of Alzheimer's disease. Pflugers Arch 459:441–449

Bezprozvanny I (2005) The inositol 1,4,5-trisphosphate receptors. Cell Calcium 38:261–272

Bezprozvanny I (2009) Calcium signaling and neurodegenerative diseases. Trends Mol Med 15:89–100

Bezprozvanny I (2011) Role of inositol 1,4,5-trisphosphate receptors in pathogenesis of Huntington's disease and spinocerebellar ataxias. Neurochem Res 36:1186–1197

Bezprozvanny IB (2010) Calcium signaling and neurodegeneration. Acta Naturae 2:72–82

Bonelli RM, Beal MF (2012) Huntington's disease. Handb Clin Neurol 106:507–526

Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM (2007) Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 3:186–191

Cai C, Lin P, Cheung KH et al (2006) The presenilin-2 loop peptide perturbs intracellular Ca^{2+} homeostasis and accelerates apoptosis. J Biol Chem 281:16649–16655

Castrioto A, Prontera P, Di Gregorio E et al (2011) A novel spinocerebellar ataxia type 15 family with involuntary movements and cognitive decline. Eur J Neurol 18:1263–1265

Chakroborty S, Goussakov I, Miller MB, Stutzmann GE (2009) Deviant ryanodine receptor-mediated calcium release resets synaptic homeostasis in presymptomatic 3xTg-AD mice. J Neurosci 29:9458–9470