Chapter 2
Survival Mechanisms of Extremophiles

Abstract It is vital for extremophiles to cope with their environments making them viable to withstand under harsh environmental conditions. Extremophiles are known to adapt to the changes in their environment and surroundings that enable them to stabilize the changes in their homeostasis. The adaptability of extremophiles arrives from alteration of varying genes and proteins. Extremophiles produce extremolytes, which helps them to maintain their homeostasis such as ectoine-mediated mechanism, which is produced by halophiles and organisms alike. Evolutionary diversity, increased catalytic activity, amino acid accumulation, aggregation resistance strategies, resistance to cell death, activation of the nuclear factor, the use of heat shock proteins, and cellular compartmentalization, are all vital tools that extremophiles take on in order to conserve their genes.

Keywords Survival mechanisms · Proteins · Genes · Evolution · Diversity · Extremolytes · Metabolites

The general mechanisms that are studied and exploited in all the therapeutic and medical applications of extremophiles relate to how the extremophiles develop defensive mechanisms to survive in harsh environments and how their metabolisms are involved in these survival processes.

Extremophiles have been able to live in extreme and harsh conditions mainly due to their adaptability (Mallik and Kundu 2014; van Wolferen et al. 2013; Singh 2013). The adaptation mechanisms of such extremophiles would help researchers to understand their survival mechanisms, which in turn would help to figure out the process by which their molecular elements (i.e., proteins and genes) could be altered and used for therapeutic implications. Table 2.1 provides an overview of the survival and defensive strategies of selected extremophiles.

Singh and Gabani (2011) reviewed and described one such survival pathway in the radiation-resistant microorganism *Deinococcus radiodurans*. The microbial resistance against ionizing radiation induces pathway-specific genes, modulated proteins, and enzymes as part of the DNA repair mechanism. Figure 2.1 summarizes the survival strategy of *D. radiodurans*. This mechanism operates in three

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Table 2.1 Survival and defensive strategies in major extremophiles to thrive under extreme environmental conditions

Extremophiles/ extremolytes	Survival and defensive strategies	References
Thermophiles/carbohydrate extremolytes/ hydroxyectoine	Stabilization of enzymes from stress and freeze drying; protection of oxidative protein damage; reduction of VLS in immunotoxin therapy	Kumar et al. (2010)
Halophiles/ecotines	Protection of skin immune cells from UV radiation; enzyme stabilization against heating, freezing, and drying; protection of the skin barrier against water loss and drying out; block of UVA-induced ceramide release in human keratinocytes	Buommino et al. (2005), Singh and Gabani (2011), Ortenberg et al. (2000)
Acidophiles/ alkaliphiles	Maintaining a circumneutral intracellular pH; constant pumping of protons in and out of cytoplasm; acidic polymers of the cell membrane; passive regulation of the cytoplasmic pools of polyamines and low membrane permeability	Baker-Austin and Dopson (2007), Horikoshi (1999), Bordenstein (2008)
Psychrophiles	Translation of cold-evolved enzymes; increased flexibility in the portions of protein structure; presence of cold shock proteins and nucleic acid binding proteins; reduction in the packing of acyl chains in the cell membranes	Berger et al. (1996), Feller and Gerdey (2003), D'Amico et al. (2006), Chakravorty and Patra (2013)
Geophiles/EPS-V264; EPS-1,2,3	Mucoidal layer enveloping cell colonies; biofilm formation as stress response to extreme environmental conditions	Arena et al. (2009), Kambourova et al. (2009), Barbara et al. (2013)
Barophiles	Homeoviscous adaptation, tight packing of their lipid membranes; and increased levels of unsaturated fatty acids; polyunsaturated fatty acids maintain the membrane fluidity; robust DNA repair systems; highly conserved pressure regulated operons; presence of heat shock proteins	Lauro and Bartlett (2007), Yano et al. (1998), Rothschild and Mancinelli (2001), Kato et al. (1995 1996a, b), Kato and Bartlett (1997), Marteinsson et al. (1999)

distinct steps, as shown in Fig. 2.2. Three different pathways of survival have been identified through the process of homologous recombination, which is responsible for gene induction. First, the UVR-induced gene *uvrA* reveals uvrABC system protein A, representing a universal function in DNA repair and survival of

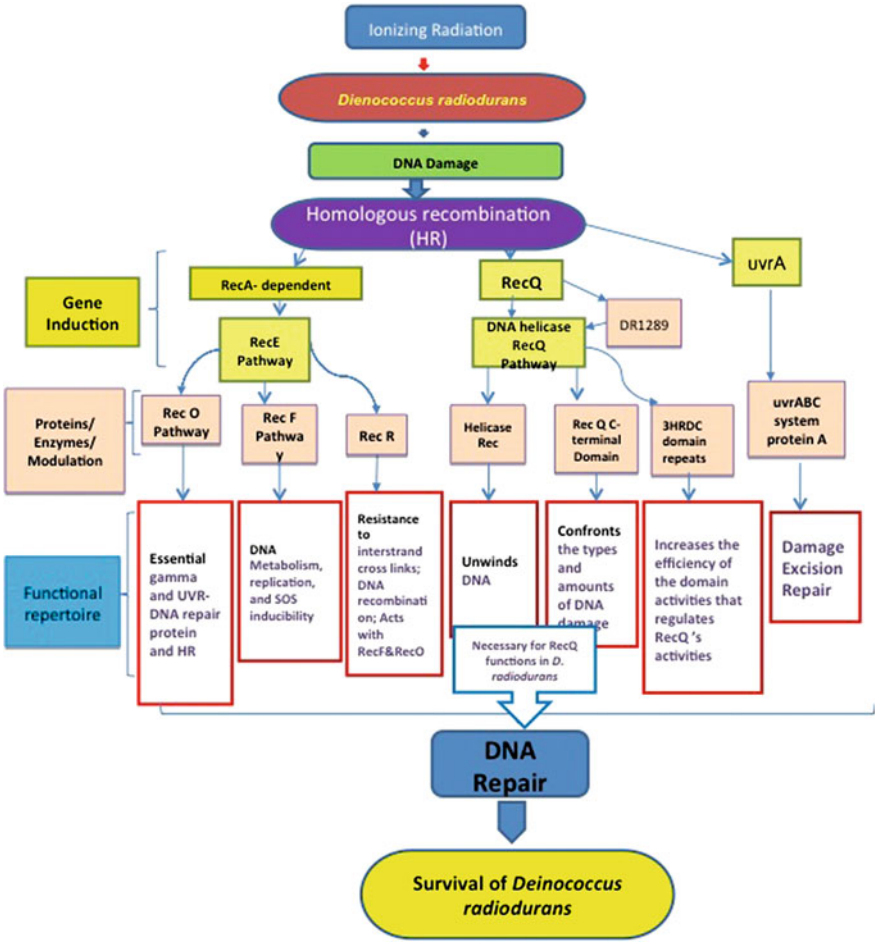

Fig. 2.1 A survival strategy of radiation-resistant microorganism *D. radiodurans* shows microbial resistance against ionizing radiation that induces pathway-specific genes, proteins, and enzymes of pathways in DNA repair mechanism (adopted with permission from Singh and Gabani 2011)

D. radiodurans (Fig. 2.2). This process of induction helps *D. radiodurans* to thrive in high-radiation conditions. UV induction in RecQ has been revealed to control DNA helicase, which further helps in managing the nature and the quantity of the DNA damage that is needed for RecQ functions in *D. radiodurans*. RecE pathway-dependent modulation in *recO* and *recF* reveals a functional repertoire of DNA repair protein, DNA metabolism, and replication and SOS inducibility. The modulation in *recR* could resist interstrand cross-links and DNA recombination acting with *recF* and *recO* (Singh and Gabani 2011). Thus, studying the defensive and survival mechanisms of the extremophiles in terms of their genome structure and the chemical properties of the compounds derived from them will help in the discovery of novel therapeutic and medical applications.

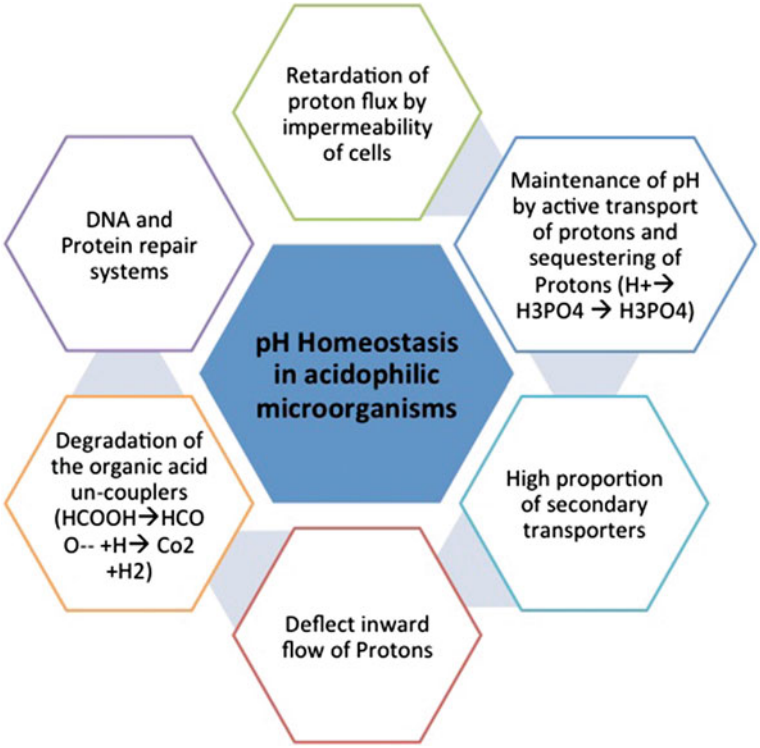

Fig. 2.2 pH homeostasis processes of acidophiles (adopted and modified from Baker-Austin and Dopson 2007)

Similar defensive mechanisms have been studied and described for other types of extremophiles. For example, in the case of acidophiles, which survive in highly acidic conditions, Baker-Austin and Dopson (2007) reviewed various survival pathways and mechanisms that enable these organisms to thrive at low pH. Impermeability of the cell membrane to protons is one such mechanism. Figure 2.2 summarizes various pH homeostasis mechanisms that have been identified (Booth 1985; Matin 1990). In general, the mechanism by which acidophiles use pH homeostasis has not been fully understood. However, efforts in sequencing the genomes of several acidophiles have shed light on several interrelated processes, including pH homeostatic mechanisms, impermeable cell membrane, cytoplasmic buffering, active proton extrusion, and organic acid degradation (Osorio et al. 2008; Cardenas et al. 2010; Liljeqvist et al. 2013; Guo et al. 2014).

Konings et al. (2002) describes the role of the cell membrane in the survival of bacteria and archaea found under extreme environmental conditions. The acidophiles have a rigid and impermeable cell membrane, which can restrict the cytoplasmic influx of protons. This helps to regulate the proton motive forces of the cell by determining the rate at which protons flow inward and pump outward

(Konings et al. 2002). Shimada et al. (2002) provided concrete evidence of this phenomenon in *Thermoplasma acidophilum*, whose cell membranes are made of tetraether lipids. Other examples of acidophiles include *Picrophilus oshimae* (van de Vossenberg et al. 1998a), *Sulfolobus solfataricus* (van de Vossenberg et al. 1998b), *Ferroplasma acidarmanus* (Macalady and Banfield 2003), and *Ferroplasma acidiphilum* (Golyshina et al. 2000; Batrakov et al. 2002; Pivovarova et al. 2002). Tyson et al. (2004) reported reconstruction of near-complete genomes of *Leptospirillum* group II and *Ferroplasma* type II and suggested that a wide variety of genes could be responsible for the impermeability of the cell membrane and preventing the inflow of protons to the cells. The above studies indicated that the genomes of organisms in microbial communities may reveal pathways for carbon fixation and nitrogen fixations, including energy generation, which will help us learn more about the survival strategies of microorganisms in extreme environments.

Michels and Bakker (1985) reported that bacteria such as *B. acidocaldarius* and *T. acidophilum* have exhibited the ability to actively pump protons out of their cytoplasm to maintain pH homeostasis. Such proton removal systems have also been reported in the *Ferroplasma* type II and *Leptospirillum* group II (*L. ferriphilum*) sequenced genomes (Tyson et al. 2004). Another key mechanism that acidophile cells use to maintain pH homeostasis is regulating the size and permeability of the cell membrane. Reducing the pore size of the cell membrane channels has been suggested as another mechanism to prevent protons from the acidic environment from entering the cell, thus helping maintain pH homeostasis. Amaro et al. (1991) characterized the outer membrane porin of the acidophile and revealed a large external loop that could be responsible for controlling the size of the pores in the cell as well as the ion selectivity. Guiliani and Jerez (2000) reported that at a pH level of 2.5, the external loop controlled the inflow of the protons across the outer membrane.

In the event of protons entering the cell membrane, acidophiles have a number of intracellular mechanisms to reduce damage that might be caused by the entering protons. The cells of acidophiles have a buffering mechanism to release the protons, as summarized in Fig. 2.2. This is possible because of the presence of certain cytoplasmic buffer molecules that contain basic amino acids such as lysine, histidine, and arginine that help in the proton sequestering process. Studying the cytoplasmic homeostasis of pH in the acidophilic bacterium *Theobacillus acidophilus*, Zychlinsky and Matin (1983) proposed that the amino acid side chains were primarily responsible for acidophile cytoplasmic buffering. Castenie-Cornet et al. (1999) supported this by finding that decarboxylation of amino acids such as arginine-induced cell buffering in *Escherichia coli* by consuming the protons and transporting them outside the cell membrane.

Another mechanism acidophiles use to maintain homeostasis is uncoupling the organic acids. This process is called cytoplasmic protonation, and is a result of the dissociation of protons in the cytoplasm. Researchers studying this organic acid degradation reported the authenticity of uncoupling reactions at low pH (Kishimoto et al. 1990; Alexander et al. 1987; Ciaramell et al. 2005).

Heliobacter pylori are known for causing gastric ulcers, and are able to survive in harsh acidic conditions. *E. coli* can survive in harsh acidic environments

(pH 2–3) for shorter time spans, even though it prefers to be at neutral pH. The mechanisms that these two different microorganisms use to withstand acid in the stomach differ significantly. It is unclear how *E. coli* is able to survive the high acid levels in the stomach; however, studies have suggested three systems that enable microorganisms to resist high levels of acid for longer periods of time (Foster 2004). In the stationary phase, alternative sigma factor is what makes the cells tolerant to the various levels of acid. Another part of this mechanism is the cAMP receptor protein (CRP), which binds with the sigma factor to create a complex that tolerates high levels of acidity (pH 1–2) in the stomach. Acidophiles also have pumps that move protons in and out of the cell in order to neutralize the cytoplasmic membrane. This is required because when bacterial cells come into contact with extreme acid stress, as is the case with acidophiles, there is an influx of protons that decreases the internal pH of the cell (Foster 2004).

The defensive and survival mechanisms used by radiation-resistant and acidophilic organisms, as well as the other specific mechanisms that enable extremophiles to adapt to various environments, make them excellent candidates for exploring beneficial properties and therapeutic implications for multiple disease types (Furusho et al. 2005; Buommino et al. 2005; Kumar and Singh 2013; Copeland et al. 2013). However, the advantages the medical world can derive from these extremophiles are only in the early stages of recognition and realization. Some extremophiles may have the solutions, but the task at hand is to find what mechanisms can be effective in synthesizing potentially useful therapeutic products. To advance our therapeutic uses of extremophiles toward treatments of specific diseases in the future, it is necessary to have a better understanding of the physiology of these extremophiles.

2.1 Survival and Potential Therapeutic Strategies

It has been recognized that the characteristics that help extremophiles to survive in extreme environmental conditions could be effectively used in medical processes to develop applications that have benefits to human health. Radiation-resistant extremophiles have been reviewed to reveal their implications for developing anticancer drugs, antioxidants, and sunscreens (Singh and Gabani 2011; Gabani and Singh 2013). Similarly, thermophilic bacteria have been known to help in DNA processing, production of proteins and enzymes, and biotechnological processes (Oost 1996). Acidophilic bacteria contribute to acid mine drainage and help to neutralize the pH of certain cytoplasmic membranes by pumping protons into the cellular space (Edwards et al. 2000).

To advance the role of extremophiles in the search for specific therapeutic mechanisms and their implications, it is pertinent to ask what metabolic products such as extremolytes and extremozymes are produced and how these primary and secondary products can be effectively exploited for medical purposes. Here we discuss some therapeutic mechanisms of the selected extremolytes.

2.1.1 Ectoine-Mediated Mechanism

Aerobic, chemoheterotrophic, and halophilic organisms contain ectoine, which is chemically identified as (5)-2-methyl-1, 4, 5, 6-tetrahydropyridine-4-carboxylic acid. High levels of radiation can alter DNA structure and produce cancer unless the structure is repaired by cellular machinery. Copeland et al. (2013) reviewed and demonstrated usage of extremolytes in their setting, and proposed an ectoine-mediated hypothetical survival mechanism (Fig. 2.3). The mechanism of ectoine biosynthesis led to UV neutralization, revealing therapeutic implications of halophiles as summarized in Fig. 2.3. Halophilic extremophiles engage in a three-step process to produce ectoine from aspartate semialdehyde (ASA) (Fig. 2.3). Nakayama et al. (2000) reported that the gene cluster of *EctA*, *EctB*, and *EctC* encodes the enzymes needed for the synthesis of ectoine (Fig. 2.3A). Ectoine was produced through fermentation of *Halobacter elongate* in a continuous process and microfiltration of the biomass, and the ectoine filtrates were purified through electrodialysis, chromatography, and crystallization (Lentzen and Schwarz 2006). Skin is protected from UVA irradiation when human keratinocyte cells are pre-treated with ectoine (Bunger and Driller 2004). The ways in which ectoine may

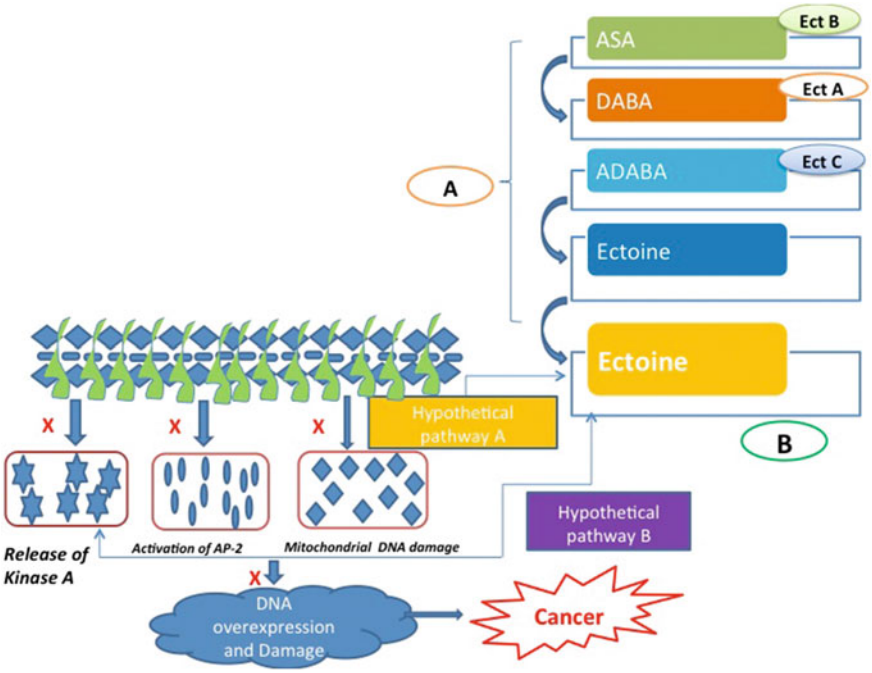

Fig. 2.3 Extremolytes in halophile bacterium *H. elongate* and proposed hypothetical survival mechanism. (*ASA* aspartate semialdehyde; *DABA* 1-2,4-diaminobutyrate; *ADABA* N-acetyl-1-2,4-diaminobutyrate) (adopted and modifed from Copeland et al. 2013)

help prevent damage to cells are shown in Fig. 2.3B: the release of secondary messengers (i.e., kinase), transcription factor AP-2 activation, intercellular adhesion molecule-1 expression, and mitochondrial DNA mutation. Beyer et al. (2000) demonstrated the immunoprotective effects of ectoine treatment through treating Langerhans cells under UV stress with 1 % ectoine. All these studies provide ample evidence of the protective properties of ectoine, which is hypothesized to provide protection from DNA damage and hence from cancer (Fig. 2.3B).

The therapeutic implication of this defensive mechanism is that ectoine helps stabilize the membrane structures, resulting in a higher level of resistance to UVA damage. Further, ectoine-mediated neutralization has been found to reduce or prevent dehydration of dry atopic skin and prevent skin aging (Singh and Gabani 2011). Similar roles of ectoine have been explored in research on apoptotic cell deaths in the contexts of Machado–Joseph disease (Furusho et al. 2005) and Alzheimer's disease (Kanapathipillai et al. 2005).

2.1.2 Evolutionary Diversity

Despite the diversity in living world, microorganisms are yet to see the tip of the iceberg. Most microorganisms existing in nature, particularly bacteria have yet to be identified. There is very little known to the current microbiologists on how to grow wide variety of microorganisms. In the sense of unknown growth medium for most microbial life, metagenomics have been considered to extract the total nucleic acid from environment with limited success to explore the hidden microbial life. The challenges remain for microbiologists to isolate novel microbial species from a variety of extreme environmental conditions.

Due to their biochemical properties, extremophiles are of high interest to both basic and applied microbiologists. Thermophiles contain DNA binding proteins, which have a potential role in maintaining DNA in a double-stranded form at high temperatures (Pereira and Reeve 1998). In order to diversify microbial community in the thermal environment, the heat-mediated alteration was reported to affect the membrane stability by opposing hydrophobic residues from each layer of the "lipid bilayer" membrane together forming the lipid monolayer instead of a bilayer that prevents the cell membrane to melt at high temperature (van de Vossenberg et al. 1998a). This diversifies the microbial survival at specific niche. However, at low temperature, proteins are being revealed to be more polar and less hydrophobic than proteins in thermophiles. In addition, psychrophiles regulate chemical composition of their membranes by maintaining the length and degree of unsaturation of fatty acids. This regulation keeps the membrane structure in sufficiently fluid form allowing transport process to occur, even below freezing temperatures (Horikoshi and Grant 1998).

Extremophiles have been reported to carry a set of essential genes that are evolutionarily conserved (Duplantis et al. 2010). These essential genes play an important role in translating the useful products that enable their survival under

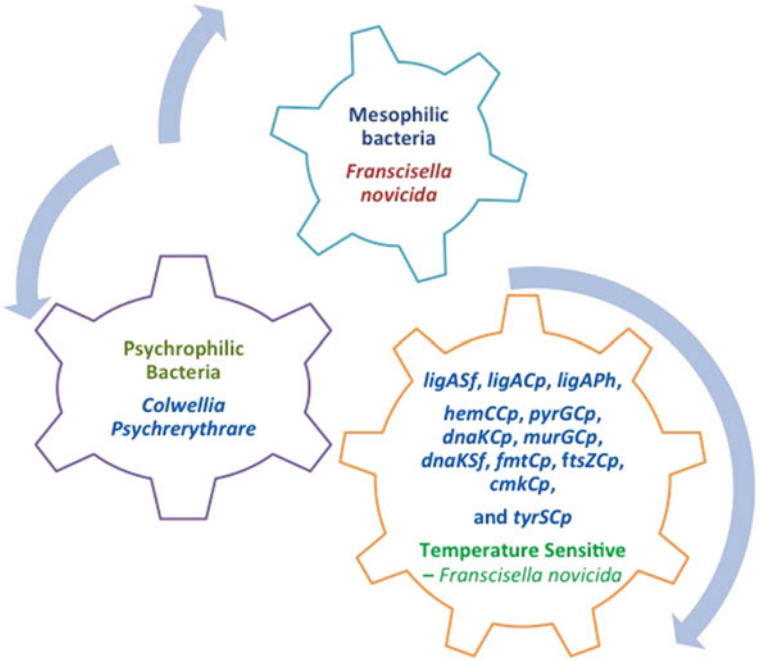

Fig. 2.4 Essential genes from a psychrophilic bacterium are transformed into temperature-sensitive mesophilic host organism (adopted and modified from Shanmugam and Parasuraman 2012)

harsh environmental conditions. The variations in extreme environmental characteristics exert pressure on essential genes (*ligASf*, *ligACp*, *ligAPh*, *hemCCp*, *pyrGCp*, *dnaKCp*, *murGCp*, *dnaKSf*, *fmtCp*, *ftsZCp*, *cmkCp*, and *tyrSCp*) that help extremophiles adapt to the environment. This phenomenon is referred to as "evolutionary diversity" and the properties of the essential genes could be used to engineer bacterial pathogens that are stable and temperature sensitive which further could be used as vaccines. Figure 2.4 summarizes the involvement of essential genes from psychrophilic bacteria transformed into temperature-sensitive mesophilic host organisms. Studies have also substituted essential genes of bacteria found in arctic environments for the genes in pathogenic organisms (Duplantis et al. 2010; Shanmugam and Parasuraman 2012).

2.1.3 Increased Catalytic Activity

Another extremophilic mechanism with the potential for therapeutic applications is the metabolic fluxes among psychrophilic microorganisms (Georlette et al. 2003). Psychrophilic organisms thrive in extreme cold habitats, produce enzymes that are

active in cold temperatures, and can cope with the low-temperature-induced reduction in chemical reaction rates. The enzymes produced by psychrophilic organisms will have high catalytic efficiency at low temperatures.

It has been suggested that at the active sites, cold-adapted DNA ligase has specific characteristics such as high conformational flexibility, increased activity at low and moderate temperatures and overall destabilization of the molecular edifice (Georlette et al. 2003), revealing potential implications for biotechnology applications. These characteristics are reversed in mesophiles and thermophiles, which show reduced activity at low temperatures, high stability, and reduced flexibility. Because of the complexity involved in understanding these properties, large entropy changes are involved in the denaturation process of these microorganisms. The results of this study, conducted by adapting the different thermal habitats, indicated functional links between activity, flexibility, and stability. Studies have also been conducted on amylases and xylanases derived from extremophiles (Elleuche et al. 2011; Qin and Huang 2014; Liu et al. 2014). The therapeutic implications of increased catalytic activity in psychrophilic organisms due to the tradeoff between the low temperature and lower thermal energy resulting in specific changes in the molecular structure need to be further exploited.

2.1.4 Amino Acid Accumulation

Some extremophilic adaptation mechanisms that produce substances useful to humans are explained (Hendry 2006). While the enzymes produced by acidophiles and alkaliphiles can be useful in extreme conditions, the organisms themselves can also regulate their cytoplasmic activities at neutral pH conditions. Halophiles, however, adapt by regulating the salt concentration in their cytoplasm; the cytoplasmic proteins of the halophiles adapt to the environment by accumulating anionic amino acids on the cell surfaces. This property is also useful in improving their stability and activity in nonaqueous solvents. Halophiles also tend to reduce their osmotic pressure by gathering high levels of low-molecular-weight neutral organic species (Hendry 2006).

2.1.5 Aggregation Resistance Strategies

Maintenance of metabolic flux and cellular mechanisms relies upon the organisms' ability to keep their functional states when they are under extreme stress. By understanding the aggregation resistance strategies of thermophilic proteins, it is possible to resolve the response of the aggregation-prone regions in proteins. Thermophiles produce proteins that help in addressing the protein aggregation that

reduces the functional state of the organisms (Merkley et al. 2011; Kufner and Lipps 2013). Thangakani et al. (2012) compared the aggregation resistance strategies adapted by thermophilic proteins and their mesophilic homologs using a dataset of 373 protein families and found that the thermophilic proteins had better utilization of the aggregation resistance strategies. Thermophiles tend to accumulate osmolyte molecules that can stabilize their proteins and macromolecules, which could help in the design and formulation of proteins and antibodies with therapeutic applications.

2.1.6 Activation of the Nuclear Factor

The ability of heat shock proteins (HSPs) to inhibit the genetic expression of proinflammatory cytokines has been explored as another mechanism by which extremophiles survive under harsh environmental conditions. Buommino et al. (2005) reported that the transcription of proinflammatory cytokines is dependent on the activation of the nuclear factor kappa-B (NF-kappaB). Studies indicate that ectoine, a biomolecule produced by halophiles, activates certain heat shock proteins. The authors used reverse transcriptase-polymerase chain reaction (RT-PCR) and immunoblot analysis to determine the increased levels of gene expression of HSPs in human keratinocytes that were treated with ectoine and heat stress. The findings had important implications for the development of additives that can be used as protective tools for treating human skin infections or inflammation.

2.1.7 Resistance to Cell Death

Other recent investigations have examined extremophiles' resistance to cell death and the pathways by which this process occurs, as shown in Fig. 2.5. One major hypothesis that has been supported by several studies involves the role of mitochondria in the death of brain cells: a set of protein components affects mitochondria and begins their destruction, leading to cell death under various conditions. Thus, further research on extremophiles and the proteins in their mitochondria may provide clues for identifying compounds that do not destroy mitochondria. Biochemical assays and protein sequencing will assist in identifying the mechanisms of molecular mediation in cell death. This can lead to the development of drugs to target proteins that cause cell degeneration and reduce the development of neurodegenerative diseases. This mechanism for using extremophiles in the development of therapeutic applications is summarized in Fig. 2.5.

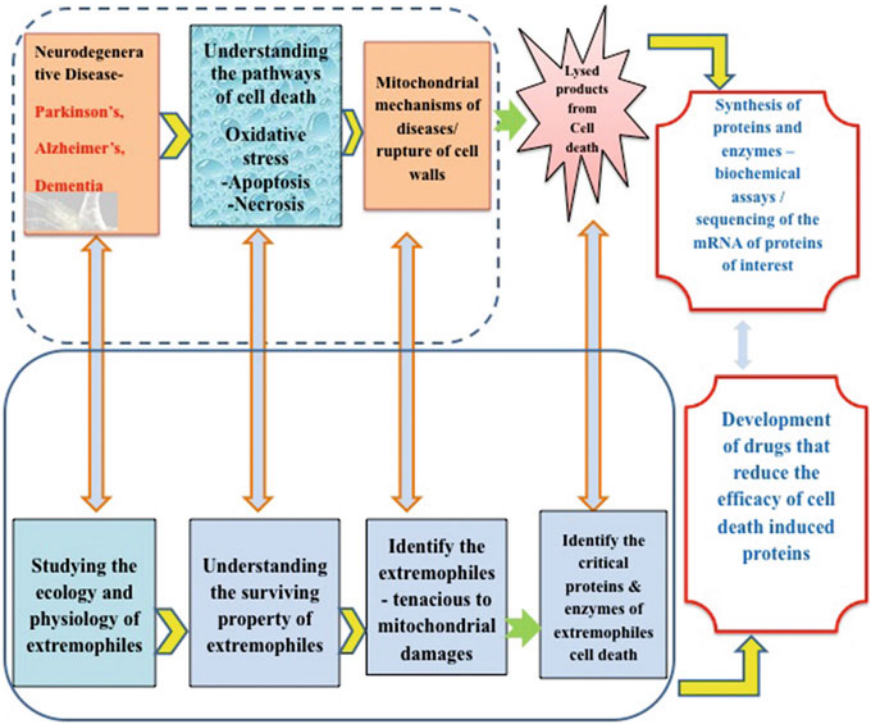

Fig. 2.5 A process of studying the mechanism for using extremophiles in the development of therapeutic applications for neurodegenerative diseases (based on: http://www.projectsmagazine.eu.com/randd_projects/mitochondrial_mechanisms_of_disease_lessons_from_extremophiles)

2.1.8 Cellular Compartmentalization

A UVR neutralization model using cellular compartmentalization of scytonemin biosynthesis in cyanobacteria was studied (Soule et al. 2009). Here, we attempt to summarize the possible therapeutic implications of this model (Fig. 2.6). The outer membrane of the cyanobacterium absorbs the UVA irradiation (Fig. 2.6, left), which further stimulates a cluster of genes such as *Tyrp*. This activates production of tryptophan and p-hydroxyphenyl pyruvate monomers from chorismate. In addition, it is proposed that certain precursors are processed by ScyA, ScyB, and ScyC and NpR1259 in the cytoplasm. Using these precursors, reduced forms of scytonemins are produced by perisplasmic enzymes (ScyD, ScyE, ScyF, DsbA, and TyrP). These reduced forms of scytonemin autooxidize from the extracellular slime layer in sufficient quantity to block the incoming UVR (Soule et al. 2009).

Singh and Gabani (2011) conceptualized this model for the eukaryotic cell. Scytonemin was anticipated to provide a novel pharmacophore for the development of protein kinase inhibitors as antiproliferative and antiinflammatory drugs. It was

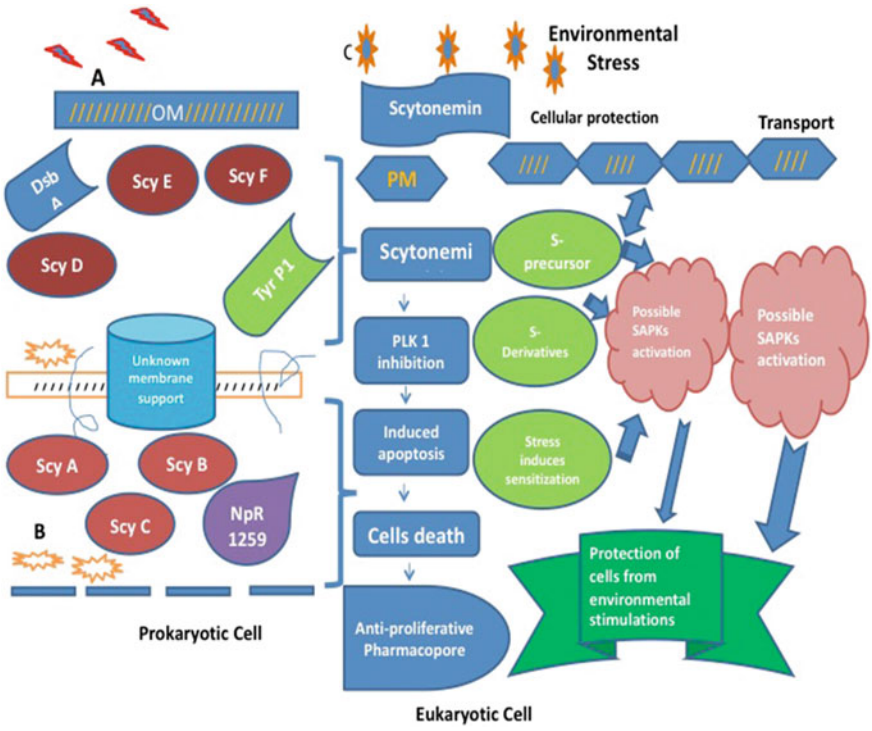

Fig. 2.6 Cellular protection of biosynthesized scytonemin in prokaryotes and hypothesized proposed mechanism of cellular protection in eukaryotic cell (adopted and modified with permission from Singh and Gabani 2011)

also hypothesized that scytonemin derivatives may be involved in the survival of healthy cells through mediated activation of stress-activated protein kinases (SAPKs), shown with dotted arrows on the right in Fig. 2.6.

Singh and Gabani (2011) reviewed the ATP-competitive inhibitors of polo-like kinases (PLKs), which have been theorized to control oncogenes in human cells, since they have the ability to switch off the activity by binding to ATP-binding sites. PLK1 has been highly regarded as a mitotic cancer target, and can be inhibited by scytonemin, which is recognized as a nonspecific ATP competitor. Further, scytonemin has the property to treat hyperproliferative disorders (Stevenson et al. 2002b). Luo et al. (2009) demonstrated that due to mitotic stress, cells become highly sensitive to PLK1 inhibition when they have mutant Ras acting as an oncogene. The scytonemin-mediated inhibition of PLK1 expression has been shown to induce apoptosis in osteosarcoma cells and other cancer cell types (Stevenson et al. 2002a; Duan et al. 2010).

These studies suggested that scytonemin could function as a novel pharmacophore for the development of protein kinase inhibitors and antiproliferative and antiinflammatory drugs (Fig. 2.6). In addition, SAPKs such as p38/RK/CSBP kinase

and c-Jun N-terminal kinase (JNK) could help in the development of therapeutic responses to shock and UV-radiation-related stress. It is known that SAPKs when activated can further activate transcription factors (c-Jun, ATF2, and Elk-1) responsible for gene expression responses to external environmental stresses. Alternatively, Singh and Gabani (2011) anticipated that scytonemin-mediated activation of SAPKs could help in eukaryotic cell survival. There also exists some complementarity of the scytonemin activity responsible for the UV insensitivity of photosynthesis in *Nostoc flagelliforme* and the UV absorption of mycosporine-like amino acids (Ferroni et al. 2010). The therapeutic propositions of these studies indicate that there is complementarity between biologically mediated UV protection and the pharmaceutical compounds used for UV protection.

2.1.9 Overexpression of Heat Shock Protein Genes

HSPs have immunomodulatory properties that could have proinflammatory functions that help in immune responses. The mechanism that HSPs use to regulate autoimmunity can be effectively harnessed to develop therapeutic tools for the treatment of autoimmune disorders and some forms of cancer. Welch (1993) showed that high levels of HSPs could be achieved by exposing the cells to various types of chemical agents including metabolic poisons, heavy metals, protein modifiers, amino acid analogs, and ionophores. In another study, Zügel and Kaufmann (1999) demonstrated that during periods of stress caused by infection or inflammation, HSP synthesis could protect prokaryotic or eukaryotic cells. Boummino et al. (2005) reported that ectoine from halophiles may help in protecting cells from stress and prevent cell damage at higher levels of HSP70. HSPs are known for their role in the cytoprotection and repair of cells and tissues against the stresses and trauma they might face in extreme conditions (Morimoto and Santoro 1998).

HSPs involve overexpression of the single or collective HSP genes to help protect the skin from various stresses such as high levels of heat, drug toxicity, UV radiation, and other pollutants (Simon et al. 1995; Zhou et al. 1998). Among modulated variations in HSPs during cellular stress, HSP70 was revealed to be a major inducible and cytoprotective protein (Buommino et al. 2005). The overexpression of HSP70 significantly reduces the release of IL-6 induced by UVA, UVB irradiation, and oxidative stress (Buommino et al. 2005). Halophilic organisms were anticipated to be an effective source of small organic molecules that can be used to treat skin diseases that originate from infections or inflammation by overexpression of HSP70. Further, ectoine, a key extremozyme from the halophiles, could be effectively used as a protective additive for skin defense and in protein synthesis by increasing the basal levels of HSP70 (Buommino et al. 2005). Relatively similar mechanisms have been identified and documented in other extremophiles, and can be effectively applied in developing products that may have therapeutic values. Liu et al. (2010) reported that CiHsp70, a molecular chaperone of the HSP family, may

play a role in enabling Antarctic ice algae *Chlamydomonas* sp. ICE-L to acclimatize to the polar environment. Yamauchi et al. (2012) studied the protein-folding mechanism of the GroEL system in psychrophilic bacterium *Colwellia psychrerythraea* 34H, and found that the CpGroEL system has an energy-saving mechanism that allows it to avoid excess utilization of ATP to ensure microbial growth at low temperatures.

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