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ダイジェスト

Featured Article of the Month

The hidden nature of protein translational control by diphthamide: the secrets under the leather

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The protein translation elongation factor eEF2 undergoes a unique posttranslational modification called diphthamidation. eEF2 is an essential factor in protein translation, and the diphthamide modification has been a famous target of the diphtheria toxin for a long time. On the other hand, the physiological function of this rare modification *in vivo* remains unknown. Recent studies have suggested that diphthamide has specific functions for the cellular stress response and active proliferation. In this review, we summarize the history and findings of diphthamide obtained to date and discuss the possibility of a specific function for diphthamide in regulating protein translation.

Keywords: diphthamide, eEF2, IRES, protein translation, stem cells

Emerging impacts of biological methylation on genetic information

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The central dogma of molecular biology explains the fundamental flow of genetic information for life. Although genome sequence (DNA) itself is a static chemical signature, it includes multiple layers of information composed of mRNA, tRNA, rRNA and small RNAs, all of which are involved in protein synthesis and is passing from parents to offspring *via* DNA. Methylation is a biologically important modification, because DNA, RNAs and proteins, components of the central dogma, are methylated by a set of methyltransferases. Recent works focused on understanding a variety of biological methylation have shed light on new regulation of cellular functions. In this review, we briefly discuss some of those recent findings of methylation, including DNA, RNAs and proteins.

Keywords: methyltransferase, demethylase, biological methylation, central dogma

BIOCHEMISTRY

Biochemistry General

Thioredoxin o-mediated reduction of mitochondrial alternative oxidase in the thermogenic skunk cabbage Symplocarpus renifolius

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Thermogenesis in plants involves significant increases in their cyanide-resistant mitochondrial alternative oxidase (AOX) capacity. Because AOX is a non-proton-motive ubiquinol oxidase, the dramatic drop in free energy between ubiquinol and oxygen is dissipated as heat. In the thermogenic skunk cabbage (*Symplocarpus renifolius*), *SrAOX* is specifically expressed in the florets. Although SrAOX harbours conserved cysteine residues, the details of the mechanisms underlying its redox regulation are poorly understood. In our present study, the two mitochondrial thioredoxin *o* cDNAs *SrTrxo1* and *SrTrxo2*, were isolated from the thermogenic florets of *S. renifolius*. The deduced amino acid sequences of the protein products revealed that SrTrx*o*2 specifically lacks the region corresponding to the α3-helix in SrTrx*o*1. Expression analysis of thermogenic and non-thermogenic *S. renifolius* tissues indicated that the *SrTrxo1* and *SrAOX* transcripts are predominantly expressed together in thermogenic florets, whereas *SrTrxo2* transcripts are almost undetectable in any tissue. Finally, functional *in vitro* analysis of recombinant SrTrx*o*1 and mitochondrial membrane fractions of thermogenic florets indicated its reducing activity on SrAOX proteins. Taken together, these results indicate that *SrTrxo1* is likely to play a role in the redox regulation of SrAOX in *S. renifolius* thermogenic florets.

Keywords: AOX, mitochondria, NADPH, redox regulation, thermogenesis

Protein Interaction and Recognition

Identification of a common epitope in the sequences of COL4A1 and COL6A1 recognized by monoclonal antibody #141

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Identification of a type IV collagen α1 polypeptide in non-triple helical form [NTH α1(IV)], possibly involved in angiogenesis, introduces the further possibility of the existence of non-triple helical forms of other collagen chains. We previously reported that an anti-NTH α1(IV) monoclonal antibody #141 recognizes not only NTH α1(IV) but also a novel non-triple helical collagen polypeptide NTH α1(VI) encoded by *COL6A1*. In this study, we identified the recognition sequence in order to better understand the properties of antibody #141 and provide clues regarding the biological function of the two non-triple helical molecules. Additionally, we determined the common epitope between COL4A1 and COL6A1 as PXXGXPGLRG, with surface plasmon resonance analyses revealing K_D values for the COL4A1 epitope as $5.56\pm1.81\times10^{-9}$M and for the COL6A1 epitope as $7.15\pm0.44\times10^{-10}$M. The specific recognition of NTH α1(IV) and NTH α1(VI) by antibody #141 can be explained by the common epitope sequence. Moreover, epitope localization supports previous finding that NTH α1(IV) and NTH α1(VI) differ in conformation from the α1 chains in triple-helical type IV and type VI collagen. These findings suggest that antibody #141 might be useful for diagnosis of type VI collagen myopathies.

Keywords: non-triple helical α1(IV) chain, non-triple helical α1(VI) chain, type IV collagen, type VI collagen, type VI collagen myopathies

Biochemistry in Diseases and Aging

Specific mutations in presenilin 1 cause conformational changes in -secretase to modulate amyloid trimming

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γ-Secretase generates amyloid beta peptides (Aβ) from amyloid precursor protein through multistep cleavages, such as endoproteolysis (ε-cleavage) and trimming (γ-cleavage). Familial Alzheimer's disease (FAD) mutations within the catalytic subunit protein of presenilin 1 (PS1) decrease γ-cleavage, resulting in the generation of toxic, long Aβs. Reducing long Aβ levels has been proposed as an AD therapeutic strategy. Previously, we identified PS1 mutations that are active in the absence of nicastrin (NCT) using a yeast γ-secretase assay. Here, we analysed these PS1 mutations in the presence of NCT, and found that they were constitutively active in yeast. One triple, 13 double, and 5 single mutants enhanced ε-cleavage activity up to 2.7-fold. Furthermore, L241I, F411Y, S438P and F441L mutations modulated trimming activities to produce more short-Aβ in yeast microsomes. When introduced in mouse embryonic fibroblasts, these mutations possessed similar or reduced ε-cleavage activity. However, two mutations, L241I and S438P, modulated trimming activities and changed the conformation of transmembrane domain 1, the substrate recognition site. These mutants had the opposite modulatory effects of FAD mutations and produced more short Aβs and fewer long Aβs. Our results provide insights into the relationship between PS1 conformational changes and γ-secretase activities.

Keywords: Alzheimer's disease, amyloid beta (Aβ), γ-secretase, intramembrane proteolysis, Saccharomyces cerevisiae

Application of machine learning algorithms for the differential diagnosis of peroxisomal disorders

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We have established diagnostic thresholds of very long-chain fatty acids (VLCFA) for the differential diagnosis of peroxisomal disorders using the machine learning tools. The plasma samples of 131 controls and 90 cases were tested for VLCFA using gas chromatography-mass spectrometry following stable isotope dilution. These data were used to construct association rules and for recursive partitioning. The C26/22 in healthy controls ranged between 0.008 and 0.01. The C26 levels between 1.61 and 3.34 µmol/l and C26/C22 between 0.05 and 0.10 are diagnostic of X-linked adrenoleukodystrophy (X-ALD). Very high levels of C26 (>3.34 µmol/l) and C26/C22 ratio (>0.10) are diagnostic of Zellweger syndrome (ZS). Significant elevation of phytanic acid was observed in Refsum (t=6.14, P<0.0001) and Rhizomelic chondrodysplasia punctata (RCDP) (t=16.72, P<0.0001). The C26/C22 ratio is slightly elevated in RCDP (t=2.58, P=0.01) while no such elevation was observed in Refsum disease (t=0.86, P=0.39). The developed algorithm exhibited greater clinical utility (AUC: 0.99–1.00) in differentiating X-ALD, ZS and healthy controls. The algorithm has greater clinical utility in the differential diagnosis of peroxisomal disorders based on VLCFA pattern. Plasmalogens will add additional value in differentiating RCDP and Refsum disease.

Keywords: sbi functional deficiency, rhizomelic chondrodysplasia punctata, very long-chain fatty acids, X-linked adrenoleukodystrophy, Zellweger syndrome

CELL

Cell General

PIKfyve accelerates phagosome acidification through activation of TRPML1 while arrests aberrant vacuolation independent of the Ca^{2+} channel

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PIKfyve phosphorylates PtdIns(3)P to PtdIns(3, 5)P2. One of the best characterized effector downstream of PtdIns(3, 5)P2 is a lysosomal Ca^{2+} channel, TRPML1. Although it has been reported that TRPML1 is involved in phagosome-lysosome fusion, the relevance of the Ca^{2+} channel in phagosome acidification has been denied. In this article, however, we demonstrated that the phagosome acidification was dependent on TRPML1. Based on the classical idea that Fluorescein isothiocyanate (FITC)-fluorescence is highly sensitive to acidic pH, we could estimate the phagosome acidification by time laps imaging. FITC-zymosan fluorescence that was engulfed by macrophages, decreased immediately after the uptake while the extinction of FITC-zymosan fluorescence was delayed in PIKfyve-deficient cells. The acidification arrest was completely rescued in the presence of Ca^{2+} ionophore A23187. Cells treated with a PIKfyve inhibitor, apilimod, also showed delayed phagosome acidification but were rescued by the overexpression of TRPML1. Additionally, TRPML1 agonist, ML-SA1 was effective to acidify the phagosome in PIKfyve-deficient cells. Another phenotype observed in PIKfyve-deficient cells is vacuole formation. Unexpectedly, enlarged vacuole formation in PIKfyve-deficient cells was not rescued by Ca^{2+} or over expression of TRPML1. It is likely that the acidification and vacuolation arrest is bifurcating downstream of PIKfyve.

Keywords: macrophage, phagosome acidification, PIKfyve, PtdIns(3, 5)P2, TRPML1

Biomembranes, Organelles, and Protein Sorting

Cleaved PGAM5 is released from mitochondria depending on proteasome-mediated rupture of the outer mitochondrial membrane during mitophagy

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PGAM5 is a unique type of protein phosphatase that exists in mitochondria. It has been shown to exist in the inner mitochondrial membrane through its transmembrane domain and to be cleaved within the transmembrane domain upon mitochondrial dysfunction. However, its submitochondrial localization remains controversial; many researchers claim that PGAM5 localizes to the outer mitochondrial membrane based on the findings that PGAM5 associates with many cytoplasmic proteins. Here, we found that cleaved PGAM5 was released from mitochondria during mitophagy, a selective form of autophagy specific for mitochondria, and that the release was inhibited by proteasome inhibitors in HeLa cells stably expressing the E3 ubiquitin ligase Parkin. However, treatment of parental HeLa cells lacking Parkin with mitophagy-inducing agents caused PGAM5 cleavage but did not cause its release from mitochondria. Thus, cleaved PGAM5 appears to be released from mitochondria depending on proteasome-mediated rupture of the outer membrane during mitophagy, which has been previously shown to precede autophagy-mediated degradation of whole mitochondria. This study suggests that PGAM5 senses mitochondrial dysfunction in the inner mitochondrial membrane and serves as a signalling intermediate that regulates the cellular response to mitochondrial stress upon its cleavage and release from mitochondria.

Keywords: mitochondria, mitophagy, Parkin, PGAM5, Proteasome

Differentiation, Development, and Aging

CREG1 promotes uncoupling protein 1 expression and brown adipogenesis in vitro

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Brown adipocytes play a critical role for adaptive thermogenesis to regulate body temperature in cold or to circumvent diet-induced obesity. In this study, we investigated the role of cellular repressor of E1A-stimulated genes 1 (CREG1) on brown adipogenesis and uncoupling protein 1 (UCP1) expression by using *in vitro* culture models. In murine mesenchymal stem cell line C3H10T1/2, *Creg1*mRNA expression significantly increased in a time-dependent manner along with *Ucp1* mRNA induction in brown adipogenesis. *Creg1* gene overexpression upregulated the expression of brown fat-related genes including *Ucp1* but its suppression downregulated these gene expression in C3H10T1/2 cells. Unlike the brown adipogenesis, *Creg1* mRNA expression

decreased significantly after differentiation stimulation in white adipogenesis of 3T3-L1 cells. Either *Creg1*gene overexpression or suppression hardly affected white adipogenesis. In addition, CREG1 protein stimulated brown adipogenesis and rescued the adipogenesis in the absence of thyroid hormone in C3H10T1/2 cells. In reporter assay, CREG1 induction stimulated *Ucp1* promoter activity, which was enhanced by co-expression with thyroid hormone receptors. The effect of CREG1 on *Ucp1*promoter activity was also stimulated by retinoic acid. These results strongly suggest that CREG1 plays an important role on the regulation of UCP1 expression and brown adipogenesis.

Keywords: adipogenesis, brown adipocyte, CREG1, thyroid hormone, UCP1

BIOTECHNOLOGY

RNA Technology

CircRNA_001569 promotes cell proliferation through absorbing miR-145 in gastric cancer

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Gastric cancer severely threatens human life, while its pathogenesis is still unclear. The present study was to explore the potential pathogenic mechanism underlying gastric cancer. Real-time PCR was performed to detect the expression of circRNA_001569 and miR-145; western blot was performed to detect the expression of NR4A2. Cell cycle and apoptosis was determined using flow cytometry, and cell viability was determined using Cell counting kit-8 (CCK-8) assay. Luciferase reporter assay was carried out to validate the relationship between miR-145 and NR4A2. Both circRNA_001569 and NR4A2 were overexpressed in tissues and cells of gastric cancer, while miR-145 was down-regulated. Overexpressed circRNA_001569 significantly increased cell viability, and decreased cell apoptosis, while down-regulated circRNA_001569 dramatically decreased cell viability and promoted cell apoptosis. CircRNA_001569 regulated the expression of miR-145, the effect of pcDNA-circRNA_001569 was abolished by miR-145 mimic and the effect of si-circRNA_001569 was abolished by miR-145 inhibitor. MiR-145 targets NR4A2 to regulate its expression. Overexpressed miR-145 suppressed cell viability and promoted cell apoptosis. Taken together, the present study indicated that overexpressed circRNA_001569 promoted cell viability of gastric cancer through suppressing the expression of miR-145, which was mediated by NR4A2. The research will provide great theoretical basis for further clinical diagnosis and therapy.

Keywords: cell apoptosis, circRNA_001569, gastric cancer, miR-145, NR4A2

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ダイジェスト

JB Special Reviews—Organelle Zone

Featured Article of the Month

Organelle zones in mitochondria

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The recent development of scientific imaging techniques have lead to the identification of various novel organellar functions. Most of these functions are perfomred in limited areas within organelles. These local functional organelle regions are referred to as ‘zones’. In mitochondria, there are various types of zones exist, including the apoptosis zone, necrosis zone, mitophagy zone, mitochondrial-derived vesicle budding zone, innate immunity zone, etc. The membrane contact site between mitochondria and the endoplasmic reticulum, which is referred to as MAM, is also considered a zone. This contact site is crucial for various biological events, such as lipid transfer, sterol exchange, Ca^{2+}transfer, autophagy and the suppression of neurological disorders. Therefore, the elucidation of organelle zones is essential towards a deeper understanding of cell biology.

Keywords: apoptosis, communication zone, MAM, mitochondria, response zone

The ER exit sites are specialized ER zones for the transport of cargo proteins from the ER to the Golgi Apparatus

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The endoplasmic reticulum (ER) is a multifunctional organelle, including secretory protein biogenesis, lipid synthesis, drug metabolism, Ca^{2+} signalling and so on. Since the ER is a single continuous membrane structure, it includes distinct zones responsible for its different functions. The export of newly synthesized proteins from the ER is facilitated via coat protein complex II (COPII)-coated vesicles, which form in specialized zones within the ER, called the ER exit sites (ERES) or transitional ER. In this review, we highlight recent advances in our understanding of the structural organization of ERES, the correlation between the ERES and Golgi organization, and the faithful cargo transport mechanism from the ERES to the Golgi.

Keywords: cargo transport, COPII-coated vesicle, ER, ERES, Golgi apparatus

Organelle contact zones as sites for lipid transfer

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Since the 1950s, electron microscopic observations have suggested the existence of special regions where the distinct organelle membranes are closely apposed to each other, yet their molecular basis and functions have not been examined for a long time. Recent studies using yeast as a model organism identified multiple organelle-membrane tethering sites/factors, such as ERMES (ER–mitochondria encounter structure), NVJ (Nuclear–vacuole junction), vCLAMP (Vacuole and mitochondria patch) and MICOS (Mitochondrial contact site). Among them, ERMES is the best-characterized contact-site protein complex, which was found to function as not only an organelle-tethering factor but also a phospholipid transfer protein complex. In this review, we will discuss recent advances in the characterization of ERMES and other organelle contact zones, vCLAMP, NVJ and MICOS in yeast.

Keywords: ERMES, MAM, phospholipid, vacuole, vCLAMP

BIOCHEMISTRY

Biochemistry General

Phosphorylation of translation initiation factor eIFiso4E promotes translation through enhanced binding to potyvirus VPg

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Interactions of phosphorylated eIFiso4E binding to VPg as a function of temperature and ionic strength were assessed employing fluorescence spectroscopic. Phosphorylation increased the binding affinity ~3.5-fold between VPg and eIFiso4E under equilibrium conditions. Binding affinity of VPg for eIFiso4Ep correlates with the ability to enhance *in vitro* protein synthesis. Addition of VPg and eIFiso4Ep together to Dep WGE enhances the translation for both uncapped and capped mRNA. However, capped mRNA translation was inhibited with addition of eIFiso4Ep alone in dep WGE, suggesting that phosphorylation prevents the cap binding and favours the VPg binding to promotes translation. Temperature dependence showed that the phosphorylated form of the eIFiso4E is preferred for complex formation. A van't Hoff analysis reveals that eIFiso4Ep binding to VPg was enthalpy driven ($\Delta H = -43.9 \pm 0.3\,kJ\,mol^{-1}$) and entropy-opposed ($\Delta S = -4.3 \pm 0.1\,J\,mol^{-1}\,K^{-1}$). Phosphorylation increased the enthalpic contributions ~33% for eIFiso4Ep-VPg complex. The thermodynamic values and ionic strength dependence of binding data suggesting that phosphorylation increased hydrogen-bonding and decreased hydrophobic interactions, which leads to more stable complex formation and favour efficient viral translation. Overall these data correlate well with the observed translational data and provide more detailed information on the translational strategy of potyviruses.

Keywords: binding, eIFiso4E, phosphorylation, protein synthesis, VPg

Protein Structure

Structural, kinetic and thermodynamic characterizations of SDS-induced molten globule state of a highly negatively charged cytochrome c

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This study presents the structural, kinetic and thermodynamic characterizations of previously unknown submicellar concentrations of SDS-induced molten globule (MG_{SDS}) state of a highly negatively charged base-denatured ferricytochrome *c* (U_B-state) at pH ~12.8 (±0.2). The far-UV CD, near-UV CD, ANS-fluorescence data of U_B-state in the presence of different concentrations of SDS indicate that the submicellar concentrations of SDS (≤0.4 mM) transform the U_B-state to MG-state. The MG_{SDS}-state has native-like α-helical secondary structure but lacks tertiary structure. The free energy change ($\Delta G°_D$) for $U_B \rightarrow$ MG transition determined by far-UV CD (~2.7 kcal mol^{-1}) is slightly higher than those determined by fluorescence (~2.0 kcal mol^{-1}) at 25°C. At very low SDS and NaCl concentrations, the MG_{SDS}-state undergoes cold denaturation. As SDS concentration is increased, the thermal denaturation temperature increases and the cold denaturation temperature decrease. Kinetic experiments involving the measurement of the CO-association rate to the base-denatured ferrocytochrome *c* at pH ≈12.8 (±0.2), 25°C indicate that the submicellar concentrations of SDS restrict the internal dynamics of base-denatured protein.

Keywords: alkali molten-globule, constrained dynamics, entropic stabilization, SDS, thermal stability

Enzymology

The crystal structure of homoserine dehydrogenase complexed with L-homoserine and NADPH in a closed form

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Homoserine dehydrogenase from *Thermus thermophilus* (*Tt*HSD) is a key enzyme in the aspartate pathway that catalyses the reversible conversion of L-aspartate-β-semialdehyde to L-homoserine (L-Hse) with NAD(P)H. We determined the crystal structures of unliganded *Tt*HSD, *Tt*HSD complexed with L-Hse and NADPH, and Lys99Ala and Lys195Ala mutant *Tt*HSDs, which have no enzymatic activity, complexed with L-Hse and $NADP^+$ at 1.83, 2.00, 1.87 and 1.93 Å resolutions, respectively. Binding of L-Hse and NADPH induced the conformational changes of *Tt*HSD from an open to a closed form: the mobile loop containing Glu180 approached to fix L-Hse and NADPH, and both Lys99 and Lys195 could make hydrogen bonds with the hydroxy group of L-Hse. The ternary complex of *Tt*HSDs in the closed form mimicked a Michaelis complex better than the previously reported open form structures from other species. In the crystal structure of Lys99Ala *Tt*HSD, the productive geometry of the ternary complex was almost preserved with one new water molecule taking over the hydrogen bonds associated with Lys99, while the positions of Lys195 and L-Hse were significantly retained with those of the wild-type enzyme. These results propose new possibilities that Lys99 is the acid–base catalytic residue of HSDs.

Keywords: catalytic residue, crystal structure, homoserine dehydrogenase, ternary complex, Thermus thermophilus

Enzyme Inhibitors

Revealing of a novel xylose-binding site of Geobacillus stearothermophilus xylanase by directed evolution

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Xylan saccharification is a key step in many important biotechnological applications. Xylose is the main product of xylan degradation and is a major xylanase inhibitor in a bioreactor; however, xylose-binding site of xylanase is not discovered yet. Evolving of xylose-tolerant xylanase variants will reduce the cost of xylanases in industry. Glycoside hydrolase family-10 thermostable *Geobacillus stearothermophilus* xylanase XT6 is non-competitively inhibited by xylose with inhibition constant k_i equals to 12.2 mM. In the absence of X-ray crystallography of xylanase–xylose complex, unbiased random mutagenesis of the whole xylanase gene was done by error-prone polymerase chain reaction constructing a huge library. Screening a part of the library revealed xylose-tolerant mutants having three mutations, M116I, L131P and L133V, clustered in the N-terminus of α-helix 3. The best xylose-tolerant mutant showed higher k_i and catalytic capability than that of the parent by 3.5- and 3-fold, respectively. In addition, k_{cat} increased 4.5-fold and K_M decreased 2-fold. The molecular docking of xylose into xylanase XT6 structure showed that xylose binds into a small pocket between N-terminus of α-helices 3 and 4 and close to the three mutations. Mobility of α-helices 3 and 4, which controls catalysis rate, is restricted by xylose binding and increased by these mutations.

Keywords: biofuel, biotechnology, genetic engineering, inhibition, lignocellulose, structure–function relationship

Reactive Oxygen and Nitrogen Species

Acute-phase protein-like properties of endoplasmic reticulum aminopeptidase 1

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Endoplasmic reticulum aminopeptidase 1 (ERAP1) is a multifunctional enzyme. In this study, we analysed its role in lipopolysaccharide-induced inflammatory response in wild-type and ERAP1-knockout mice. Following lipopolysaccharide injection, ERAP1 was secreted into the blood, increasing leucine aminopeptidase activity and NO synthesis therein. Among the amino acids tested, arginine concentration was significantly increased in wild-type mice compared to ERAP1-knockout mice. These results suggest that ERAP1 behaves similar to acute-phase proteins, which are secreted into the blood in response to infectious/inflammatory stimuli and are involved in enhancing NO synthesis as a host defense mechanism.

Keywords: acute phase, amino acid, aminopeptidase, lipopolysaccharide, nitric oxide

MOLECULAR BIOLOGY

Gene Expression

The ahpD gene of Corynebacterium glutamicum plays an important role in hydrogen peroxide-induced oxidative stress response

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In this study, we analysed the *ahpD* gene from *Corynebacterium glutamicum*, which may function in a H_2O_2-mediated stress responses. Cells overexpressing *C. glutamicum ahpD* (P_{180}-*ahpD*) showed increased sensitivity to H_2O_2 when exposed to the latter in concentrations of 8 mM or greater while showing reduced expression of *katA*, which encodes catalase. On the other hand, cells that lack *ahpD* (Δ*ahpD*) displayed increased sensitivity when exposed to low levels of H_2O_2 while showing *katA* transcription that was comparable to the level in the wild-type strain. Accordingly, transcription of *ahpD* and *katA* was stimulated by low and high concentration of H_2O_2, respectively. Further, the NAD^+/NADH ratio was severely reduced in the Δ*ahpD* (3.03) and P_{180}-*ahpD* (0.47) strains as compared with that in the wild-type (4.55) strain. Transcriptional analysis indicated that *ahpD* and upstream genes such as cg2675, cg2676, cg2677 and cg2678, which were annotated as ABC-type transporter, were organized into an operon. Collectively, these findings indicate that *C. glutamicum* possesses bi-level defence pathways against hydrogen peroxide, involving *katA* and *ahpD*. Further, *ahpD*, along with cg2675–cg2678 genes, may play a novel role in cellular activities against oxidative stress.

Keywords: ahpD, alkyl hydroperoxidase, Corynebacterium glutamicum, hydrogen peroxide

Molecular Genetics

Genome analyses for the Tohoku Medical Megabank Project towards establishment of personalized healthcare

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Personalized healthcare (PHC) based on an individual's genetic make-up is one of the most advanced, yet feasible, forms of medical care. The Tohoku Medical Megabank (TMM) Project aims to combine population genomics, medical genetics and prospective cohort studies to develop a critical infrastructure for the establishment of PHC. To date, a TMM CommCohort (adult general population) and a TMM BirThree Cohort (birth+three-generation families) have conducted recruitments and baseline surveys. Genome analyses as part of the TMM Project will aid in the development of a high-fidelity whole-genome Japanese reference panel, in designing custom single-nucleotide polymorphism (SNP) arrays specific to Japanese, and in estimation of the biological significance of genetic variations through linked investigations of the cohorts. Whole-genome sequencing from >3,500 unrelated Japanese and establishment of a Japanese reference genome sequence from long-read data have been done. We next aim to obtain genotype data for all TMM cohort participants (>150,000) using our custom SNP arrays. These data will help

identify disease-associated genomic signatures in the Japanese population, while genomic data from TMM BirThree Cohort participants will be used to improve the reference genome panel. Follow-up of the cohort participants will allow us to test the genetic markers and, consequently, contribute to the realization of PHC.

Keywords: genome reference panel, Japonica array, personalized healthcare, Tohoku Medical Megabank Project, whole genome sequencing

JB COMMENTARY

CELL

Biomembranes, Organelles, and Protein Sorting

Paradigm shift from ‘Compartment’ to ‘Zone’ in the understanding of organelles

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Organelles are intracellular compartments that are delineated by lipid bilayers and play specific roles in regulating various cellular events. Organelle dysfunction contributes to the pathological mechanisms of various diseases. The development and prevalence of super-resolved fluorescence microscopy have enabled the characterization of various functional regions and organellar dynamics by a number of cell biologists. These local functional organelle regions are named ‘zones’, and three review articles in this issue summarize three different organelle zones, namely, the ‘Response zone’, ‘Communication zone’ and ‘Sorting zone’. This newest organellar concept may shed light on a novel biological aspect and the elucidation of mechanisms of unresolved diseases.

Keywords: communication zone, organelle zone, organellar communication, response zone, sorting zone