Alzheimer Mechanisms and Therapeutic Strategies

Cell

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Review

Alzheimer Mechanisms and Therapeutic Strategies

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DOI 10.1016/j.cell.2012.02.040

There are still no effective treatments to prevent, halt, or reverse Alzheimer's disease, but research advances over the past three decades could change this gloomy picture. Genetic studies demonstrate that the disease has multiple causes. Interdisciplinary approaches combining biochemistry, molecular and cell biology, and transgenic modeling have revealed some of its molecular mechanisms. Progress in chemistry, radiology, and systems biology is beginning to provide useful biomarkers, and the emergence of personalized medicine is poised to transform pharmaceutical development and clinical trials. However, investigative and drug development efforts should be diversified to fully address the multifactoriality of the disease.

Introduction

Alzheimer's disease (AD) is characterized by progressive loss of memory and other cognitive functions. Typically, a decade or so passes before the illness has taken its course and patients die in a completely helpless state. The long duration of AD and its attack on the fragile structures that harbor the very essence of who we are place an enormous emotional and financial burden on patients, their families, and society. AD is estimated to have cost the world $604 billion in 2010 alone (Wimo and Prince, 2010). These costs are staggering, particularly in light of predictions that the worldwide number of AD cases, currently estimated at 36 million, will triple by 2050 (Wimo and Prince, 2010). Few health care systems will be able to cope with this development. This Review highlights some of the most informative developments in AD research and raises major unresolved issues.

Substrates of Cognitive Decline

AD causes a large loss in brain weight and volume and affects some brain regions and neuronal populations more than others (Gómez-Isla et al., 1996). Although AD clearly causes loss of neurons in specific brain regions (e.g., of pyramidal cells in lamina II of the entorhinal cortex and in the CA1 region of the hippocampus), much of the overall loss of brain volume appears to be due to the shrinkage and loss of neuronal processes.

Progress in radiological imaging techniques has advanced morphometric measurements from postmortem tissues to live patients (Hampel et al., 2010). For example, progressive decreases in cortical thickness can be detected in multiple brain regions by magnetic resonance imaging (MRI) in AD patients, correlate with cognitive decline, and predict conversion from mild cognitive impairment (MCI) to AD (Frisoni et al., 2010; Putcha et al., 2011). Consequently, this measure is increasingly used in the early diagnosis of AD and as a biomarker in clinical trials.

Beyond such anatomical alterations, functional MRI (fMRI) has revealed alterations in neural network activities in patients with AD and people at risk for developing the disease. These include abnormal activity and connectivity in the so-called default mode network, which in healthy people is most active when they do not think about anything in particular, and hyperactivation of the hippocampus during the execution of memory tasks (Sperling et al., 2010), which correlates with decreased hippocampal volume and abnormal cortical thinning in AD-vulnerable brain regions (Putcha et al., 2011). Consistent with electrophysiological and biochemical data obtained in related transgenic mouse models (Palop and Mucke, 2010; Verret et al., 2012), these observations suggest that AD does not simply silence neurons and neural networks, but rather causes aberrant network activity that might actively interfere with the intricate processes underlying learning, memory and other cognitive functions. In addition, overstimulation of specific neuronal populations could result in excitotoxicity, which likely contributes to neurodegeneration in AD and related conditions. It is interesting in this regard that AD is associated with an increased incidence of epileptic seizures, which is most evident in patients with early-onset forms of the disease (Palop and Mucke, 2009). Findings in transgenic mouse models suggest that these complications may be the tip of an iceberg, representing an escalation of more subtle alterations of neural network activity (Palop and Mucke, 2010; Verret et al., 2012).

Much evidence suggests that synapses and dendrites, the specializations through which neurons send and receive signals, respectively, are particularly vulnerable to AD. Loss of synapses and dendritic spines correlates better with cognitive decline in AD than loss of neurons (Palop et al., 2006). Synaptodendritic rarefaction is also observed in neuronal cultures and in brains of transgenic mice exposed to factors suspected of causing AD. In these models, the degeneration is preceded by alterations in synaptic function and aberrant network activity (Marchetti and

- Cancer Epigenetics: From Mechanism to Therapy

Cell

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Review

Cancer Epigenetics: From Mechanism to Therapy

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http://dx.doi.org/10.1016/j.cell.2012.06.013

The epigenetic regulation of DNA-templated processes has been intensely studied over the last 15 years. DNA methylation, histone modification, nucleosome remodeling, and RNA-mediated targeting regulate many biological processes that are fundamental to the genesis of cancer. Here, we present the basic principles behind these epigenetic pathways and highlight the evidence suggesting that their misregulation can culminate in cancer. This information, along with the promising clinical and preclinical results seen with epigenetic drugs against chromatin regulators, signifies that it is time to embrace the central role of epigenetics in cancer.

Chromatin is the macromolecular complex of DNA and histone proteins, which provides the scaffold for the packaging of our entire genome. It contains the heritable material of eukaryotic cells. The basic functional unit of chromatin is the nucleosome. It contains 147 base pairs of DNA, which is wrapped around a histone octamer, with two each of histones H2A, H2B, H3, and H4. In general and simple terms, chromatin can be subdivided into two major regions: (1) heterochromatin, which is highly condensed, late to replicate, and primarily contains inactive genes; and (2) euchromatin, which is relatively open and contains most of the active genes. Efforts to study the coordinated regulation of the nucleosome have demonstrated that all of its components are subject to covalent modification, which fundamentally alters the organization and function of these basic tenants of chromatin (Allis et al., 2007).

The term "epigenetics" was originally coined by Conrad Waddington to describe heritable changes in a cellular phenotype

The information conveyed by epigenetic modifications plays a critical role in the regulation of all DNA-based processes, such as transcription, DNA repair, and replication. Consequently, abnormal expression patterns or genomic alterations in chromatin regulators can have profound results and can lead to the induction and maintenance of various cancers. In this Review, we highlight recent advances in our understanding of these epigenetic pathways and discuss their role in oncogenesis. We provide a comprehensive list of all the recurrent cancer mutations described thus far in epigenetic pathways regulating modifications of DNA (Figure 2), histones (Figures 3, 4, and 5), and chromatin remodeling (Figure 6). Where relevant, we will also emphasize existing and emerging drug therapies aimed at targeting epigenetic regulators (Figure 1).

Characterizing the Epigenome

Our appreciation of epigenetic complexity and plasticity has

Restructuring G-Protein-Coupled Receptor Activation

Cell

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Restructuring G-Protein-Coupled Receptor Activation

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http://dx.doi.org/10.1016/j.cell.2012.09.003

G-protein-coupled receptors serve as key signal transduction conduits, linking extracellular inputs with diverse cellular responses. These receptors eluded structural characterization for decades following their identification. A landmark structure of rhodopsin provided a basis for structure-function studies and homology modeling, but advances in receptor biology suffered from a lack of receptor-specific structural insights. The recent explosion in GPCR structures confirms some features predicted by rhodopsin-based models, and more importantly, it reveals unexpected ligand-binding modes and critical aspects of the receptor activation process. The new structures also promise to foster studies testing emerging models for GPCR function such as receptor dimerization and ligand-biased signaling.

Introduction

G-protein-coupled receptors are seven transmembrane domain (TM) proteins that are located in the plasma membrane and transduce signals through their interactions with both extracellular small-molecule ligands and intracellular G proteins to initiate signaling cascades that allow cells to respond to changes within their environment. With more than 800 members in the human

of the conformational changes leading to the activation of G-protein-dependent and -independent signaling, thus yielding the needed information to understand drug action and support rational design.

Although GPCRs have been known for more than 40 years, the first high-resolution structure, that of the visual receptor rhodopsin, wasn't solved until 2000 (Palczewski et al., 2000),

The Impact of the Gut Microbiota on Human Health: An Integrative View

Cell

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Review

The Impact of the Gut Microbiota on Human Health: An Integrative View

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DOI 10.1016/j.cell.2012.01.035

The human gut harbors diverse microbes that play a fundamental role in the well-being of their host. The constituents of the microbiota—bacteria, viruses, and eukaryotes—have been shown to interact with one another and with the host immune system in ways that influence the development of disease. We review these interactions and suggest that a holistic approach to studying the microbiota that goes beyond characterization of community composition and encompasses dynamic interactions between all components of the microbiota and host tissue over time will be crucial for building predictive models for diagnosis and treatment of diseases linked to imbalances in our microbiota.

Introduction

We have only recently started to appreciate that the human body is home to far more than human cells: we harbor at least 100 trillion (10^{14}) microbial cells (Whitman et al., 1998) and a quadrillion viruses in and on us (Haynes and Rohwer, 2011). Collectively, the microbial associates that reside in and on the human body constitute our microbiota, and the genes they

gut between viruses, eukaryotes, bacteria, and the host immune system. We then discuss how imbalances in the composition of the microbiota, and the induced changes in interactions with the host, relate to diseases such as obesity or Crohn's disease. In each section we highlight lessons that have been learned about various interacting parts of the microbiota and argue that adopting an integrated perspective will foster a deeper understanding

Resveratrol Ameliorates Aging-Related Metabolic Phenotypes by Inhibiting cAMP Phosphodiesterases

Cell

Resveratrol Ameliorates Aging-Related Metabolic Phenotypes by Inhibiting cAMP Phosphodiesterases

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SUMMARY

Resveratrol, a polyphenol in red wine, has been reported as a calorie restriction mimetic with potential antiaging and antidiabetogenic properties. It is widely consumed as a nutritional supplement, but its mechanism of action remains a mystery. Here, we report that the metabolic effects of resveratrol result from competitive inhibition of cAMP-degrading phosphodiesterases, leading to elevated cAMP levels. The resulting activation of Epac1, a cAMP effector protein, increases intracellular Ca^{2+} levels and activates the CamKKβ-AMPK pathway via phospholipase C and the ryanodine receptor Ca^{2+}-release channel. As a consequence, resveratrol increases NAD^+ and the activity of Sirt1. Inhibiting PDE4 with rolipram reproduces all of the metabolic benefits of resveratrol, including prevention of diet-induced obesity and an increase in mitochondrial function, physical stamina, and glucose tolerance in mice. Therefore, administration of PDE4 inhibitors may

underlying the beneficial effects of CR. Based on studies of the budding yeast *Saccharomyces cerevisiae*, it was initially proposed that CR extends life span via the activity of Sir2 (Lin et al., 2000), the founding member of the conserved sirtuin family of NAD^+-dependent protein deacetylases (Guarente, 2006). Although it remains unclear whether Sir2 plays a direct role in the antiaging effects of CR (e.g., Kaeberlein et al., 2004), overexpression of Sirt1, the mammalian homolog of Sir2, has been reported to protect mice from aging-related phenotypes that are similar to type 2 diabetes (Banks et al., 2008; Bordone et al., 2007; Pfluger et al., 2008), cancer (Herranz et al., 2010), and Alzheimer's disease (Donmez et al., 2010). Suggesting that Sirt1 activity does not protect against aging-related diseases by delaying the aging process, overexpression of Sirt1 does not extend life span in mice (Herranz et al., 2010).

The positive health effects of CR and sirtuin activity in animal models have provoked intense interest in the development of small-molecule activators of Sirt1 to prevent or delay aging-related diseases. An in vitro screen performed using a fluorophore-tagged substrate identified resveratrol as an activator of Sirt1 deacetylase activity (Howitz et al., 2003). Resveratrol is a natural polyphenol produced by plants in response to environ-

A Whole-Cell Computational Model Predicts Phenotype from Genotype

Theory

Cell

A Whole-Cell Computational Model Predicts Phenotype from Genotype

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http://dx.doi.org/10.1016/j.cell.2012.05.044

SUMMARY

Understanding how complex phenotypes arise from individual molecules and their interactions is a primary challenge in biology that computational approaches are poised to tackle. We report a whole-cell computational model of the life cycle of the human pathogen *Mycoplasma genitalium* that includes all of its molecular components and their interactions. An integrative approach to modeling that combines diverse mathematics enabled the simultaneous inclusion of fundamentally different cellular processes and experimental measurements. Our whole-cell model accounts for all annotated gene functions and was validated against a broad range of data. The model provides insights into

First, until recently, not enough has been known about the individual molecules and their interactions to completely model any one organism. The advent of genomics and other high-throughput measurement techniques has accelerated the characterization of some organisms to the extent that comprehensive modeling is now possible. For example, the mycoplasmas, a genus of bacteria with relatively small genomes that includes several pathogens, have recently been the subject of an exhaustive experimental effort by a European consortium to determine the transcriptome (Güell et al., 2009), proteome (Kühner et al., 2009), and metabolome (Yus et al., 2009) of these organisms.

The second limiting factor has been that no single computational method is sufficient to explain complex phenotypes in terms of molecular components and their interactions. The first approaches to modeling cellular physiology, based on ordinary differential equations (ODEs) (Atlas et al., 2008; Browning et al., 2004; Castellanos et al., 2004, 2007; Domach et al.,

Three-Dimensional Folding and Functional Organization Principles of the Drosophila Genome

Cell

Three-Dimensional Folding and Functional Organization Principles of the *Drosophila* Genome

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SUMMARY

Chromosomes are the physical realization of genetic information and thus form the basis for its readout and propagation. Here we present a high-resolution chromosomal contact map derived from a modified genome-wide chromosome conformation capture approach applied to *Drosophila* embryonic nuclei. The data show that the entire genome is linearly partitioned into well-demarcated physical domains that overlap extensively with active and repressive epigenetic marks. Chromosomal contacts are hierarchically organized between domains. Global modeling of contact density and clustering of domains show that inactive domains are condensed and confined

Understanding chromosome structure fully is therefore a fundamental task in genomic and epigenetic research, and different hypotheses on the causative or consequential nature of chromosomal folding patterns have major implications on our understanding of how genetic information is encoded and interpreted. Various mathematical models have been proposed to explain the effects of different physical factors on chromosome fiber folding (reviewed in Heermann, 2011; Lieberman-Aiden et al., 2009; Mateos-Langerak et al., 2009; Münkel et al., 1999; Sachs et al., 1995), but high-resolution, genome-wide measurements of DNA fragment interdistances or interaction frequency are required for their rigorous assessment.

The development of the chromosome conformation capture (3C) technique, which allows detection of genomic regions that are in close proximity in vivo (Dekker et al., 2002), and its integration with genomic methods have allowed chromatin topology

Cell

A Role for Small RNAs in DNA Double-Strand Break Repair

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SUMMARY

Eukaryotes have evolved complex mechanisms to repair DNA double-strand breaks (DSBs) through coordinated actions of protein sensors, transducers, and effectors. Here we show that ~21-nucleotide small RNAs are produced from the sequences in the vicinity of DSB sites in *Arabidopsis* and in human cells. We refer to these as diRNAs for DSB-induced small RNAs. In *Arabidopsis*, the biogenesis of diRNAs requires the PI3 kinase ATR, RNA polymerase IV (Pol IV), and Dicer-like proteins. Mutations in these proteins as well as in Pol V cause significant reduction in DSB repair efficiency. In *Arabidopsis*, diRNAs are recruited by Argonaute 2 (AGO2) to mediate DSB repair. Knock down of Dicer or Ago2 in human cells reduces DSB repair. Our findings reveal a conserved

fashion. It can cause deletions or insertions at the break site because of the modification of DNA ends before joining (Lieber, 2010). In contrast, HR is considered error free, but it requires resection of the DSB and a sister chromatid as template for repair (Moynahan and Jasin, 2010; San Filippo et al., 2008; Sasaki et al., 2010). Single-strand annealing (SSA) is a particular type of HR that takes place when DSB resection occurs at repetitive sequences, providing complementary single strands that can then anneal (Ciccia and Elledge, 2010; Hartlerode and Scully, 2009). These repair pathways all require well-regulated and coordinated enzymatic actions of protein sensors, transducers, and effectors in the DSB signaling cascade (Ciccia and Elledge, 2010; Huen and Chen, 2008; Polo and Jackson, 2011).

Small RNAs have emerged as key players in various aspects of biology. Three major classes of small RNAs have been discovered in eukaryotes: microRNAs (miRNAs), small interfering RNAs (siRNAs), and Piwi-interacting RNAs (piRNAs). miRNAs and siRNAs are processed by RNase III domain-containing Dicer

Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Resource

Cell

Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

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SUMMARY

Personalized medicine is expected to benefit from combining genomic information with regular monitoring of physiological states by multiple high-throughput methods. Here, we present an integrative personal omics profile (iPOP), an analysis that combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual over a 14 month period. Our iPOP analysis revealed various medical risks, including type 2 diabetes. It also uncovered extensive, dynamic changes in diverse molecular components and biological pathways across healthy and diseased conditions. Extremely high-coverage genomic

INTRODUCTION

Personalized medicine aims to assess medical risks, monitor, diagnose and treat patients according to their specific genetic composition and molecular phenotype. The advent of genome sequencing and the analysis of physiological states has proven to be powerful (Cancer Genome Atlas Research Network, 2011). However, its implementation for the analysis of otherwise healthy individuals for estimation of disease risk and medical interpretation is less clear. Much of the genome is difficult to interpret and many complex diseases, such as diabetes, neurological disorders and cancer, likely involve a large number of different genes and biological pathways (Ashley et al., 2010; Grayson et al., 2011; Li et al., 2011), as well as environmental contributors that can be difficult to assess. As such, the combination of genomic information along with a detailed molecular

Single-Cell Expression Analyses during Cellular Reprogramming Reveal an Early Stochastic and a Late Hierarchic Phase

Cell

Single-Cell Expression Analyses during Cellular Reprogramming Reveal an Early Stochastic and a Late Hierarchic Phase

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SUMMARY

During cellular reprogramming, only a small fraction of cells become induced pluripotent stem cells (iPSCs). Previous analyses of gene expression during reprogramming were based on populations of cells, impeding single-cell level identification of reprogramming events. We utilized two gene expression technologies to profile 48 genes in single cells at various stages during the reprogramming process. Analysis of early stages revealed considerable variation in gene expression between cells in contrast to late stages. Expression of Esrrb, Utf1, Lin28, and Dppa2 is a better predictor for cells to progress into iPSCs than expression of the previously suggested reprogramming markers Fbxo15, Fgf4, and Oct4. Stochastic gene expression early in reprogramming is followed by a late hierarchical phase with Sox2 being the upstream factor in a gene expression hierarchy. Finally, downstream factors derived from the late phase, which do not include Oct4, Sox2, Klf4, c-Myc, and Nanog, can activate

generate iPSCs that functionally and molecularly resemble embryonic stem cells (ESCs).

To further understand the reprogramming process, transcriptional and epigenetic changes in cell populations were analyzed at different time points after factor induction. For example, microarray data showed that the immediate response to the reprogramming factors was characterized by dedifferentiation of mouse embryonic fibroblasts (MEFs) and upregulation of proliferative genes, consistent with c-Myc expression (Mikkelsen et al., 2008). It has been shown that the endogenous pluripotency markers Sox2 and Nanog are activated after early markers such as alkaline phosphatase (AP) and SSEA1 (Stadtfeld et al., 2008). Recently, gene expression profiling and RNAi screening in fibroblasts revealed three phases of reprogramming termed initiation, maturation, and stabilization, with the initiation phase marked by a mesenchymal-to-epithelial transition (MET) (Li et al., 2010; Samavarchi-Tehrani et al., 2010).

Given these data, a stochastic model has emerged to explain how forced expression of the transcription factors initiates the process that eventually leads to the pluripotent state in only a small fraction of the transduced cells (Hanna et al., 2009; Yamanaka, 2009). Most data have been interpreted to support a stochastic model (Hanna et al., 2009) posing that the reprog-

Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human

Cell

Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human

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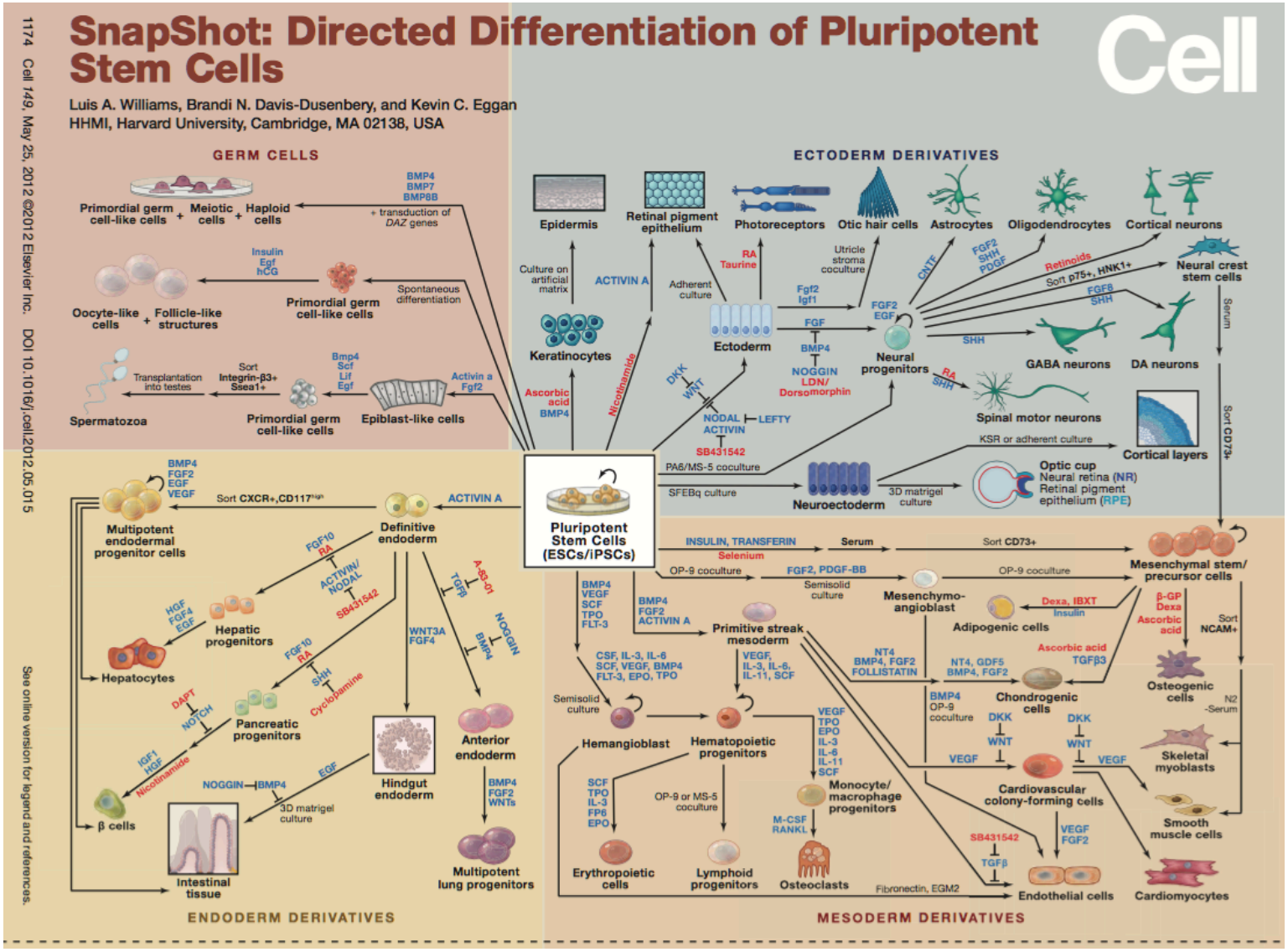
SUMMARY

Brown fat generates heat via the mitochondrial uncoupling protein UCP1, defending against hypothermia and obesity. Recent data suggest that there are two distinct types of brown fat: classical brown fat derived from a myf-5 cellular lineage and UCP1-positive cells that emerge in white fat from a non-myf-5 lineage. Here, we report the isolation of "beige" cells from murine white fat depots. Beige cells resemble white fat cells in having extremely low basal expression of UCP1, but, like classical brown fat, they respond to cyclic AMP stimulation with high UCP1 expression and respiration rates. Beige cells have a gene expression pattern distinct from either white or brown fat and are preferentially sensitive to the polypeptide hormone irisin. Finally,

depots after infancy. Recent data indicate that adult humans contain significant deposits of UCP1-positive brown fat that can be detected by positron emission tomography (PET)-scanning methods, particularly in the supraclavicular and neck region (Cypess et al., 2009; Mirbolooki et al., 2011; Orava et al., 2011; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). The physiological significance of adult human brown fat has not yet been fully explored.

It has been known for many years that some white adipose tissues contain cells that can express high levels of UCP1 and take on a multilocular appearance upon prolonged stimulation by cold or pathways that elevate intracellular cyclic AMP (cAMP) (Cousin et al., 1992; Young et al., 1984). Recent data have shown that classical brown fat, exemplified by the interscapular depots of rodents, is derived from a myf-5 muscle-like cellular lineage (Seale et al., 2008). The "brown-like" cells within white adipose depots are not derived from the myf-5 lineage and have been called "beige" or "brite" cells (Ishibashi

Directed Differentiation of Pluripotent Stem Cells



Regulation of the Hippo-YAP Pathway by G-Protein- Coupled Receptor Signaling

Cell

Regulation of the Hippo-YAP Pathway by G-Protein-Coupled Receptor Signaling

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http://dx.doi.org/10.1016/j.cell.2012.06.037

SUMMARY

The Hippo pathway is crucial in organ size control, and its dysregulation contributes to tumorigenesis. However, upstream signals that regulate the mammalian Hippo pathway have remained elusive. Here, we report that the Hippo pathway is regulated by G-protein-coupled receptor (GPCR) signaling. Serum-borne lysophosphatidic acid (LPA) and sphingosine 1-phosphophate (S1P) act through G12/13-coupled receptors to inhibit the Hippo pathway kinases Lats1/2, thereby activating YAP and TAZ transcription coactivators, which are oncoproteins

function of the Hippo pathway in organ size regulation is conserved in mammals (reviewed in Zhao et al., 2010a).

The kinase cascade of MST1/2 and Lats1/2 represents a core component of the mammalian Hippo pathway. MST1/2, in complex with a regulatory protein salvador (Sav1), phosphorylate and activate Lats1/2 kinases, which also form a complex with a regulatory protein Mob1 (Zhao et al., 2010a). The transcription coactivator Yes-associated protein (YAP) is a major downstream effector of the Hippo pathway (Dong et al., 2007). Lats1/2 inhibit YAP by direct phosphorylation at S127, which results in YAP binding to 14-3-3 and cytoplasmic sequestration (Dong et al., 2007; Hao et al., 2008; Zhao et al., 2007). YAP acts mainly through TEAD family transcription factors to stimulate expression of genes that promote proliferation and inhibit apoptosis (Zhao