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STIFTUNG PROFESSOR DR. MAX CLOËTTA

Heft Nr. 42

Prof. Dr. Marc Y. Donath

«Targeting Inflammation in the Treatment of Type 2 Diabetes: Time to Start»

Prof. Dr. Henrik Kaessmann

«The Evolution of Mammalian Gene Expression: Dynamics and Phenotypic Impact»

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VORWORT

Professor Adriano Fontana
Präsident des Stiftungsrates

Die Stiftung Prof. Dr. Max Cloëtta verleiht dieses Jahr zwei Preise; einen im Bereich Klinische Forschung und einen im Bereich der Grundlagenforschung.

Als hervorragender Kliniker und Forscher erhält Professor Marc Donath von der Universität Basel den Preis für seine Pionierleistung bei der Erforschung des Entstehungsmechanismus des Typ-2-Diabetes, gegen den er neue therapeutische Ansätze entwickelt hat. Die Stiftung Prof. Dr. Max Cloëtta hat den begabten Arzt bereits vor seiner Habilitation mit einer Cloëtta-Forschungsstelle gefördert. Die jetzige Auszeichnung honoriert sein Schaffen umfassend. Mit dieser Vergabung möchte die Stiftung ein Zeichen für die Forschung auf klinischem Gebiet setzen. Klinik und Forschung! Sie sollten ein Tandem bilden, aus welchem neue Forschungserkenntnisse in das Wissen und Handeln der klinischen Medizin Eingang finden.

Für die Ärzteschaft wird die Kluft zwischen Klinik und Forschung immer tiefer. Die klinische Tätigkeit mit einer Forschungsaktivität zu kombinieren und letztere nicht nur zu betreiben, sondern zielführend zu echten Neuwerten wachsen zu lassen, ist eine unglaubliche Herausforderung. Der Alltag in der Medizin ist geprägt von der Verantwortung, als Arzt dem Patienten gegenüber mit seinem besten Wissen und all seiner Kraft zur Seite zu stehen. Dazu kommen immer komplexere ethische Fragen und neue medizinische Technologien zur Diagnostik und Therapie. Arbeitszeitbeschränkung und Stellenknappheit gewähren zudem nur wenig Freiraum für eine die Klinik begleitende Tätigkeit. Die Forschung ihrerseits wird immer komplexer, kompetitiver und zeitlich fordernder. Die Mitarbeit in internationalen Netzwerken und das Mitwirken in Forschungsgremien sind wichtige, aber zeitraubende Aktivitäten, um am Puls des wissenschaftlichen Schaffens zu bleiben. Umso wichtiger ist die För-

derung klinisch tätiger Forscher durch entsprechende Institutionen. Eine «Auszeit», wie sie die Stiftung Prof. Dr. Max Cloëtta und der Schweizerische Nationalfonds geeigneten Medizinern zur Ausübung einer wissenschaftlichen Tätigkeit offerieren, erlaubt den Geförderten, sich für 4–6 Jahre mehrheitlich der Forschung zuzuwenden.

Die medizinisch-biologische Forschung wird jedoch massgebend durch die Grundlagenforschung bereichert. Und so besteht seitens der Stiftung Prof. Dr. Max Cloëtta auch ein grosses Interesse, im Bereiche der Grundlagenforschung tätige Forschungspersönlichkeiten zu ehren. Professor Henrik Kaessmann von der Universität Lausanne erhält den Cloëtta-Preis für seine fundamental neuen Entdeckungen im Bereich der Molekulargenetik. Heftig diskutiert wird unter Paläontologen und Molekulargenetikern die Art der Diversifizierung der höheren Säugetiere. Die Arbeiten von Professor Kaessmann über die molekularen Veränderungen, welche mit dieser Entwicklung einhergehen, haben international grosses Aufsehen erlangt. Durch die Weiterentwicklung und Anwendung modernster molekularbiologischer Techniken und Datenanalysesystemen gelang es Prof. Kaessmann, seine brillanten Ideen umzusetzen.

Prof. Dr. med. Adriano Fontana

Brigitt Küttel
Geschäftsführerin

Stiftungsrat

Wie ist es einer Stiftung wie der Stiftung Prof. Dr. Max Cloëtta möglich, seit nunmehr über vierzig Jahren kontinuierlich auf wissenschaftlich hohem Niveau zu bleiben und den Forschernachwuchs in der Schweiz wirkungsvoll zu fördern?

Richtig: Das geht nur dank immer wieder neuen fachlich hoch kompetenten Persönlichkeiten, die sich unentgeltlich in den Dienst der Stiftung und damit der Förderung der medizinischen Forschung zu stellen bereit sind – neben denjenigen, die ihr Fachwissen über viele Jahre im Stiftungsrat einbringen. *Was bleibt, ist die Veränderung; was sich verändert, bleibt.* Als Geschäftsführerin bedaure ich es jedes Mal, wenn ein Mitglied des Stiftungsrates das Gremium verlässt, freue mich aber gleichzeitig auf die immer spannende Zusammenarbeit mit neuen Persönlichkeiten. Allen, den ausscheidenden und den neuen Kräften, gebührt unser herzlicher Dank.

Frau Prof. Dr. Susanne Suter trat auf Ende 2013 nach fünf Jahren als Stiftungsrätin zurück. Sie war 2008 als Nachfolgerin von Prof. Michel Vallotton und als erste Frau in der Geschichte der Stiftung in den Stiftungsrat berufen worden. Vom ersten bis zum letzten Tag sorgte sie hartnäckig und gleichzeitig sehr liebenswürdig dafür, dass die Pädiatrie, die klinische Forschung und nicht zuletzt die Sache der Frau den ihnen zustehenden Stellenwert bekamen.

Neu in den Stiftungsrat gewählt wurden Frau Prof. Dr. med. Daniela Finke, Leiterin der Forschungsabteilung des Universitäts-Kinderspitals beider Basel (UKBB) und Ordinaria für molekulare Medizin in der Pädiatrie, und Prof. Dr. Walter Reith vom Departement für Pathologie und Immunologie an der Universität Genf. Als Immunologe wurde er 2009 für seine Forschung auf dem Gebiet der Histokompatibilität mit dem Cloëtta-Preis ausgezeichnet. Beide werden sie den Medizinischen Aus-

schuss vervollständigen, der die fünf medizinischen Fakultäten der Schweiz sowie den Schweizerischen Nationalfonds repräsentiert.

An dieser Stelle möchten wir wieder einmal allen danken – den Mitgliedern des Stiftungsrates, die ihr Fachwissen einbringen, sei es im wissenschaftlichen Bereich oder zu den Themen Finanzen und Recht, aber auch den Expertinnen und Experten, die uns mit ihren Gutachten bei der Entscheidungsfindung z.B. bei der Zusprache des Cloëtta-Preises unterstützen.

Cloëtta-Preis

In den letzten Jahren hat die angespannte Wirtschaftslage auch die Stiftung Cloëtta dazu gezwungen, die Finanzen sorgfältig im Blick zu behalten. Dies hat dazu geführt, dass wir – neben anderen Sparmassnahmen – nur noch einen Preis vergeben haben statt zwei. Dieses Jahr hat der Stiftungsrat entschieden, der Tradition zu folgen und wieder zwei Preisträger auszuzeichnen, je einen für Forschung auf dem Gebiet der klinischen Medizin und einen für die medizinische Grundlagenforschung. Da die beiden Preisträger aus verschiedenen Landesteilen stammen, Prof. Marc Donath aus Basel und Prof. Henrik Kaessmann aus Lausanne, findet die Preisverleihung dieses Jahr wieder in Zürich statt, wo die Stiftung seit ihrer Gründung ihren Sitz hat.

Forschungsstellen

Das Forschungsstellenprogramm ist für die Stiftung Prof. Dr. Max Cloëtta – und für den akademischen Mittelbau in der Schweiz – von grosser Bedeutung. Finanziert werden Stellen an schweizerischen Hochschulen, Kliniken oder Instituten für bereits ausgebildete und selbstständig arbeitende Forscherinnen und Forscher bis max. 40 Jahre. Mit diesem Programm will die Stiftung einem Mangel an Forschernachwuchs in der Schweiz entgegenwirken und den Stelleninhabern helfen, die manchmal nicht einfache Phase bis zur Berufung auf eine ordentliche Professur zu

überbrücken. Die Stipendien werden alle zwei Jahre vergeben. Die Evaluation der Bewerbungen 2014 endet im Februar 2015.

2014 finanzierte die Stiftung Prof. Dr. Max Cloëtta folgende Forscher an Schweizer Universitäten mit fünfjährigen Grants:
Dr. Rajesh Jayachandran, 1977, Biozentrum der Universität Basel. Projekt: Role for Coronin 1 signaling in the development of autoimmunity and T cell mediated disorders. Unterstützungsdauer 1.7.2011–30.6.2016.
Dr. Daniel Fuster, 1972, Universität Bern, Institut für Biochemie und Molekulare Medizin. Projekt: Novel mammalian sodium/hydrogen exchanger family NHA – a quest for biological function. Unterstützungsdauer 1.6.2009–31.5.2014.
Dr. Benjamin Marsland, 1977, Centre Hospitalier Universitaire Vaudois, Service de pneumologie. Projekt: Innate and adaptive immune responses in the lung: implications for protective immunity. Unterstützungsdauer 1.7.2009–30.6.2014.

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta in Zusammenarbeit mit der Uniscientia Stiftung, Vaduz, Stipendien «Klinische Medizin Plus». Medizinerinnen und Medizinern werden während oder unmittelbar nach Abschluss der Facharztausbildung Stipendien von drei bis maximal zwölf Monaten für die Absolvierung einer Spezialausbildung an einer renommierten, vornehmlich ausländischen Institution ausgerichtet.
Der Vertrag mit der Uniscientia Stiftung endet 2015 – wir hoffen sehr, dass diese bewährte Zusammenarbeit auch darüber hinaus fortgesetzt werden kann.

2014 wurden folgende Medizinerinnen und Mediziner unterstützt:
Dr. med. Heidemarie Gast, 1967, Oberärztin an der Universitätsklinik für Neurologie am Inselspital Bern. Projekt: To investigate the hypothesis that burst firing of single neurons in humans is a marker for seizure suppressive state. Gastinstitut: Klinik für Epileptologie, Universität Bonn, DE, 6.2013–5.2014

Dr. med. Alexia Anagnostopoulos, 1978, wissenschaftliche Mitarbeiterin am Universitätsspital Zürich. Projekt: Research Fellowship Epidemiology. Subject: Barriers to Treatment in HIV/Hepatitis C Virus Co-Infected Intravenous Drug Users. Gastinstitut: Johns Hopkins Bloomberg School of Public Health, Dept. of Epidemiology, Baltimore, Maryland USA, 1.7.2015–31.12.2015

Dr. med. Baharak Babouee Flury, 1977, wissenschaftliche Mitarbeiterin am Universitätsspital Basel. Projekt: Emerging Carbapenem-Resistance in Enterobacter spp: what is the threat we face? Gastuniversität: Antimicrobial Resistance and Healthcare Associated, Infections Reference Unit (AMRHAI) of the Health and Protection Agency UK, Colindale/ London, 1.10.2014–30.9.2015

Dr. med. Frederique Hovaguimian, 1981, wissenschaftliche Mitarbeiterin mit 50 % klinischer Aktivität am Universitätsspital Zürich. Projekt: Master of Clinical Research Methods and clinical research project. Gastinstitut: Department of Epidemiology, Monash University, Melbourne, AU and Department of Anaesthesiology, Alfred Hospital, Melbourne, AU, 1.3.2014–28.2.2015

Dr. med. Sophie Yammine, 1980, wissenschaftliche Mitarbeiterin am Universitätsspital Bern und PhD Studentin an der Universität Bern. Projekt: Bronchiolitis obliterans syndrome (BOS), idiopathic pneumonia syndrome/cooperation between Bern, Basel and Melbourne. Gastinstitut: Murdoch Childrens Research Institute at the Royal Children's Hospital, Melbourne, AU, 1.2.2014–30.4.2014

Zusammen mit dem Team der Geschäftsstelle freue ich mich, die Stiftung Prof. Dr. Max Cloëtta in eine aktive Zukunft für die Förderung der medizinischen Forschung in der Schweiz begleiten zu dürfen. Dem Stiftungsrat, unseren Stipendiatinnen und Stipendiaten und den medizinischen Fakultäten danken wir herzlich für die jederzeit sehr angenehme Zusammenarbeit.

lic. jur. Brigitt Küttel

DER CLOËTTA-PREIS 2014
WIRD VERLIEHEN

HERRN PROFESSOR DOKTOR

MARC Y. DONATH

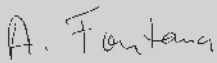
GEBOREN 1963 IN BERN
PROFESSOR FÜR ENDOKRINOLOGIE AN DER UNIVERSITÄT BASEL
UND CHEFARZT ENDOKRINOLOGIE, DIABETOLOGIE
UND METABOLISMUS AM UNIVERSITÄTSSPITAL BASEL

FÜR SEINE HERAUSRAGENDEN FORSCHUNGSARBEITEN
AUF DEM GEBIETE DER PATHOPHYSIOLOGIE UND THERAPIE DES
DIABETES MELLITUS TYP-2 («ALTERSDIABETES»).

ZÜRICH, 14. NOVEMBER 2014

FÜR DEN STIFTUNGSRAT:

DER PRÄSIDENT



DER VIZEPRÄSIDENT

EIN MITGLIED

Prof. Dr. Marc Y. Donath

BIOGRAPHY

Marc Y. Donath is Professor and Head of the Clinic for Endocrinology, Diabetes and Metabolism at the University Hospital of Basel. He was born in 1963 in Berne. After studying medicine and receiving his doctorate in medical research from the University of Zurich in 1990, he went on to work at locations such as ETH Zurich and Hadassah University Hospital in Jerusalem (Israel). In 1998 he was awarded the title of SMA (Swiss Medical Association) specialist in internal medicine and endocrinology/diabetes. From 1999 to 2004 he held a medical research position financed by the Professor Dr Max Cloëtta Foundation. He completed his habilitation thesis at the University of Zurich in 2002, and was subsequently awarded a SNSF professorship. From 2003 to 2009 he was SNSF professor at the University of Zurich and attending physician at the Division of Endocrinology, Diabetology and Clinical Nutrition at University Hospital Zurich. Marc Donath has received numerous awards for his research, including the research prize of the Swiss Diabetes Foundation in 2002 and the Novartis Prize in Diabetes in 2008.

His research focuses on the mechanisms of type 2 diabetes (adult-onset diabetes), for which he has developed a sensational new therapy. His assumption is that this most common type of diabetes is attributable to a form of inflammation of insulin-producing cells, which has opened up new perspectives in the therapy of type 2 diabetes. He is a father of three children.

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Targeting inflammation in the treatment of type 2 diabetes: time to start. ***Nature Reviews Drug Discovery*** 13(6):465–76

TARGETING INFLAMMATION IN THE TREATMENT OF TYPE 2 DIABETES: TIME TO START

Marc Y. Donath

Abstract

The role of inflammation in the pathogenesis of type 2 diabetes mellitus and associated complications is now well-established. Islets of patients with type 2 diabetes display the typical features of an inflammatory process characterized by the presence of cytokines, chemokines, immune cell infiltration, impaired function and tissue destruction with fibrotic areas. Functional studies have shown that targeting inflammation may improve insulin secretion and sensitivity. In particular clinical proof of concept studies using antagonists of the IL-1□ pathway demonstrated the role of the innate immune system in type 2 diabetes. This program has now entered the phase 3 of clinical development. In this article we discuss the mechanisms of islet inflammation in type 2 diabetes and review the opportunity of clinical translation.

According to the International Diabetes Federation, 382 million people were affected by diabetes in 2013 (http://www.idf.org/diabetesatlas)[1]. The prevalence of the disease is expected to rise to 592 million by 2035. Of note, it is a worldwide epidemic, although the vast majority (80%) of people with diabetes lives in low-income and middle-income countries. Type 2 diabetes is a disease that tends to affect people as they age, especially those with genetic and epigenetic predispositions. It is strongly promoted by over-nutrition and physical inactivity. In predisposed individuals, an insulin secretion defect can be detected concomitantly with a reduced response to insulin-stimulated glucose uptake in fat, liver and adipose tissues, a condition known as insulin resistance[1-5]. At the individual level, insulin resistance remains relatively constant over time, and increases only mildly with age. By contrast, after an initial increase in insulin production, the onset and progression of type 2 diabetes is caused by a continuous deterioration of the insulin-secretory capacity of pancreatic □ cells. Thus, insulin secretion no longer compensates for the increased peripheral insulin demand. The progression from prediabetes to diabetes is largely dictated by changes in islet secretory capacity, necessitating an increasing need for medication that culminates in insulin replacement (Figure 1).

Islet inflammation in type 2 diabetes

Multiple mechanisms underlie defective insulin secretion and responses in type 2 diabetes. These include glucotoxicity, lipotoxicity, oxidative stress, ER stress, alterations of the gut microbiota, endocannabinoids, and formation of amyloid deposits in the islet[6-10]. The relative contribution of each of these mechanisms remains unclear. They probably all participate in the pathology of the disease, with inter-individual differences depending on genetic background, nutrition, physical activity, the use of antibiotics, and other environmental factors. Interestingly, all of these mechanisms are associated with inflammatory responses[11-19]. In pancreatic islets, elevated glucose concentrations increase islet cell metabolic activity, leading to elevated ROS formation which promotes NLRP3 inflammasome and caspase 1 activation, thus enabling the production of ma-

[1] *Part of this text is reproduced from Donath MY: Nature reviews Drug discovery 2014, 13:465–76.*

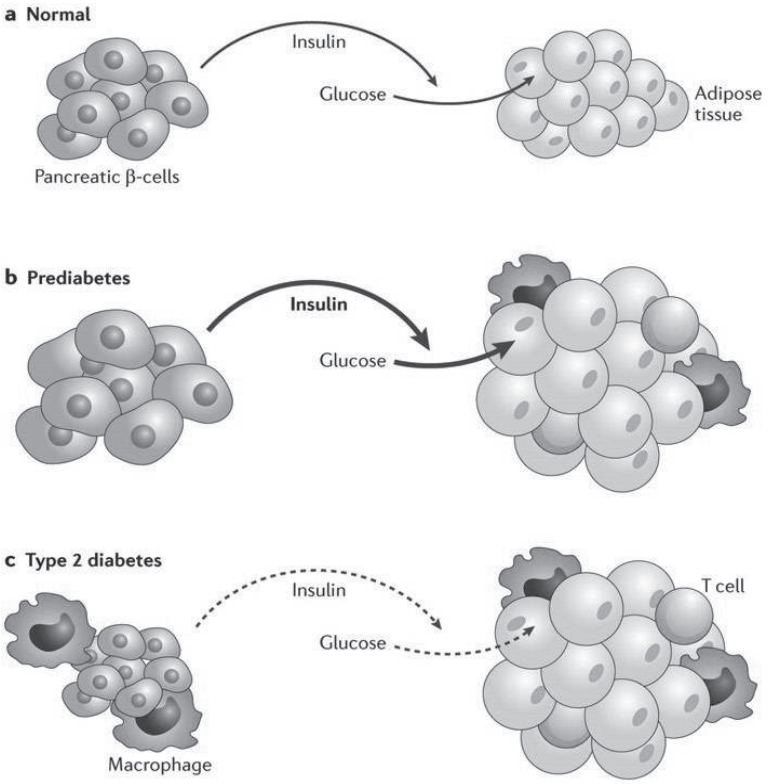

Figure 1. *Type 2 diabetes is caused by a continuous deterioration of the insulin-secretory capacity of pancreatic □-cells, which does not allow compensation for an increased peripheral insulin demand. In healthy individuals, insulin secretion by the pancreatic islet allows for normal glucose disposal in the insulin-sensitive tissues: fat, liver and adipose tissues (Upper panel). During prediabetes, genetic predisposition, overnutrition and physical inactivity reduce the response to insulin-stimulated glucose uptake that is compensated for by an increase in insulin production (Middle panel). In patients with type 2 diabetes insulin secretion no longer compensates for the increased peripheral insulin demand (Lower panel). The progression from prediabetes to diabetes is largely dictated by changes in islet secretory capacity while insulin resistance remains relatively constant over time. (Reproduced from Donath MY: Nature reviews Drug discovery 2014, 13:465–76)*

ture IL-1□[20, 21] (Figure 2). Increased insulin demand and production induces ER stress which also activates the inflammasome[18]. Furthermore,

lipopolysaccharides from bacterial cell walls (endotoxins) or free fatty acid bound to Fetuin-A activate TLR2 and TLR4, leading to NF-□B translocation and induction of inflammation[22, 23]. All these components will induce very low concentrations of islet-derived IL-1□. Initially this inflammatory process may be beneficial, promoting □-cell proliferation and insulin production that compensate for insulin resistance[24]. IL-1□ will induce various cytokines and chemokines including IL-6, IL-8, TNF□ and MCP1 that lead to the attraction of macrophages and other immune cells,[25-27] probably depending on the duration of IL-1□ exposure and stress level. This recruitment of immune cells will be enhanced by the vicious cycle of IL-1□ auto-stimulation[28]. Furthermore, islets produce amyloid polypeptide that aggregates to form amyloid fibrils in patients with type 2 diabetes. Recent data suggest that human islet amyloid polypeptide interacts with immune cells to promote the synthesis of IL-1□ via the inflammasome[14-16]. Thereby, resident islet macrophages adopt a pro-inflammatory phenotype that induces islet dysfunction. Indeed, depletion of islet macrophages improves glucose metabolism in mice expressing human islet amyloid polypeptide,[14] and the IL-1 receptor antagonist improves glycemia in diabetic mouse recipients of islets isolated from mice expressing human islet amyloid polypeptide[15]. Finally, endocannabinoids which mediate satiety in the hypothalamus[29] and are upregulated in the liver during obesity[30], may also promote macrophage activation[17].

Blockade of IL-1 in the treatment of type 2 diabetes

Since the first observation assigning a role for IL-1□ in the pathogenesis of type 2 diabetes[20], numerous observations[31, 32] and clinical studies[33-41] in humans suggest its involvement in impaired insulin secretion and in insulin resistance. An initial proof of concept clinical study randomly assigned 70 patients with type 2 diabetes to receive either anakinra (a recombinant human IL-1–receptor antagonist) or placebo for 13 weeks[34]. Anakinra improved glycaemia and □ cell secretory function and reduced markers of systemic inflammation. In accordance with the initial protocol, after anakinra withdrawal, the patients were followed-up for 39 additional weeks in a blinded manner[33]. At that time, insulin secretion was still preserved and inflammation was still decreased, suggesting that IL-1

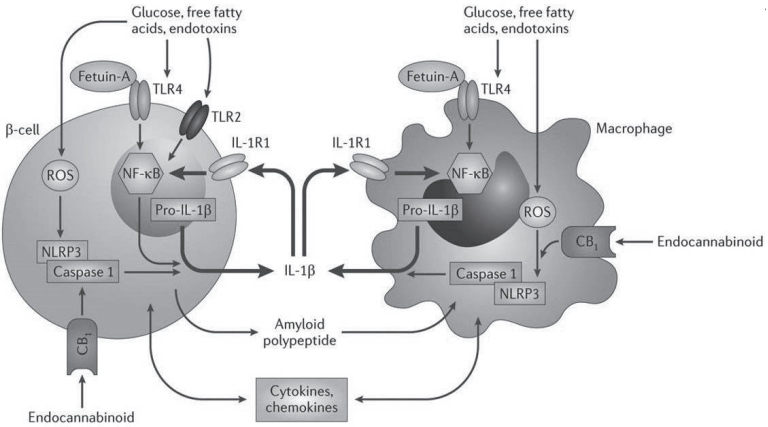

Figure 2. *Islet inflammation in type 2 diabetes. Prolonged exposure of pancreatic islet □-cells to elevated concentrations of glucose and free fatty acids increases islet cell metabolic activity leading to elevated ROS formation. This promotes NLRP3 inflammasome and caspase 1 activation, thus enabling the production of mature IL-1□. Lipopolysaccharides from the bacterial cell wall (endotoxins) or free fatty acid bound to Fetuin-A activate TLR2 and TLR4 and induce the expression of proinflammatory factors via NF-□B. Endocannabinoids may also activate the inflammasome via the CB1 receptor. IL-1□ autostimulation further amplifies inflammation, engendering a vicious cycle (thick arrows). IL-1□ induces various cytokines and chemokines that lead to the attraction of immune cells. Macrophages may then be activated by human islet amyloid polypeptide, high glucose, free fatty acids, endotoxins, and endocannabinoids leading to deleterious concentrations of IL-1□. (Reproduced from Donath MY: Nature reviews Drug discovery 2014, 13:465–76)*

the vicious cycle of IL-1 auto-induction[28]. Two interesting follow up studies using anakinra in pre-diabetic individuals[35] and in those with impaired glucose tolerance[37] showed that even at these very early stages of the disease, antagonizing the IL-1 system improves □ cell secretory function and thus may prevent or delay the onset of type 2 diabetes. Furthermore, in a preliminarystudy in patients with type 1 diabetes who also have insulin resistance caused by obesity and elevated glucose concentrations (glucotoxicity), treatment with anakinra improved insulin sensitivity and glycemic control[36]. These proof of concept studies with anakinra demonstrate the role of IL-1 in the pathogenesis of defective insulin secretion and insulin resistance in type 2 diabetes. However, ana-

kinra requires daily injections and often causes adverse effects at the injection site. Humanized antibodies against IL-1□ have therefore been developed by multiple groups and tested in various diseases, including type 2 diabetes. The half-life of these antibodies is around 3 weeks, allowing for monthly or less-than-monthly dosing. Each of these antibodies has had beneficial effects in patients with type 2 diabetes. A single dose of the anti-IL-1□ antibody gevokizumab improved placebo-corrected glycated hemoglobin (a measure of blood glucose levels) by up to 0.9 % after 3 months. This single dose also enhanced insulin secretion and sensitivity, and reduced markers of systemic inflammation and of leukocyte activity (C-reactive protein and spontaneous and inducible pro-inflammatory cytokines)[38]. Two studies in patients with type 2 diabetes have been conducted with another anti-IL-1□ antibody, canakinumab. The first study used a single dose of antibody in individuals with impaired glucose tolerance or with well-controlled (glycated hemoglobin of around 7.0 %) type 2 diabetes[40]. Although the number of patients was small (27–33 per arm), a trend towards an improved insulin secretion rate was observed. The second study aimed to find the optimal dose of canakinumab needed to improve glucose control in patients with type 2 diabetes[39]. A 4-month course of monthly canakinumab injections resulted in a numerical reduction in placebo-corrected glycated hemoglobin of 0.2 %. This seemingly modest improvement in glycaemia can be explained by the low starting glycated hemoglobin; most patients reached the treatment target of 7.0 %. Finally, weekly injections of the anti-IL-1□ antibody LY2189102 for 12 weeks improved placebo-corrected glycated hemoglobin by 0.4 % and improved fasting and postprandial glycaemia and inflammatory biomarkers[41]. Importantly, similar to the original study using anakinra, long-lasting effects of IL-1 antagonism were observed after the end of treatment, with a placebo-corrected decrease in glycated hemoglobin of 0.6 % at week 24.

On the basis of these eight independent clinical studies, IL-1□ has the capacity to improve glucose metabolism in patients with diabetes. Importantly, IL-1 antagonism was well-tolerated with no evidence of drug-related adverse events, apart from reactions at the anakinra injection site.

Challenges

Several questions remain in the development of anti-inflammatory drugs for the treatment of type 2 diabetes. These include the magnitude of the effects, safety of the drug, cost of treatment, and whether anti-inflammatory drugs can be used concomitantly for other indications.

To assess the magnitude with which drugs decrease glycaemia it is important to consider the starting level of blood glucose. Several studies of anti-inflammatory drugs were conducted in patients with near-normal glycated hemoglobin levels, which limits the possibility to uncover the maximum glucose-lowering effect as these drugs will not drive insulin secretion to cause hypoglycaemia. By contrast, sulfonylureas and exogenous insulin are equipotent at all blood glucose levels. Furthermore, very few studies with anti-inflammatory agents have been conducted in drug-naive patients. Taking these factors into account, the observed effects with anti-inflammatory drugs are in the same range as the effects obtained with the dipeptidyl peptidase 4 inhibitors that are approved as hypoglycaemic agents: linagliptin decreased glycated haemoglobin by 0.2 % from a baseline of 7.7 %[42]; saxagliptin reduced placebo-corrected glycated haemoglobin by 0.3 % from a baseline of 8.0 %[43].

Type 2 diabetes is a slowly progressing chronic disease. Accordingly, the long-term safety of therapeutic agents is critical. Several anti-inflammatory drugs being evaluated for the treatment of diabetes are already in use for other indications, so some safety data are already available. For example, >100,000 patients with rheumatoid arthritis have been treated with anakinra. Infections were rarely reported, despite concomitant use of other immunosuppressive drugs. Of note, tempering the IL-1 system may even improve the healing of diabetic wounds[44]. This apparently surprising observation can be explained by the normalization of an overactive immune system. This theory remains speculative, and possible adverse effects will have to be balanced with therapeutic benefits.

As the number of people with diabetes increases, the disease will require an increasing proportion of health-care budgets. Therefore, the cost of

anti-diabetic drugs is a major issue. In low-income countries, diabetes care can cost up to 25 % of a family's income (http://www.who.int/mediacentre/factsheets/fs236/en/). However, the most expensive item in diabetes expenditures appears to be hospital admissions for the treatment of long-term complications, not anti-diabetic medications. These hospital costs could be decreased by more efficient anti-diabetic drugs. Furthermore, the effects of some anti-inflammatory agents (such as antibodies) last for several weeks, reducing the amount of required drug.

Individualized clinical translation

An increasing number of diseases seems to be caused or promoted by pathological activation of the immune system[45]. Some of them appear to be driven by molecular pathways that also affect metabolism. Novel therapeutic approaches based on pathways underlying the pathogenesis of the disease rather than on the manifestation of symptoms belonging to a specific clinical discipline could therefore be developed. In several cases this can already be implemented. For example, the role of IL-1□ is well-established in mediating acute gouty arthritis[46, 47] and IL-1□ antagonism is highly effective to treat this condition[48]. In the large number of patients suffering from both gout and type 2 diabetes, IL-1□ blockade may improve the manifestations of both dieases.

Future developments

The existing data support a role for inflammation in the pathogenesis of type 2 diabetes and anti-inflammatory drugs can improve glycaemia without the danger of hypoglycemia. Treatments addressing inflammation, the cause of the disease, could be used to prevent the progressive decrease in insulin secretion[34] and action[49, 50]. Although the adipose tissue and pancreas have been the mostly studied, in patients with type 2 diabetes, disease manifestation in the brain, liver, muscle, heart and periodontal tissues are also associated with signs of inflammation. Therefore treatment may benefit also these organs and improve multiple interconnected metabolic circuits. This interplay is also evident in animal models where the total body genetic or pharmacologic interventions have generate more consistent results compared to tissue specific genetic studies which may not resemble the real physiology.

However, several questions remain unanswered. The interruption of vicious cycles of IL-1□ auto-induction (and possibly of other mediators), and the long half-life of some drugs, particularly those that are antibody-based, means that some drugs could have long-lasting effects[33]. The optimal dose and treatment duration therefore need to be carefully considered. Thus, it is conceivable that after restoration of normoglycaemia, some patients may require a boost of anti-inflammatory drugs only a few times per year, during recurrent flares. Future genetic and biomarker studies may profile patients with type 2 diabetes to identify those responding best to a specific anti-inflammatory drug. Inflammation is also an important pathogenic pathway in the development of diabetic complications, including cardiovascular disease[51, 52]. On the basis of this observation, a phase III trial of an IL-1□ antagonist (canakinumab) has been initiated (http://www.clinicaltrials.gov/ct2/show/NCT01327846), to investigate the potential of this drug to protect patients from cardiovascular disease and to prevent or improve type 2 diabetes. Finally, some anti-inflammatory treatments (anti-IL-1□) seem to be more effective at improving insulin secretion, while others (anti-TNF□, salsalate) may primarily affect insulin-sensitive tissues, probably reflecting the different pathways involved in the immune response during the course of diabetes. Thus, by combining various anti-inflammatory drugs, broader and more efficacious therapeutic strategies could be developed. So judiciously adding or sequentially using these novel anti-diabetic treatments could provide a tailored solution to treat inflammation in patients with type 2 diabetes.

Table 1. Clinical studies using IL-1 antagonists to treat patients with type 2 diabetes

Mechanism	Drug	Treatment duration	Main findings*	Remarks/Limits	Source
IL-1 receptor blockade	Anakinra (Kineret)	13 weeks	HbA1c↓, leukocyte↓, CRP↓ insulin secretion↑	Dose not adapted to body weight	34
IL-1 receptor blockade	Anakinra (Kineret)	Follow up for 39 weeks	Sustained CRP↓, insulin secretion↑, insulin requirement↓	Follow up study of the one above (N Engl J Med. 356:1517-26; 2007)	33
IL-1 receptor blockade	Anakinra (Kineret)	4 weeks	insulin secretion↑	Prediabetic patients	35
IL-1β antagonsim	Single dose of anti-IL-1β antibody (gevokizumab)	13 weeks	HbA1c↓, CRP↓ insulin secretion↑	High basal HbA1c. Strong effects on gylcaemia	38
IL-1β antagonsim	Single dose of anti-IL-1β antibody (canakinumab)	4 weeks	insulin secretion↑CRP↓	Low basal HbA1c	40
IL-1β antagonsim	Anti-IL-1β antibody (canakinumab)	16 weeks	CRP↓, HbA1c↓ insulin secretion↑(not statistical significant).	Underpowered for low basal HbA1c	39
IL-1β antagonsim	Anti-IL-1β antibody (LY2189102)	12 weeks and follow up for 24 weeks	HbA1c↓, CRP↓ insulin secretion↑	Further improvement of HbA1c at week 24	41
IL-1 receptor blockade	Anakinra (Kineret)	1 week and follow up for 4 weeks	insulin sensitivity↑	Patients with type 1 diabetes and insulin resitance due to obesity and glucotocity.	36
IL-1 receptor blockade	Anakinra (Kineret)	4 weeks	insulin secretion↑ (1st phase insulin secretion improved)	Subjects with impaired glucose tolerance	37

HbA1c, glycated haemoglobin; IKK□, I□B kinase-□; NF-□B, nuclear factor-□B; CRP, C-reactive protein; FBG, fasting blood glucose. (Modified from Donath MY: Nature reviews Drug discovery 2014, 13:465–76.)

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EVOLUTIONÄREN GENOMIK

ZÜRICH, 14. NOVEMBER 2014

FÜR DEN STIFTUNGSRAT:

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BIOGRAPHY

Henrik Kaessmann has been a full professor at the Center for Integrative Genomics at the University of Lausanne since 2014 and Group Leader at the Swiss Institute of Bioinformatics since 2010. He received his PhD in evolutionary anthropology from the University of Leipzig in 2001 after working on the genetic diversity of humans and the great apes in the laboratory of Dr Svante Pääbo at the University of Munich and subsequently at the Max Planck Institute for Evolutionary Anthropology in Leipzig. For his postdoctoral training, he joined the lab of Dr Wen-Hsiung Li in the Department of Ecology and Evolution at the University of Chicago, where he worked on the origin of human genes and gene structures. In 2003, he joined the Center for Integrative Genomics at the University of Lausanne as an assistant professor, where he was then subsequently appointed as associate professor in 2007 at the age of 36.

His research focuses on the evolutionary analysis of mammalian genomes, with the aim to uncover molecular changes (mutations) that underlie phenotypic differences between species. For the purpose of this work, his lab combines state-of-the-art experimental technologies (such as high-throughput sequencing machines) and sophisticated bioinformatics approaches.

The success of the work of Henrik Kaessmann is reflected in several publications in leading journals such as Science (2004), Nature Genetics (2004 and 2009), PNAS (2006), Genome Research (2010 and 2013), PLoS Biology (2005, three in 2008, 2012) and Nature (2011 and two in 2014). His scientific excellence has also been recognised with the award of the Friedrich Miescher Prize of the Swiss Society of Biochemistry (2010), the EMBO Young Investigator Award (2005) and prestigious funding, such as the ERC Starting Grant (2009) and the ERC Consolidator Grant (2013). In 2014, he was elected to full EMBO membership and was also awarded the Jürg Tschopp Life Science Prize by the University of Lausanne as well as the Cloëtta Prize for medical research from the Professor Dr Max Cloëtta Foundation.

Henrik Kaessmann was born in 1971 in Germany and is a father of three children.

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THE EVOLUTION OF MAMMALIAN GENE EXPRESSION: DYNAMICS AND PHENOTYPIC IMPACT

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Summary

Evolutionary changes in gene expression, due to regulatory mutations, probably explain many or even most phenotypic differences between species. However, large-scale comparative gene expression analyses have only recently become possible, thanks to the advent of high-throughput RNA sequencing technologies, which allow accurate and sensitive assessments of transcript sequences and expression levels. Here I present an overview of the many new insights that the first generation of comparative transcriptome studies has provided into the functional evolution of mammalian genomes. Together with various large-scale genomic and epigenomic data, these studies have uncovered the dynamics of gene expression evolution across various biological dimensions, which include the different coding and non-coding gene types, mammalian lineages, organs, developmental stages, chromosomes and sexes. This work has also provided fascinating new evidence with respect to the regulatory foundation and phenotypic relevance of gene expression changes during mammalian evolution.

Introduction

A major goal in biology is to understand the molecular basis of phenotypic evolution, in particular that of humans and other mammals. Shared mammalian traits include lactation, hair, and relatively large brains with unique structures (e.g., the neocortex). In addition, individual species or lineages evolved distinct anatomical, physiological and behavioral characteristics, relating to differences in reproduction, life span, cognitive abilities and disease susceptibility. For example, humans have evolved particularly large and complex brains, even when compared to their closest evolutionary relatives, the chimpanzees, and also exhibit profound differences in disease susceptibility (e.g, chimpanzees do not develop AIDS upon HIV infection), life span (the maximum life span of a human is approximately twice that of a chimpanzee), and various, more obvious, anatomical differences relative to chimpanzees and other primates[1]. Examples of distinct (reproductive) features of the major mammalian lineages include the placenta of placental mammals, the elaborate lactation system of marsupials, and the intriguing combination of egg yolk nourishment and lactation of the young in monotreme mammals such as the platypus.

What are the genomic changes and molecular mechanisms underlying all of these phenotypic innovations? When and how did they occur? What is the nature of the associated selective pressures? Answers to these questions, which motivate our research, can be sought in the analysis of several types of genomic alterations. In fact, mutations that may underlie phenotypic innovation can be grouped into only two major classes. The first class consists of mutations that change the sequence and, consequently, the function of the final gene product (i.e., the protein or RNA). The second class encompasses mutations in regulatory sequences (e.g. in promoter regions) that affect transcription, post-transcriptional processing, translation, or transcript/protein degradation. But it should be noted that certain gene product sequence alterations that change the function of the protein (e.g., mutations in transcription factors[2]) may also affect gene regulation.

How do these mutations drive phenotypic evolution? Generally, both classes of mutations may contribute to the evolution of distinct tissue mor-

phologies if they affect developmental programs. The specific morphologies may, in turn, provide the basis for species- or lineage-specific physiology and behavior. However, in addition, mutations may also directly shape phenotypic properties of adult organs, without influencing developmental trajectories.

Thus, the question arises: which of the two classes of mutations contributed more to phenotypic evolution? This question has been debated ever since the late 1960ies[3-7]. The current hypothesis in the field is that regulatory mutations (i.e., mutations of the second class) should underlie most phenotypic innovations, because protein-coding mutations (i.e., mutations belonging to the first class) are expected to more often have deleterious consequences[6,7], given that they necessarily affect all tissues and developmental stages in which a gene is expressed (given that the genome sequence is the same across tissues), whereas regulatory changes can be spatially and temporally restricted. Also, coding sequence mutations may be too scarce to explain the sometimes profound phenotypic differences even between closely species[3] (e.g., humans and chimpanzees).

However, only with the rise of the genomic era in the past decade it has become possible to start to systematically explore the molecular basis of phenotypic evolution and thus to empirically address the hypothesis of a dominant role of regulatory mutations in phenotypic evolution. Direct comparisons of mammalian genome sequences, which are accumulating at an accelerating pace, have uncovered many amino acid substitutions[8] that were apparently driven by positive selection (i.e., natural selection that increases the rate of fixation of new favorable mutations in the population) and may thus be of phenotypic relevance. Sophisticated analyses have even revealed potentially adaptive promoter sequence alterations[9]. Importantly, the concomitant development of large-scale genomics technologies has generally not only facilitated genome-wide analyses of expression patterns and changes but also of underlying regulatory mechanisms. Thus, initial microarray-based expression comparisons between closely related mammals identified potential phenotypically relevant expression level changes and initial clues initial to the general evolutionary rules that dictate the evolution of tissue transcriptomes[10,11]. However, given that microarrays rely on hybridization of RNA/DNA to species-

specific probes, they do not lend themselves well for between-species comparisons. Consequently, the recent development of high-throughput sequencing technologies[12], which allow essentially unbiased qualitative and quantitative comparisons of gene expression and regulatory mechanisms between divergent species on a genome-wide scale, constituted a quantum leap in the evolutionary genomics field. Thus, gene expression evolution and its regulatory foundation can now be conveniently studied[12] using, in particular, approaches based on high-throughput RNA sequencing (RNA-seq) and chromatin immunoprecipitation coupled with sequencing (ChIP-seq).

In this review, I will discuss, in the context of earlier work, the intriguing observations and insights that these novel approaches already have provided into the patterns, dynamics and phenotypic implications of gene expression change in mammals and vertebrate outgroup species. I will round off my review by outlining potentially fruitful and/or important future research directions.

Different aspects of the transcriptome evolve at different rates

Protein-coding genes: evolution of overall expression levels. One major observation of evolutionary transcriptome comparisons is that overall expression levels of protein-coding genes evolve more slowly than most other transcribed parts of the genome studied so far. For example, protein-coding gene expression levels were shown to be overall similar in primates[11,13,14], likely due to negative (purifying) natural selection (i.e., selection that eliminates deleterious mutations in the population). Thus, expression differences between livers from human and chimpanzees are, on average, only 20 % higher than differences observed between livers from pairs of individuals from the same species[14]. A recent RNA-seq-based study for a range of organs from representative mammals and amniote outgroup species confirmed that gene expression level evolution is generally constrained. Thus, protein-coding gene expression divergence does not increase linearly with time, as would be expected under neutral evolution[15], but eventually saturates between divergent species such as human and chicken. Notably, even for these two species, expression levels are highly correlated (with correlation coefficients above 0.7 for so-

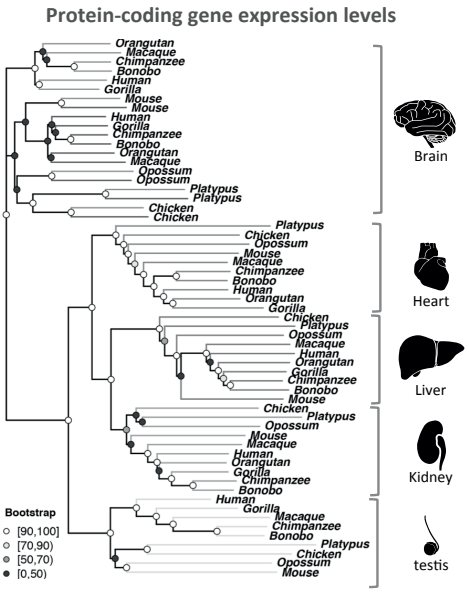

Figure 1. *The evolution of protein-coding gene expression levels in mammals. A mammalian gene expression phylogeny based on expression data[16] (constitutive exons) for six tissues from 9 representative mammals and one bird (chicken), used as an evolutionary outgroup. The Neighbour-joining tree displayed is based on pairwise expression level distance matrices (distances are based on 1 – rho, Spearman's correlation coefficient). The tree illustrates the organ-dominated clustering of gene expression level data from different species (see main text for details).*

matic organs). These observations suggest that conservation of core organ functions limits the divergence of protein-coding genes[16]. That is, similar expression levels for the same key subsets of genes in a given organ are required to sustain physiological organ functions across all mammals/amniotes. Thus, overall, different organs are more divergent than different amniotes (even the most distantly related) for the same organ in terms of protein-coding gene expression levels. Consequently, in phylogenies that are directly based on gene expression levels in the different organs and species, samples cluster together according to the organ from which they are derived[16] (Figure 1). Within each organ cluster, species generally group according to their phylogenetic relationships, reflecting the fact that regulatory changes accumulate over evolutionary time (until they eventually saturate – see above), such that more closely related species have more similar expression levels[16] (Figure 1). Altogether, these findings are consistent with the fact that mammalian/amniote organs originated in vertebrate ancestors long before the emergence and subsequent divergence of amniote lineages. Thus, a grouping of amniote species by

organs, which have common vertebrate origins and functions, in such expression analyses could, in principle, have been expected.

Protein-coding genes: evolution of alternative splicing. However, it turns out that divergence rates are much higher for other portions of the transcriptome than for protein-coding gene expression levels, leading to very different expression divergence patterns. The most rapidly evolving parts of the transcriptome investigated so far are those that result from alternative splicing events. Indeed, recent work revealed that alternative splicing evolves extremely rapidly, such that alternative splicing shows highly species-specific patterns[17,18]. The rapid evolution of alternative splicing is illustrated by a species-dominated pattern of clustering: exon skipping frequencies are more similar between different organs from the same species than between different species for a given organ[17,18] (Figure 2). Thus, for example, a human brain is more similar to a human liver than to a chimpanzee brain in terms of alternative splicing, in spite of the fact that these species are very closely related and brains and livers very likely have overall similar functions in both species (i.e., a human brain is functionally certainly more diverged from a human liver than from a chimpanzee brain). This pattern is thus exactly the inverse of that observed for protein-coding gene expression levels (Figure 1). Notably, the high species-specificity of alternative splicing was convincingly demonstrated to be driven by changes in *cis*-acting regulatory elements, based on the finding that a mouse model carrying a copy of human chromosome 21 shows human-specific exon skipping frequencies on the inserted chromosome (mouse-specific patterns would be expected if trans-acting regulatory factors were predominant[18]).

Noncoding genes. Assessments of the expression evolution of noncoding portions of the transcriptome have revealed both slowly and rapidly evolving categories of genes. MicroRNAs (miRNAs) seem to overall evolve slowly in terms of both DNA sequence[19] and expression[20]. Expression analyses thus reveal an organ-dominated clustering pattern that is reminiscent to that of protein-coding genes. Long noncoding RNAs (lncRNAs), however, show a rather rapid mode of expression evolution. LncRNA repertoires experience rapid turnover[20-22], and lncRNA sequences and expression levels tend to evolve rapidly[20,21] compared to those of protein-

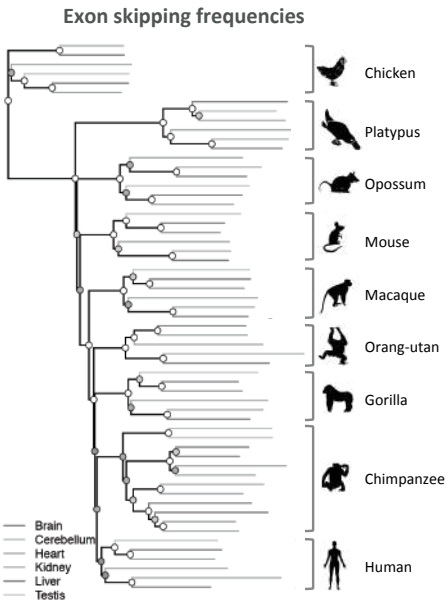

Figure 2. *The evolution of alternative splicing in mammals. A mammalian phylogeny based on alternative splicing (i.e., exon skipping) frequencies assessed from expression data[16] (constitutive exons) for six tissues from 9 representative mammals and one bird (chicken). The Neighbour-joining tree displayed is based on pairwise euclidean distances computed on the inclusion frequencies of orthologous skipped exons, for all organs. The tree illustrates the species-dominated clustering of alternative splicing data and thus constitutes the inverse pattern of that observed for global gene expression level data, as displayed in Figure 1 (see main text for details).*

coding genes. Nevertheless, hundreds of lncRNAs that are highly conserved at one or both levels have been identified[20,23]. It should be noted that the usually low abundance of lncRNA transcripts, which adds noise to expression measurements, may lead to overestimation of expression divergences[20]. Overall, comparisons of lncRNA expression levels reveal a mixed species/organ clustering, which likely reflects the presence of both fast-evolving and conserved organ-specific genes, but probably also the fact that lncRNA expression estimates are noisier than those for the more highly expressed protein-coding genes.

Rates of expression evolution are different in different mammalian lineages

Comparative transcriptome analyses have revealed that rates of expression change not only vary across the coding and noncoding transcriptome but also across mammalian lineages[10,11,16]. For example, gene expression levels evolve faster in primates (in particular in the human lineage) than

in rodents[16] (Figure 3). Similarly, novel alternatively spliced isoforms also accumulate at a higher rate in primates than in other mammalian lineages[17]. Thus, curiously, transcriptome evolution in primates is generally accelerated, in spite of the low mutation rate in this mammalian lineage[24] (e.g., rodents have approximately two to three times higher mutations rates), which implies a relatively small number of regulatory mutations in each generation.

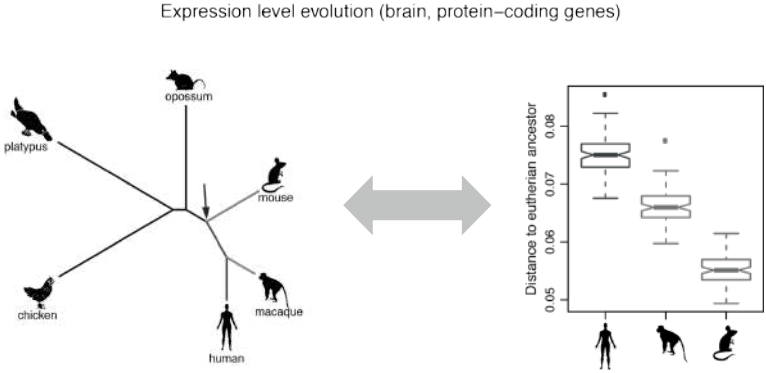

Figure 3. *Rates of gene expression evolution in different mammalian lineages. To the left: Neighbor-joining tree of protein-coding gene expression levels in the amniote brain. The tree was constructed based on pairwise distances between samples, estimated as 1-rho, where rho is Spearman's correlation coefficient. The arrow indicates the position of the ancestor of the three species. Expression data was taken from ref.[16]. To the right: Distance between each of the three placental mammal species and their common ancestor, in the expression tree displayed on the left. The boxplot represents the distribution observed with 100 bootstrap replicates, in which the same numbers of genes are resampled with replacement. The figures illustrate that gene expression evolution proceeds at a higher rate in primates and particular in humans compared to the rodent lineage due to the reduced efficiency of natural selection in primates (see main text for details).*

Given that the acceleration was observed for all organs studied so far[16], it is unlikely that it is explained by primate-specific adaptations. Furthermore, other lineages (e.g., monotremes) also show significantly higher rates of expression evolution than rodents[16]. It turns out that substantial differences in long-term effective population sizes among mammalian lineages explain the observed rate differences. For example, the long-

term effective population size of rodents[25] has been estimated to be at least ten times higher than that of humans[26,27] or chimpanzees[28]. Similarly, monotremes have had smaller long-term effective population sizes than rodents[29]. Importantly, lower effective population sizes imply less efficient natural selection. Thus, the accelerated transcriptome evolution in primates and monotremes relative to rodents is likely due to the accumulation of larger numbers of (slightly) deleterious regulatory mutations that cannot be purged by natural selection during evolution due to its inefficiency[16]. Evolutionary rate differences among mammalian lineages are thus consistent with a nearly neutral model of expression evolution, in which most mutations affecting gene expression are (slightly) deleterious[30,31]. Gene expression evolution is thus also consistent with the general notion that genetic drift is a primary force in molecular evolution, in particular in taxa with small effective population sizes[32].

Rates of expression change in different organs

In addition to cross-transcriptome and cross-lineage comparisons, expression rates have also been compared across a third dimension: organs. This work uncovered substantial rate differences among organs, likely reflecting the different selective pressures to which they are subjected. Thus, at one end of the evolutionary rate spectrum neural tissues stand out, with the overall lowest rates of gene expression divergence for the tissue examined so far[11,16,20,33] (Figure 4). This pattern reflects a genome-wide trend, as it holds true for both protein-coding[11,16,33] and lncRNA genes[20]. Notably, previous work also revealed that protein sequence divergence of brain-expressed genes also proceeds at a low rate[11,34]. These observations are surprising in view of the substantial remodeling of the size, structure, and cellular composition of the brain during evolution[16]. They are also notable when considering the difficulty in sampling and comparing corresponding brain regions across species[16], as these likely exaggerated actual biological expression differences. It was thus surmised that the brain has particularly sensitive and fine-tuned regulatory networks that are highly constrained during evolution. In this view, rapid remodeling of expression network components, for example through (developmental) expression changes of only a few key regulators[35] (e.g., miRNAs or transcription factors), which leave overall (adult)

transcriptomes unaltered, may have provided the basis for major phenotypic brain innovations – which undoubtedly took place (e.g., the sudden and pronounced increase of brain size and complexity in the human lineage[35]).

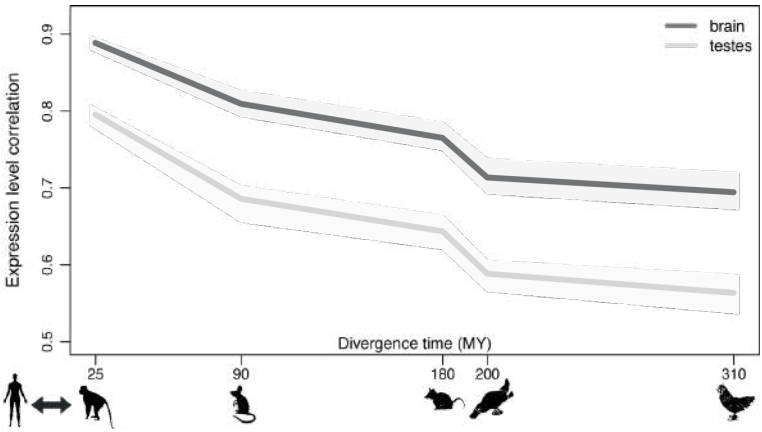

Figure 4. *Different rates of gene expression evolution in major mammalian organs. Pairwise Spearman's correlation coefficients between human and other species, as a function of the divergence time (in millions of years) between the two species, for brain and testis protein-coding gene expression levels. Expression data was taken from ref.[16]. The figure thus illustrates that expression levels evolve substantially more slowly in neural tissues than in the testes (see main text for details).*

While other somatic organs than the brain show intermediate rates of transcriptome change, the testis stands out at the other end of the spectrum, with an especially high rate of expression evolution[11,16,20] (Figure 4), consistent with rapid coding sequence evolution of testis genes[10,65]. There are likely two major reasons for this observation. First, the testis has been subject to strong positive selection throughout its evolution, which is likely associated with specific sex-related evolutionary pressures[36], in particular that of the co-called «sperm competition»; that is, the competitive process between spermatozoa of different males to fertilize the female egg. Second, purifying selection may generally be relaxed in the testis at the gene regulatory level. Indeed, transcription seems to overall be less tightly regulated and even partly «promiscuous» due to an overall per-

missive chromatin conformation (in particular during and just after meiosis) resulting from extensive repackaging of DNA during spermatogenesis[37].

Sex-related transcriptome evolution

Sex chromosomes represent the genomic hotspots of sex-related expression evolution. Recent work revealed that sex chromosomes emerged twice independently in mammals[38,39]. The original placental and marsupial (therian) sex chromosomes originated in the therian ancestor approximately 180 million years ago[39]. At about the same time, monotreme sex chromosomes[39] emerged (Figure 5). Notably, these two sex chromosomes are derived from different ancestral pairs of ordinary autosomes. The differentiation process of these sex chromosomes encompassed dramatic chromosome-wide remodeling of gene repertoires and expression patterns due to the emerging sex-related selective forces (Figure 5).

First, the specialization of the Y on sex determination and male functions, together with recombination arrests that weakened selection efficiency, entailed drastic losses of Y genes during mammalian evolution[39] (Figure 5). Several remaining Y genes evolved testis-specific expression patterns[39], consistent with the male-limited transmission of the Y and associated specialization on male functions. Strikingly, however, most Y genes apparently perform general regulatory functions (e.g., at the transcriptional and translation level) and maintained the ancestral ubiquitous expression patterns, although their expression levels overall decreased[39]. Altogether, these observations and other considerations (e.g., that regulatory genes are commonly dosage sensitive) led to the conclusion that most Y genes were initially preserved because of dosage constraints, in order to maintain (together with their X counterparts) the ancestral gene copy number. Thus, these Y genes contribute to proper functioning of male somatic tissues[39,40]. Notably, the functions in females are expected to be carried out by the corresponding two X copies in females. Consistent, with this dosage hypothesis, these genes escape X inactivation in females[39].

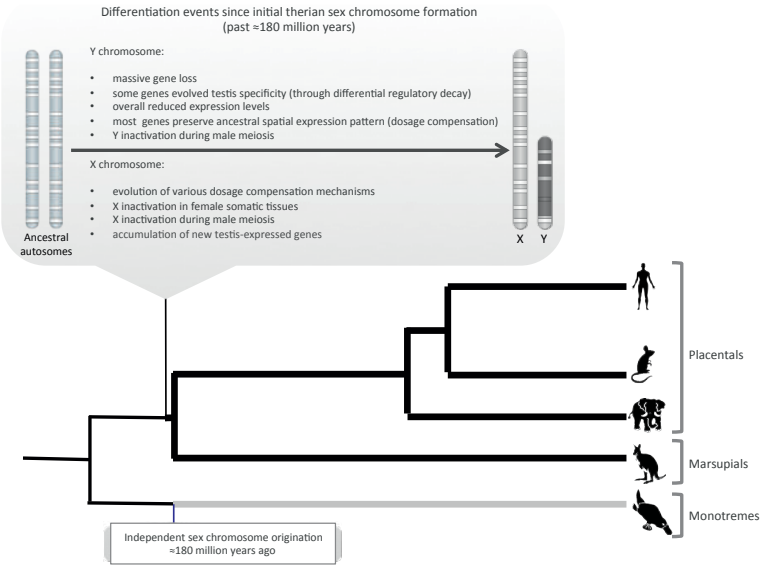

Figure 5. *Origins and functional evolution of mammalian sex chromosomes. The independent origins of sex chromosomes in the ancestor of therians (placentals and marsupials) and monotremes, and an overview of major gene content/expression remodeling events during therian sex chromosome evolution (see main text for details).*

However, this reasoning also raises the question of how the massive loss of all other genes from the Y was compensated. It is unlikely that among the hundreds of genes lost from the Y during sex chromosome differentiation there were no other dosage sensitive genes. The traditional and still prevailing hypothesis postulates that a two-fold upregulation of the single remaining X gene copies in males generally restored ancestral expression outputs[41,42]. It was further postulated that this upregulation was not specific to males and also affected females, which then would have twice too much expression output from the X. Common theory posits that this overexpression was, in turn, compensated by the by the well known process of female X chromosome inactivation. However, surprisingly, it was recently shown that the overall expression output of X-linked genes is only half that inferred for proto-sex chromosomes, at least in placental mammals[43,44] (marsupials do show signs of global upregulation of the

active X in several tissues[43,44]). Notably, it remains possible that individual X genes may nevertheless have become actively upregulated in placentals through specific mechanisms[43,45], although it has become clear that other mechanisms also contributed to X dosage compensation[43]. Furthermore, a number of genes may have been insensitive to dosage alterations altogether[43]. However, the reason underlying the evolution of chromosome-wide X inactivation in females remains unclear in view of the lack of an overall two-fold upregulation of the X in placentals.

Phenotypically relevant gene expression change

So far I have discussed global patterns of gene expression change and associated selective pressures across various biological dimensions. However, the ultimate goal in the evolutionary gene expression field is the identification of phenotypically relevant expression alterations. Specific approaches, developed to assess the selective pressures that have shaped gene expression patterns[13,14,16,46-48], have uncovered a number of lineage-specific expression changes of individual genes that may have been driven by positive selection. For example, comparisons among primates revealed an over-representation of transcription factors among potentially selectively-driven gene expression increases in the human lineage[13,49]. Other significant expression shifts in the human lineage include genes involved in metabolic pathways, consistent with the hypothesis that dietary changes may be associated with human-specific adaptations[49,50] and with previous reports of positive selection in the promoters of nutrition-related genes[9]. In most cases, the observed lineage-specific expression shifts are organ-specific[16,49]. Generally, across mammals, few lineage-specific expression shifts have been detected for the brain. The testis, on the other end, showed numerous expression shifts. Overall, these observations are consistent with highly differential selective pressures on gene expression in different organs[16] (see also above).

Given that genes commonly exert their functions together with other genes, concerted expression changes of distinct sets of functionally related genes during evolution are likely to be phenotypically relevant[16] (i.e., they are less likely to have been caused by genetic drift than expression changes of individual genes). Thus, a powerful approach to detect ex-

pression changes with a phenotypic impact may be the joint analysis of gene modules; that is, groups of genes with coherent expression patterns across a subset of samples, potentially including different species/organ/condition combinations[51]. This approach has revealed numerous modules of genes with highly conserved, organ- or tissue-specific expression[16,52,53] but also simultaneous lineage-specific expression shifts[16,54].

In a related approach, expression patterns are analyzed across multiple conditions (tissues, developmental stages, treatments etc.) and species to reconstruct an evolutionarily co-expression network[55]. Two genes are connected in this network if they show correlated expression levels in multiple species. Co-expression connections are enriched for functionally related genes[55] and thus can predict functions for previously uncharacterized genes, including lncRNAs[20]. Thus, this approach unveiled general functional properties of lncRNAs, such as that most of them likely act as negative regulators of gene expression, that many of them may have key roles in regulatory networks, and that lncRNAs are involved in key functional processes in various tissues[20] (e.g., spermatogenesis in the testis or synaptic transmission in the brain). More detailed scrutiny of individual genes in these networks uncovered intriguing individual gene expression shifts[20]. For example, a potential functional «partner» for the *H19* lncRNA was discovered. The spatial expression pattern of this lncRNA, termed *H19X,* a placenta-enriched X-linked lncRNA that acts as a miRNA precursor[20], significantly changed during evolution, from ancestral testis-specificity to placenta-predominant expression in placental mammals. This suggests that *H19X* contributed to the emergence and functional evolution of the placenta during mammalian evolution[20].

Regulatory basis of transcriptome evolution

Various insights into the underlying biological mechanisms underlying transcriptome evolution have recently emerged from intra- and inter-specific analyses of genome, epigenome and transcriptome variation. For example, genome-wide association studies in human populations have identified DNA sequence variants potentially underlying various molecular phenotypes, including gene expression, alternative splicing patterns, histone modifications or transcription factor binding patterns[56-58]. Interes-

ting examples for between-species regulatory changes that were detected based on genome sequence comparisons include human-specific alterations of promoter sequences, potentially driven by positive selection, for opioid hormone[59] genes and genes involved in neural development[9].

However, recent technological developments now enable more direct assessments of gene regulatory evolution. For example, cross-species ChIP-seq analyses have revealed that binding of the liver-specific transcription factors CEBPA and HNF4A is highly species-specific[60], contrary to the strong evolutionary conservation observed for the more general factor CTCF[61]. Comparative analyses of DNA methylation[62,63] and histone modification patterns[64] in primates also identified numerous lineage-specific changes of these epigenetic marks.

Outlook

The first wave of the new generation of transcriptome studies in mammals, facilitated by next generation sequencing technologies (in particular RNA-seq) have revealed intriguing commonalities and differences in evolutionary patterns for different parts of the transcriptome (protein-coding and noncoding gene expression levels and alternative splicing), mammalian lineages, chromosome types, cell types, organs and sexes.

However, the exploration of mammalian transcriptome evolution has only begun. First, little is known about the evolution of certain aspects of the transcriptome, such as untranslated regions of protein-coding genes, noncoding PIWI-interacting RNAs (piRNAs), or the recently discovered circular noncoding RNAs[65,66]. Second, with a few exceptions[35,67-69], most comparative transcriptome investigation have so far have centered around the analysis of adult organs. Thus, these studies have provided initial clues to the relevance of gene expression changes for the evolution of species- or lineage-specific organ physiologies. However, adult organ anatomies, which define physiological functions, are rooted in development. Hence, the bulk of phenotypically relevant expression change may occur during development. Future studies should thus seek to include developmental samples. Third, the use of samples representative of whole organs in hitherto existing studies is also sometimes potentially problematic due to

between-species differences in the cellular composition of tissues. Recent technological developments, such as the advent of sensitive single-cell RNA sequencing methods[70], will allow to resolve this limitation in future studies. Fourth, while considerable advances have been made regarding the investigation of regulatory changes underlying gene expression change, only few attempts have been made to study regulatory mechanisms and gene expression patterns at the same time. In particular, it will be important to investigate how changes in transcription factor binding patterns affect expression evolution, especially given the recent observations that most interactions between transcription factors and chromatin do not result in significant changes in the expression of putative target genes[71]. Notably, such studies face the complex task of identifying accurate regulator-target gene relationships, which have so far often relied on the simplifying notion that the closest gene to regulatory sequence is the target of regulation[72]. Future work will thus benefit from chromatin conformation capture techniques to more rigorously identify regulatory element-gene relationships[73]. Fifth, an important limitation of current gene expression comparisons is that they have mostly relied on comparisons at the transcriptome level. Given that expression regulation for protein-coding genes may also occur in the several layers that succeed transcription (e.g., translation, protein degradation), future studies should seek to also compare protein synthesis and actual protein abundance levels, in order to fully understand gene expression evolution and its phenotypic impact.

Finally, gene expression comparison can only identify candidates for potentially adaptive expression changes. The next and in many ways more challenging step is to perform detailed functional characterizations of detected expression shifts (e.g., through knockout or transgene experiments[74]), with the aim to actually demonstrate their phenotypic implications.

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