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STIFTUNG PROFESSOR DR. MAX CLOËTTA

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Prof. Dr. François Mach
«Inflammation is a Crucial Feature of Atherosclerosis and a Potential Target to Reduce Cadriovascular Events»

Prof. Dr. Nouria Hernandez
«Mechanisms of RNA Polymerase III Transcriptions in Human Cells»

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VORWORT

Prof. Max M. Burger
Präsident des Stiftungsrates

«Weshalb unternehmt ihr nicht mehr in der Schweiz, um den ‹Braindrain›, der nun Jahrzehnte anhält, langsam aber sicher zu unterbinden?» Dies fragte mich eine 37-jährige Schweizerin, ETH-Absolventin und Ressortchefin im Harvard-Rektorat, die ich vor einigen Wochen traf. Sie ist mit einem Amerikaner verheiratet, hat Kinder und liebäugelt wegen der politischen Lage in den Vereinigten Staaten von Zeit zu Zeit mit dem Gedanken, in die Schweiz zurückzukehren. Ihr Diplomleiter an der ETH empfahl ihr, für die Promotion ans Caltech zu gehen, fand aber keine Schweizer Finanzquelle für ein Doktorandenstudium im Ausland. Dank eines Stipendiums aus US-Quellen konnte sie dann aber doch ans Caltech gehen. Einige Jahre später nahm sie eine Offerte für eine Assistenzprofessur an der Harvard University an, nachdem drei Schweizer Universitäten nichts Vergleichbares offerieren konnten.

Ein zweites Beispiel: Ein 30-jähriger schweizerischer Psychiatrie-Assistent bildete sich in seiner Freizeit mit Informatik weiter und erhielt deshalb auch ein US-Stipendium für ein Neuroinformatik-Masterstudium an der Universität Boston. Drei Schweizer Kliniken und eine in Deutschland fanden keinen «Platz», um ihm bei der Rückkehr den klinischen Ausbildungsabschluss zu ermöglichen. Am McLean Hospital (Psychiatrische Uniklinik Harvard) fand er dann eine Assistenzprofessur und kombiniert seither Klinik und Informatik an einer kalifornischen Uniklinik.

Was lief in diesen Beispielen schief, wie in verschiedenen anderen? In beiden Fällen war es schwierig oder gar unmöglich, Schweizer Quellen zu finden, die den Start im Ausland garantierten. Nicht zuletzt deshalb gingen die Verbindungen mit Schweizer Spitälern und Universitäten verloren. Man kann sich in beiden Fällen fragen, ob bei gutem Willen und etwas Flexibilität nicht auch eine Schweizer Uniklinik eine vernünftige Gegenofferte hätte machen können.

Ich habe hier letztes Jahr darauf hingewiesen, dass eigentlich jede Stiftung die Aufgabe hat, die Nützlichkeit ihrer Arbeit kontinuierlich zu hinterfragen und zu überprüfen.

Wir begannen uns deshalb schon anlässlich des 30-Jahr-Jubiläums unserer Stiftung vor vier Jahren mit dieser Aufgabe auseinanderzusetzen und kamen zum Schluss, dass die Grundsatzfrage sich einfach so formulieren liesse: Bleiben wir beim letztlich bewährten Forschungsstellenprogramm, modifizieren wir es, oder gehen wir einen völlig neuen Weg?

Eine befriedigende Antwort auf diese Frage bedarf eines mehrstufigen Prozesses und einer Vernehmlassung unter Forschern. Bevor wir dieses Jahr nun den Prozess in Gang setzten, kam unser medizinischer Ausschuss zum Schluss, dass ein neues Förderungsprogramm unserer Stiftung die folgenden drei Kriterien erfüllen müsste:

1. Es müsste Pioniercharakter haben,
2. erfolgreich einen wichtigen Förderungsbedarf erfüllen und
3. Signalwirkung haben. Solche hatte auch schon unser Forschungsstellenprogramm, das den Nationalfonds zur Schaffung der START- und SCORE-Stipendien und später der Förderprofessuren inspirierte.

Bis jetzt hat unser Findungsprozess drei Stufen durchlaufen:
1. Das Sammeln von Vorschlägen erfahrener Forscher/innen aus den Gebieten der Biomedizin und der Klinik. Dabei wiesen wir ausdrücklich darauf hin, dass auch die ausgefallensten Ideen erwartet und ernsthaft diskutiert werden.
2. Ein zweitägiges Brainstorming unseres medizinischen Ausschusses zusammen mit vier Grundlagenforscher(inne)n und Kliniker(inne)n, unter ihnen ein ehemaliger Präsident und die derzeitige Präsidentin des Nationalen Wissenschaftsrates.
3. Mögliche Projekte wurden durch einen kleinen Ausschuss des Stiftungsrates aussortiert, modifiziert und in eine engere Wahl aufgenommen.

Vorgesehen ist nun eine eingehende Abwägung der Ideen durch den medizinischen Ausschuss und die Antragstellung an den Stiftungsrat, der aber erst im Laufe des nächsten Jahres entscheiden dürfte.

Entscheidungen sind keine gefallen. Zentral im Vordergrund steht die Förderung junger Spitzenleute, wobei nicht nur die biomedizinische, sondern auch die klinische Forschung von einem neuen Programm profitieren muss. Der Ausschuss denkt derzeit eher daran, das Forschungsstellen-Programm weiterzuführen und ein begrenztes, innovatives und realistisches neues Programm in einer längeren Pilotphase zu prüfen und – wenn erfolgreich – gegebenenfalls zu erweitern.

So wie die Stiftung möglicherweise nach langjähriger Tätigkeit von einem Programm Abschied nehmen dürfte, so heisst es leider auch Abschied nehmen von Menschen, die den Werdegang der Stiftung immer wieder mitbeeinflusst und begleitet haben. Am 12. Dezember 2006 verstarb nach langer Krankheit Professor Alfred Pletscher im 90. Altersjahr. Professor Pletscher war von 1980 bis 1993 Stiftungsrat und Mitglied des medizinischen Ausschusses und hat sich zeitlebens und nicht nur in unserer Stiftung für Innovation, Spitzenforschung und Grundlagenforschung eingesetzt, dies auch in einem anwendungsorientierten Umfeld, der Industrie. Am 1. August 2007 verstarb nach kurzer Krankheit Professor Henri Isliker. Er war von 1989 bis 1996 Stiftungsrat und Mitglied des medizinischen Ausschusses und hat ebenfalls nicht nur in der Stiftung die Unabhängigkeit von zukünftigen Spitzenforschern gefördert, sondern dieses Konzept auch am ISREC und der Universität Lausanne gegen Widerstand verwirklicht. Mit beiden haben wir für die Stiftung und deren Etablierung in der Forschungslandschaft Schweiz zwei ausserordentlich engagierte Kollegen verloren, die wir gerne in bester Erinnerung behalten.

Nun zu unsern diesjährigen Preisträgern:

Professor François Mach begab sich nach einer breiten wie auch soliden klinischen Ausbildung in Kardiologie in Genf für eine dreijährige Weiterbildung zu Peter Libby nach Boston. Dort führte seine Forschung ins Gebiet der Entstehung der Atherosklerose und bald zu Bahn brechenden Publikationen über die entzündliche Komponente der Arteriosklerose. Zurück in Genf folgten neue Erkenntnisse aus seiner eigenen Gruppe über immunsuppressive Effekte anti-atherosklerotischer Statin-Therapeutika, deren Bedeutung mittlerweile international

anerkannt ist und mit dem Pfizer-Preis und dem Prix Leenaards dokumentiert wurde. Hervorzuheben ist, dass Professor Machs wissenschaftliche Leistungen trotz seiner umfangreichen klinischen Tätigkeiten zustande kamen und der selten gewordene Begriff des international anerkannten «Physician Scientist» in vollem Umfang zutrifft.

Mehr darüber hören wir in der Laudatio von Professor Marco Baggiolini, Co-Direktor am Swiss National Supercomputing Center (CSCS) in Manno und langjähriges Mitglied unseres medizinischen Ausschusses und Stiftungsrates.

Frau Professor Hernandez besuchte in Genf das Gymnasium, erhielt ihr Diplom in Biologie von der Uni Genf und ist nun seit zwei Jahren wieder zurück in der Schweiz, als Direktorin des Centre Intégratif de Génomique der Uni Lausanne. Dazwischen liegt eine eindrückliche Reise durch Spitzenforschungsinstitutionen und steile Karrierestationen: Promotion in Heidelberg, Postdoc in Yale und Professorin am Cold Spring Harbor Laboratory. Ihre Bahn brechenden Beiträge zur Transkription von DNA in RNA und dem genauen Aufbau dieser Übersetzungsmaschine und deren Kontrolle führte zur Aufnahme als Investigator ins Howard Hughes Medical Institute. Einer unserer Gutachter bezeichnete Frau Hernandez als eine der feinsten, originellsten und produktivsten Molekularbiologinnen ihrer Generation.

Wir freuen uns auf die Laudatio von Frau Professor Elisabetta Ullu von der Yale University in New Haven, Departement Interne Medizin und Zellbiologie, Sektion Infektionskrankheiten.

Wie jedes Jahr möchte ich an dieser Stelle nicht nur meinen vier Kollegen vom medizinischen Ausschuss und den übrigen drei Mitgliedern des Stiftungsrates für ihren ehrenamtlichen Einsatz während des vergangenen Jahres herzlich danken, sondern auch Frau Brigitt Küttel und Frau Irène Thomann mit ihrem Team in unserer Geschäftstelle für den perfekten Ablauf der Preisverleihung und ihren erheblichen Einsatz durch das ganze Jahr hindurch.

LE PRIX CLOËTTA 2007
EST DÉCERNÉ À

MONSIEUR LE PROFESSEUR

FRANÇOIS MACH

NÉ EN 1961, DE GENÈVE,
DIRECTEUR DU SERVICE DE CARDIOLOGIE
DU DÉPARTEMENT DE MÉDECINE INTERNE
DE L'HÔPITAL UNIVERSITAIRE DE GENÈVE,
POUR SES REMARQUABLES TRAVAUX DANS LE DOMAINE
DE LA COMPRÉHENSION ET DU TRAITEMENT
DE L'ATHÉROTHROMBOSE VASCULAIRE.

ZURICH, LE 30 NOVEMBRE 2007

AU NOM DU CONSEIL DE FONDATION:

LE PRÉSIDENT

LE VICE-PRÉSIDENT

UN MEMBRE

Prof. Dr. François Mach

CURRICULUM VITAE

Name:	Mach
First Name:	François
Date of Birth:	25 September 1961
Citizenship:	Switzerland, Geneva
Marital status:	Married, 3 children

Education and Training

1982	Scientific Matura, Geneva, Switzerland
1989	Final Federal Examination of Medicine, Faculty of Medicine, University of Geneva, Switzerland
1989–1990	Clinical fellow, Internal Medicine, Hospital of Aigle VD, Switzerland
1990–1993	Clinical fellow, Internal Medicine, Geneva University Hospital, Geneva, Switzerland
1993	Senior fellow, Internal Medicine, Geneva University Hospital, Geneva, Switzerland
1993–1995	Clinical fellow, Cardiology Division, Geneva University Hospital, Geneva, Switzerland
1995–1998	Research Fellow, Vascular Medicine and Atherosclerosis Unit, Department of Medicine, Division of Cardiovascular, Brigham and Women's Hospital, Boston, USA

1999–2005	Program SCORE A, SNF Assistant Professor, Principal Investigator, Division of Cardiology, Geneva University Hospital, Geneva Faculty of Medicine, Geneva, Switzerland
2006–	Associate Professor, Geneva Faculty of Medicine, Cardiology Division, Geneva University Hospital, Geneva, Switzerland

Academic Appointments

1994	Doctoral Thesis, Geneva Faculty of Medicine, Geneva, Switzerland
1995	Board-certified Internal Medicine FMH (Swiss Medical Association)
1999	Board-certified Cardiology FMH (Swiss Medical Association)
2001	Privat Docent, Geneva Faculty of Medicine, Geneva, Switzerland
2006	Full professorship, Geneva Faculty of Medicine, Head of Cardiology, Cardiology Division, Geneva University Hospital, Geneva, Switzerland

Awards and Prizes

1984	Crew member of the sailing boat «UBS Switzerland» winner of the race around the world in 1984–1985
1999	Prize of the Swiss Vascular Biology meeting
2000	Prize of the Swiss Society of Cardiology

2000	Prize of the Leenaards Foundation
2002	Pfizer Research Prize
2003	Prize of the Swiss Society of Cardiology (Dr. B. Kwak from the laboratory)
2005	Prize of the Swiss Society of Cardiology (Dr. S. Steffens from the laboratory)
2007	Prize Prof. Dr. Max Cloëtta

Memberships and Committees

Swiss Society of Cardiology
Swiss Vascular Biology Working Group
Swiss Atherosclerosis and Lipids
European Society of Cardiology
Councillor of the European Society of Clinical Investigation
European Vascular Genomic Network
International Vascular Biology Organisation
Ethical Commission, Geneva University Hospital

KEY PUBLICATIONS

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3. Mach F., Schönbeck U., Sukhova G.K., Atkinson E., Libby P. Reduction of atherosclerosis in mice by inhibition of CD40 signaling. *Nature* 1998 394:200–203.

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5. Kwak B., Mulhaupt F., Myit S., Mach F. Statins (HMG-CoA reductase inhibitors) as a novel type of immunosuppressor. *Nat. Med.* 2000 6:1399–1402.

6. Veillard N., Kwak B., Pelli G., Mulhaupt F., James R.W, Proudfoot A.E.I., Mach F. Antagonist of RANTES receptors reduces atherosclerotic plaque formation in mice. *Circ. Res.* 2004 94:253–261.

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9. Veillard N.R., Steffens S., Pelli G., Kwak B.R., Gerard C., Lu B., Charo I.F., Mach F. Differential influence of the chemokine receptors CCR2 and CXCR3 in the development of atherosclerosis in vivo. *Circulation* 2005 112:870–878.

10. Steffens S., Burger F., Pelli G., Dean Y., Elson G., Kosco-Vilbois M., Chatenoud L., Mach F. Short-term treatment with CD3 antibody reduces the development and progression of atherosclerosis in mice through the induction of FoxP3-expressing regulatory T cells. *Circulation* 2006 114:1977–84.

INFLAMMATION IS A CRUCIAL FEATURE OF ATHEROSCLEROSIS AND A POTENTIAL TARGET TO REDUCE CARDIOVASCULAR EVENTS

François Mach

Summary

Atherosclerosis, and its devastating complications cerebral and myocardial infarction and gangrene of the extremities, is the leading cause of death. Atherogenesis in humans develops over many years, often reckoned in decades. Early lesion formation may even occur in adolescence. Lesion progression depends on genetic make-up, gender and certain well-recognized risk factor as well as a number of non-traditional risk factor that are currently the subject of intense investigation.

Our concepts of atherogenesis have evolved from vague ideas of inevitable degeneration to a much better defined scenario of molecular and cellular events. As we enhance our understanding of its fundamental mechanism, we can begin to approach atherogenesis as a modifiable rather than ineluctable process. Recently, inflammatory and immunological mechanisms have been increasingly implicated in the pathogenesis of this disease. Postulates for the involvement of innate and adaptive immunity with cellular as well as humoral components have met with considerable experimental support. It is now well recognized that atherosclerotic lesions contain activated, immunocompetent cells, including T lymphocytes and monocyte/macrophages. Inflammatory and/or immune mechanisms appear to be particularly active when plaques are activated and rupture and they may therefore cause acute coronary syndromes or stroke. Increasing knowledge of the basic mechanisms enables us to understand how current therapies for atherosclerosis may act. Insights derived from recent scientific advances should aid the discovery of new therapeutic targets that would stimulate development of novel treatment. Such new treatments could further reduce the considerable burden of morbidity and mortality due to this

modern scourge, and reduce reliance on costly technologies that address the symptoms rather than the cause of atherosclerosis. Eventually, mastery of the cell and molecular biology of atherosclerosis may permit development of novel strategies for mitigating this prevalent disease. Our research group has produced several evidences to shown new mechanism of immune cell cross-talk and activation. In this review I will describe some anti-inflammatory agents capable reducing these inflammatory processes and atherosclerosis.

Introduction

Health trends in the next 25 years will be determined by the ageing of the world's population, the decline in age-specific mortality rates from communicable, maternal, perinatal, and nutritional disorders, the spread of HIV, and the increase in tobacco-related mortality and disability. Today, ischemic heart disease is the leading cause of death in developed countries with more than 3 million death/year, followed by stroke (1.6 million) and lung cancer (0.7 million) [1]. By 2020, based on current trends, ischemic disease will be the leading cause of disease burden worldwide, followed by unipolar major depression, road traffic accidents, stroke and chronic obstructive lung disease. For worldwide ischeamic disease only, the number of Disability-Adjusted Life Years or DALYs estimated for 2020 is about 82.3 millions per year [2]. Thus, despite changes in lifestyle and the use of new pharmacological approaches, atherosclerosis and its devastating clinical complications such as ischemia and infarction of the heart, the brain and other vital organs, ruptured aortic aneurysm and peripheral vascular insufficiency, continue to account for the majority of mortality and morbidity in the adult population of industrialized countries, and would be so worldwide by 2020 [3].

Atherosclerosis is a progressive disease process that generally begins in childhood and has clinical manifestations in middle to late adulthood. Atherosclerosis focally affects the aorta, carotid, coronary, iliac and femoral arteries. This disease is characterized by lesions (called atheroma), localized in the intima of the vessel wall. From the initial phases

of leukocyte recruitment, to eventual rupture of the vulnerable atherosclerotic plaque, inflammatory mediators appear to play a key role in the pathogenesis of atherosclerosis [4]. Thus, atherosclerosis is not any longer considered to be a degenerative process because of the accumulation of lipid and necrotic debris in the advanced lesions. Indeed, already in 1856 Virchow proposed that "A form of low-grade injury to the artery wall resulted in a type of inflammatory insudation, which in turn caused increased passage and accumulation of plasma constituents in the intima of the artery"[5]. Three fundamental biological processes generate atherosclerotic lesions: 1) LDL-cholesterol infiltration and activation within the intima of arteries; 2) endothelial activation and dysfunction, with adhesion molecule expression; 3) leukocyte recruitment from the blood stream with the consequent production of pro-inflammatory cytokines, chemokines and proteases, responsible for the maintaining of these inflammatory process within the vessel wall. These soluble mediators induce also the proliferation on smooth muscle cells and the production of acute phase reactants by the liver [6]. This complex process induces the developing of a systemic pro-inflammatory state in which different soluble factors and cellular players are involved. Accumulating evidence suggests that inflammatory processes play a fundamental role in each of these stages in atherogenesis. Although the first event of atherogenetic cascade remains unknown, the inflammatory processes have to be considered as key components of the developing of the disease and promising targets for novel and more selective treatments. Therefore, the discovery of new molecular mechan-isms, which could be contrasted by novel therapeutic strategies, represents an important possibility for humans to mitigate atherosclerosis. In this regard, the development of murine models of atherosclerosis has revolutionized the approach to evaluating potential roles of specific factors in lesion development. These models are based on targeted disruption of the low-density lipoprotein (LDL) receptor or apolipoprotein E (apoE) genes [7]. Feeding of these knock out mice with cholesterolrich diet results in massive hypercholesterolemia and, thus, to atherosclerosis development. The implication of various inflammatory mediators in atherosclerosis has been clarified by crossing these animals with mice that overexpress or lack possible candidate genes.

My main research field was focused on leukocyte recruitment to inflammatory sites and inflammatory cell activation. Then, I identified promising therapeutic strategies (statins, anti-chemokines and cannabinoids) to reduce these inflammatory processes and thus the progression of atherosclerosis.

Inflammation

Inflammation is a protective reaction against a variety of exogenous (microbial, chemical, physical) or endogenous (immunological, neurological) disturbances, which is characterized by the accumulation of specific subsets of leukocytes to sites of infection or tissue damage, and their subsequent activation [8]. The attraction of leukocytes to tissues is essential for inflammation and the host response to infection [9]. This migration is a directional, nonrandom and selective process. The process of leukocyte trafficking manifests itself as inflammation with four classic cardinal signs: redness, swelling, heat and pain. In order to recruit leukocytes, the capillary blood flow and the vascular permeability are increased. This allows for enhanced migration of the leukocytes through the vascular endothelium, which is the boundary between the capillaries and the tissue, towards the site of inflammation. Depending on the cause, inflammation can resolve rapidly or develop into a complex process involving different leukocytes as well as endothelial and mesenchymal cells. When an infection or a lesion appears, the organism acts as quickly as possible in order to get rid of the injury. Among the first immune cells to arrive at the lesional site are neutrophils, which initiate a rapid, nonspecific phagocytic response [10, 11]. These cells produce toxic substances including proteases and oxygenic radicals that suppress the pathogen quickly but non-specifically. Whilst this process is efficient, a more specific antigenic recognition mechanism has evolved. In the specific antigen recognition process, antigen-presenting cells migrate to the site where antigen is present, followed by specific subsets of T and B lymphocytes [12]. The combination and activation of leukocytes generates the antigen-specific immune response, which results in the production of appropriate antibodies and activation of cytotoxic T lymphocytes [8].

There are two classes of inflammation: acute inflammation, which is of short duration and is characteristically accompanied by plasma fluid exudates and neutrophils accumulation; and chronic inflammation which involves other leukocyte types such as monocytes/macrophages, T cells, eosinophils, basophils, mast cells and dendritic cells. This class of inflammation is of longer duration and is characterized by dense cellular infiltrates. Emerging evidence supports involvement an implication of chronic inflammation as the crucial cornerstone of atherogenesis [13–17].

Atherosclerosis and inflammation

A role for inflammation has become well established over the past decade or more in theories describing the atherosclerotic disease process. From a pathological viewpoint, all stages, ie, initiation, growth, and complication of the atherosclerotic plaque might be considered to be an inflammatory response to injury. In a variety of animal models of atherosclerosis, signs of inflammation occur hand-in-hand with incipient lipid accumulation in the artery wall. For example, blood leukocytes, mediators of host defenses and inflammation, localize in the earliest lesions of atherosclerosis, not only in experimental animals but in humans as well. The basic science of inflammation biology applied to atherosclerosis has afforded considerable new insight into the mechanisms underlying this recruitment of leukocytes. The normal endothelium does not in general support binding of white blood cells. However, early after initiation of an atherogenic diet, arterial endothelial cells begin to express on their surface selective adhesion molecules that bind to various classes of leukocytes. Interestingly, the foci of increased adhesion molecule expression overlap with sites in the arterial tree particularly prone to develop atheroma. Considerable evidence suggests that impaired endogenous atheroprotective mechanisms occur at branch points in arteries, where the endothelial cells experience disturbed flow. For example, absence of normal laminar shear stress may reduce local production of endothelium-derived NO. This endogenous vasodilator molecule also has anti-inflammatory properties [18]. In addition to inhibiting natural protective mechanisms, disturbed

flow can augment the production of certain leukocyte adhesion molecules [19]. Augmented wall stresses may also promote the production by arterial smooth muscle cells of proteoglycans that can bind and retain lipoprotein particles, facilitating their oxidative modification and thus promoting an inflammatory response at sites of lesion formation.

Once adherent to the endothelium, monocytes and T lymphocytes penetrate into the intima. Chemoattractant molecules appear to be responsible for the direct migration of monocytes and T lymphocytes into the intima at sites of lesion formation [20–23]. Once resident in the arterial wall, the blood-derived inflammatory cells participate in and perpetuate a local inflammatory response. The macrophages express scavenger receptors for modified lipoproteins, permitting them to ingest lipid and become foam cells. Several pro-inflammatory mediators, such as macrophage colony-stimulating factor (M-CSF) contribute to the differentiation of circulating monocytes into the macrophage foam cell [24]. T lymphocytes likewise encounter signals that cause them to elaborate inflammatory cytokines, such as interferon-γ, interleukins, or tumor necrosis facto-α, which in turn can stimulate macrophages as well as vascular endothelial cells and SMCs [25]. Inflammatory processes not only promote initiation and evolution of atheroma, but also contribute decisively to precipitating acute thrombotic complications of atheroma. Most coronary arterial thrombi that cause fatal acute myocardial infarction arise because of a physical disruption of the atherosclerotic plaque. The activated macrophage abundant in atheroma can produce proteolytic enzymes capable of degrading the collagen that lends strength to the plaque's protective fibrous cap, rendering that cap thin, weak, and susceptible to rupture. Interferon arising from the activated T lymphocytes in the plaque can halt collagen synthesis by SMCs, limiting its capacity to renew the collagen that reinforces the plaque [8]. Macrophages also produce tissue factor, the major procoagulant and trigger to thrombosis found in plaques. Inflammatory mediators regulate tissue factor expression by plaque macrophages, demonstrating an essential link between arterial inflammation and thrombosis [14–16].

Anti-inflammatory effects on atherogenesis
CD40

More than a decade ago, discovery of the B lymphocyte receptor CD40, which mediates B cell activation, proliferation and survival when engaged by antibodies, initiated a search for its respective native ligand. Due to the observation that interaction with T lymphocytes mimics the process observed in B lymphocytes after engagement of CD40 by an activating antibody, several groups independently identified the CD40 ligand (also referred to as gp39, TRAP, or TBAM), recently renamed CD154, as the native ligand [26–28]. CD154 was characterized as an integral membrane protein restricted to activate CD4+ helper T lymphocytes. Subsequent studies established that the interaction of CD154 with its receptor CD40 is essential for appropriate thymus-dependent humoral immune response [29–31]. The fundamental role for CD40/CD154 receptor-ligand dyad in these responses was further established by the demonstration that mutations in the gene encoding for the ligand result in the X-linked immunodeficiency hyper IgM syndrome, which is characterized by drastic or complete inhibition of the T lymphocyte-helps humoral immune response [32, 33]. Studies of CD40- and CD154-deficient mice further outlined the essential function for this receptor-ligand dyad in secondary immune responses. However, it has become evident in recent years that both CD154 and CD40 are expressed on other leukocytes and, even more interestingly, on non-hematopoetic cell types as well [34]. The discovery of a broad distribution pattern naturally implied the potential importance of CD40/CD154 interactions in processes other than originally consider-ed. Indeed, recent findings revealed elevation of CD40 and CD154 in chronic inflammatory diseases, such as rheumatoid arthritis [35], systemic lupus erythematosus [36], multiple sclerosis [37], and graft-versus-host disease [38, 40]. This suggested to us to study the implication of CD40-CD40 ligand interaction in inflammatory processes involving leukocytes and vascular cells and governing atherosclerotic processes. We first demonstrated that CD40 and CD154 were highly expressed (most predominantly in the shoulder region of the plaque, the border between the lesion and the unaffected portion of the artery) by atheroma-associated cells in tissue-section obtained from of human carotid atheroma [41].

Then, we showed that, by inducing the expression of matrix-degrading proteinases and of tissue factor procoagulant, CD40 signalling in macrophages may contribute to the triggering of acute coronary events [42]. Furthermore, also smooth muscle cells are activ-ated by this system in an inflammatory microenvironment of atherosclerotic plaques [43]. Also T lymphocytes are activated through CD40 triggering [44]. The most important evidence of an involvement of this interaction in atherosclerotic process was strongly support by reduction of atherosclerosis progression in mice treated with an antibody blocking CD154 signalling [45]. Therefore, we observed that CD40-CD40 ligand interaction is crucial for several events in atherosclerotic processes.

Chemokines

Chemokines were first identified as a family of chemoattractant cytokines, over 10 years ago [46]. Chemokines constitute a large family of small proteins (8-10 kDa) that are involved in both the basal leukocyte trafficking and the activation and recruitment of specific cell populations during disease. Chemokines have a broad spectrum of biological activities [47]. To date, these proteins have been shown to be implicated in a wide range of immune inflammatory responses:
By 2006, the use of either conventional cloning techniques or signal sequence trapping methods brought the number of human chemokine sequences to around 60, most of them identified in past few years. With this high number of distinct chemokines known, the extent of complexity in the chemokine superfamily is unrivaled within the field of cytokines. If the estimate of 100,000 for the total number of distinct human genes which are transcribed into mRNAs (and ultimately translated into proteins) is accurate, then it is likely that the entire number of cDNA fragments characterized to date represent probably only 25–35% of the total. On this basis, it is possible that the complete number of chemokines, when known, could exceed 100 [48].

The chemokines act through receptors belonging to a superfamily that span the membrane seven times [49–51]. The number of chemokine receptors has recently increased significantly. As there are so many

ligands with apparently similar chemoattractant properties, a highly active field of research has been to try to identify their respective receptors. The explosion in the number of ligands identified has meant that many orphan receptor sequences have been finally paired up with at least one cognate ligand.

Due to the growing evidence that inflammatory cells migrating from the circulation to the vascular wall are key players during atherogenesis, there are increasing reports demonstrating expression and implication of chemokines and their receptors in the atherosclerosis process [52]. Few years ago, the chemokine MCP-1 and IL-8 has been detected within human and animal atherosclerotic lesions, expressed by lesional macrophages-derived foam cells and by endothelial cells or SMCs at several different stage of the disease [53]. Both of these chemokines were not present in normal artery. Then, the chemokines MCP-4 and RANTES were also identify within atherosclerotic plaques [54]. In the same time, the chemokines receptors CCR2 and CXCR1, were also identified at the surface of monocyte-macrophages within lesions. But the strong evidence that chemokines and their receptors play important role in atherogenesis came in 1998 with two reports using animal model to block the CCR2-MCP-1 pathway. In the first study, the investigators generated a CCR2 knock-out (-/-) mice, which they then crossed to ApoE-/- mice, a well-known and documented mice model of atherosclerosis. Compared to ApoE-/-mice, the CCR2-/- / ApoE-/- present an overall decrease in atherosclerotic lesion size and fewer macrophages were noted in the aortas, without any effect on cholesterol plasma levels [55].

Despite these increasing evidence for involvement of T lymphocytes in atherogenesis, the mechanism of T lymphocyte recruitment within the vascular atherosclerotic lesions remains incompletely defined. In this prospective, we studied the expression of the three IFNγ-inducible CXC chemokines IP-10, Mig and I-TAC, known to exert potent chemotaxis on activated-Th1 lymphocyte in other inflammatory dise-ases such as psoriasis or sarcoidosis [56]. All three chemokines signal through a common receptor, CXCR3, expressed by activated-Th1 lymphocyte, but not by monocytes or neutrophils. Using immunohistochem-istry and Western

blot techniques we were able to demonstrate a differential expression of IP-10, Mig and I-TAC by atheroma associated cells [57]. Interestingly, we found a high expression of the receptor CXCR3 by all T lymphocytes within human atherosclerotic lesions. In vitro experiments showed that the pro-inflammatory cytokines TNFα and IL-1β, as well as CD40 ligand potentate IP-10 expression from IFNγ-stimulated endothelial cells. Moreover, nitric oxide (NO) treatment decreased IFNγ induction of IP-10. These findings suggest that the differential expression of IP-10, Mig and I-TAC by atheroma associated cells plays a role in the recruitment and retention of activated T lymphocytes observed within vascular wall lesion during atherogenesis. We also showed that blocking chemokine signalling in vivo through deletion of the chemokine receptors CCR2 and CXCR3 has differential effects during atherogenesis with particular consequences for the regulatory T lymphocytes during early atherogenesis [58]. On the basis of these evidences, we have also investigated the role of other chemokines on atherosclerotic plaque development, showing a crucial role for CCR5 (Fig. 3) [59]. Furthermore, we were able to demonstrate for the first time that chronic treatment with a chemokine receptor antagonist (Met-RANTES) limits the progression of atherosclerosis in vivo [60].

CRP

Recent clinical trials showed that C-reactive protein (CRP) is a powerful independent predictor of future cardiovascular events [61]. CRP is also the best physiological marker for measuring inflammation, the occult killer in cardiovascular disease. CRP, the major acute-phase reactant in humans, is mainly produced by hepatocytes in response to interleukin-6 (IL-6) and is then secreted into systemic circulation. Recent studies reported that, besides its predictive role in determining cardiovascular risk, CRP could exert a direct pro-atherogenic role. Indeed, it has been shown that CRP accelerates the progression of atherosclerosis in Apolipoprotein E-deficient mice [64]. Evidence for the pro-atherogenic role of CRP is further provided by in vitro studies reporting that CRP modulates the activity and expression of multiple factors implicated in atherogenesis. CRP downregulates endothelial

nitric oxide synthase (eNOS), resulting in decreased release of NO, and thus facilitation of endothelial cells apoptosis and inhibition of angiogenesis. In addition, CRP stimulates the production of the vasoconstrictor endothelin-1 (ET-1) and the inflammatory marker IL-6 by endothelial cells [63]. Furthermore, CRP increases the expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin and monocyte chemoattractant protein-1 (MCP-1), resulting in enhanced leukocyte transmigration [64].

The statin connection

In primary and secondary prevention, the lipid-lowering drug statins (HMG-CoA reductase inhibitor) have shown great efficacy in reducing cardiovascular events and deaths. Since the results of the Scandinavian Simvastatin Survival Study (4S) were first reported over 10 years ago, many other trials have corroborated the beneficial effects of this class of drugs [65]. Some results of these trials indicate that statins may have anti-inflammatory effects. In 2005, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial clearly demonstrated that CRP is a marker of CV risk in primary and secondary prevention [66]. The PROVE-IT investigators also showed that some statins might have greater power to reduce CRP than others. In this trial, atorvastatin, 80 mg/day, reduced CRP significantly more than pravastatin, 40 mg/day, within the remarkably short interval of 30 days.

Pleiotropic effects of statins target CRP

There is no doubt that statins have lipid-lowering effects, but these agents also appear to have pleiotropic effects (beyond their lipid lowering properties). We recently demonstrated for the first time that statins regulate IL-6-induced CRP expression in human hepatocytes, its site of production (Figure 1) [67]. This reduction in CRP expression occurs both at the protein and the mRNA level, indicating that statins exert their effect at the transcriptional level. In our in vitro model, statins were used at doses corresponding to those measured in human plasma (Figure 1). We observed that, similar to the results in humans, atorvastatin seems to be the most potent inhibitor of CRP release. Although numerous clinical studies have reported that statins lower plasma levels

of CRP, it is the first study showing a direct effect of statins on IL-6-induced CRP expression in hepatocytes. In our study, we also show that the statin-mediated reduction of CRP release can be mimicked by GGTI (geranylgeranyl transferase inhibitors). Thus, it seems that the effect of statins on CRP release occurs via the inhibition of protein geranylgeranylation.

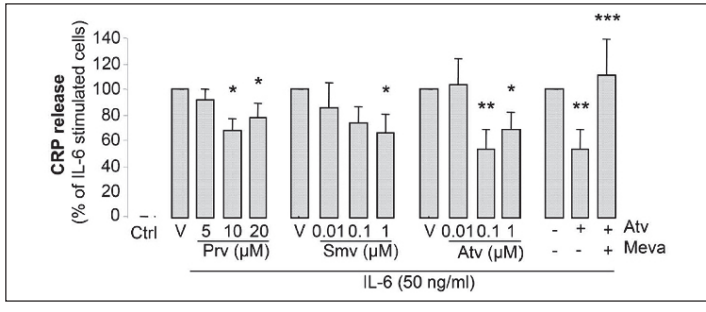

Figure 1
Statins reduce IL-6-induced CRP in hepatocytes.
*CRP release measured by ELISA in supernatants of hepatocytes cultured for 24 hours in normal media (Ctrl=control); activated by 50 ng/mL IL-6 alone (V=vehicle of statin); or in the presence of pravastatin (Prv 5, 10, and 20 μmol/L); simvastatin (Smv 0.01, 0.1, and 1 μmol/L); atorvastatin (Atv 0.01, 0.1, and 1 μmol/L), or 0.1 μmol/L atorvastatin; and 400 μmol/L L-mevalonate (Meva). *P<0.05 vs IL-6; **P<0.001 vs IL-6; ***P<0.05 vs IL-6+Atv. [67].*

In our investigations we also showed that statin pretreatment significantly reduced STAT3 phosphorylation on serine, but not on tyrosine residues. The signaling pathways leading to STAT3 phosphorylation are well known and differ among tyrosine or serine residues. In the first case, the tyrosine phosphorylation is mediated by the tyrosine kinase activity of the stimulated IL-6 receptor complex (IL-6Rα/gp130/JAK). In the other case, recent reports indicate that the serine phosphorylation is mediated by protein kinase C-delta, which in turn is activated by a signal transduction pathway consisting of Vav, Rac-1, MEKK and SEK-1. In our study, we have shown that statins reduce IL-6-induced CRP expression *via* the inhibition of protein geranylgeranylation. STAT3 is known to be regulated by Rac-1, a member of the Rho family, which needs to be geranylgeranylated to activate downstream

cascade. In conclusion, we hypothesize that, by suppressing the geranylgeranylation of Rac-1 in hepatocytes, statins reduce IL-6-induced phosphorylation of STAT3, thus resulting in reduced CRP expression (Figure 2). Such direct anti-inflammatory consequences may improve the understanding of the clinical effects of statins on cardio-vascular events and mortality.

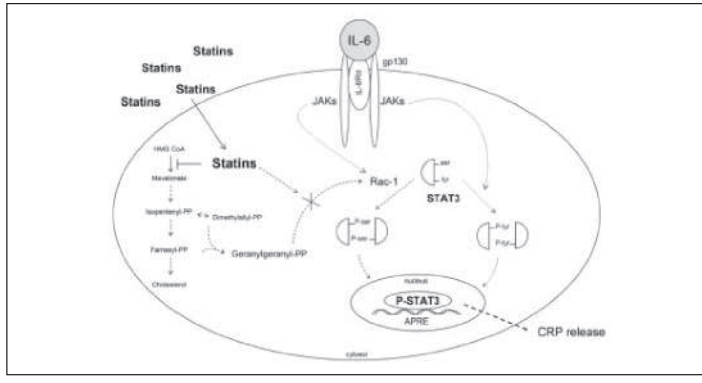

Figure 2
Proposed signaling pathways leading to statin-induced reduction of CRP release in hepatocytes (JAK indicates Janus kinase; APRE: acute phase response element; P-STAT3: phospho-STAT3) [67].

The endocannabinoid system

The discovery of membrane receptors that bind the psychoactive compound of marijuana, Δ9-tetrahydrocannabinol (THC) and their endogenous ligands has led to the description of the endocannabinoid system. At present, the system is composed of two receptors that have been cloned, and endogenous ligands or endocannabinoids including anandamide, 2-arachidonoylglycerol, and others. All endocannabinoids identified so far are derivatives of long-chain polyunsaturated fatty acids and exhibit varying selectivity for the two cannabinoid receptors [68].

Both cannabinoid receptors are G protein-coupled receptors that modulate second messengers and signaling components such as adenylate

cyclase, mitogen-activated protein kinases or members of the NF-κB family. The tissue distribution of the two receptors is likely to account for the well-known psychotropic and peripheral effects of THC. Cannabinoid receptor 1 (CB_1) is expressed predominantly in the central and peripheral nervous system, while cannabinoid receptor 2 (CB_2) is present on immune cells [69]. Thus, CB_2 receptors may have physiological importance in immune response, inflammation and chronic pain.

Immunosuppressive and anti-inflammatory properties

The development of selective agonists, antagonists, and transgenic mice lacking CB_1 and CB_2 receptors has contributed to broaden our current understanding of cannabinoid biology. As a consequence, the capacity of cannabinoids to regulate immune function is now well established. In vitro, THC treatment of human immune cells inhibits secretion of pro-inflammatory cytokines and chemokines and triggers the differentiation into a Th2 phenotype [70]. As demonstrated, a CB_2-specific antagonist abrogates the majority of these immunomodulatory effects [70]. Moreover, THC-mediated inhibition of T helper cell activation is absent in CB2-deficient mice, supporting the hypothesis that the immunomodulatory effects of cannabinoids are CB2-dependent [71].

Cannabidiol, the major non-psychotropic constituent of the Cannabis sativa plant, has been reported to ameliorate chronic inflammation in murine collagen-induced arthritis, a mouse model of rheumatoid arthritis, by inhibiting antigen-specific lymphocyte proliferation and interferon-(IFN)-γ secretion [72]. More recently, marijuana-derived cannabidiol was shown to inhibit macrophage chemotaxis in vitro and in vivo in a CB_2 receptor-dependent manner [73].

CB2 is expressed within plaques

To investigate whether CB2 receptor was expressed in atherosclerotic lesions, we visualized the receptors in human coronary and mouse aortic plaques using immunostaining techniques. We observed abundant CB2 receptor expression in both mouse and human plaques, while none was found in normal arteries [74]. Double immunofluorescence staining revealed that the CB2 receptor is mainly expressed on macrophages and CD4+ T cell lymphocytes within atherosclerotic plaques.

Cannabinoids and atherogenesis

To investigate whether THC treatment might reduce the burden of atherosclerotic disease, we placed apolipoprotein E (apoE)-knockout mice on a high-fat cholesterol diet. After 5 weeks on the diet, THC was administered to the treatment-randomized mice and these were compared to controls 6 weeks later. In the control mice, lesions increased on the high-cholesterol diet; however, lesion progression decreased significantly in the mice treated with a very low dose of oral THC (Figure 3).

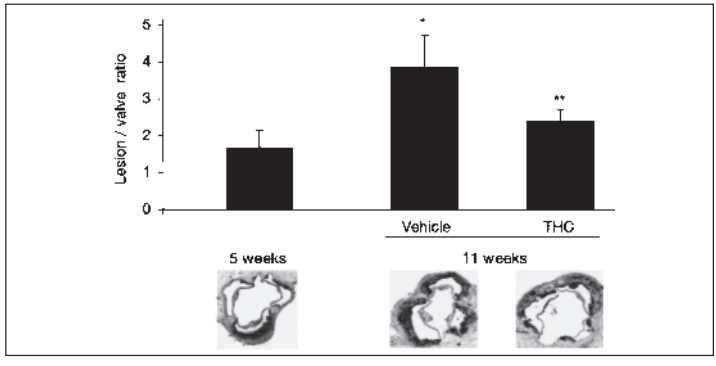

Figure 3

*Treatment with THC reduces atherosclerotic plaque development in ApoE-/-mice. Atherosclerotic lesions within aortic roots were analysed by Sudan IV staining for lipid deposition. Quantification of lipid deposition (immunostaining) was performed by computer image analysis. *P<0.05 compared with ApoE$^{-/-}$ mice at 5 weeks; **P<0.05 compared with ApoE$^{-/-}$ mice at 11 weeks without THC (vehicle) [75].*

When we added a specific CB2 receptor blocker, the protective effect of THC was completely abolished, indicating that the atheroprotection was due exclusively to the CB2 receptor pathway. T cell activation and proliferation as well as IFN-γ production declined in the lymph nodes of THC treated mice, but no effect was found on anti-inflammatory cytokine production. We also demonstrated reduced migration of peritoneal cavity macrophages from the same THC-treated apoE-knockout mice, in vivo, with stimulation by IFN-γ or tumor necrosis factor (TNF)-α. This effect was also clearly linked to the CB2 receptor, since migration was unaffected in CB2 knockout mice [75]. CCR2 (ß-sub-

class) receptors are among the most important chemokine receptors responsible for macrophage attraction from the circulation to vascular tissue and plaques. CCR2 expression was strongly reduced in splenocytes from apoE-knockout mice treated with THC, in vitro, at doses corresponding to effective in vivo dosages (Figure 4). This could explain the reduction, in vivo, of macrophage migration and atherogenesis. It is particularly noteworthy that the observed in vitro and in vivo effects of THC were dose-dependent. The dose dependency showed a U-shaped curve, where both higher and lower doses were inactive. The effective dose was lower than the dose usually associated with psychotropic effects of THC.

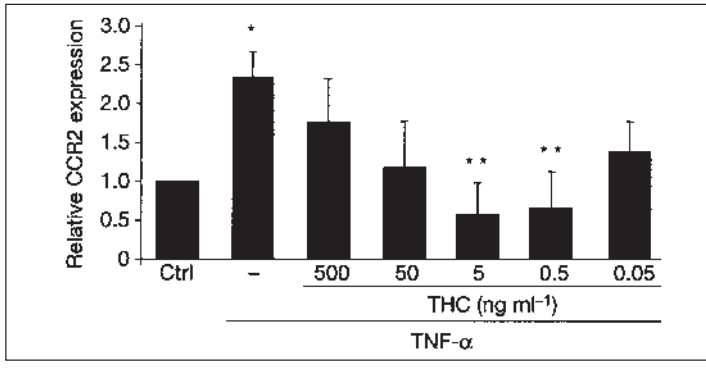

Figure 4
Treatment with THC reduces CCR2 mRN A expression in vitro.
*Isolated splenocytes obtained from ApoE$^{-/-}$ mice were stimulated with 10 ng/ml TNF-α in the presence or absence of different doses of THC. Relative expression levels of CCR2 messenger RNA were determined by quantitative real-time PCR. Data represent mean values + s.e.m. *P<0.05 compared with control, unstimulated cells; **P<0.05 χομπαρεδ ωιτη ΤΝΦ-α-stimulated cells [75].*

Cannabinoids as therapeutic agents

Our study has demonstrated that THC, by acting on CB_2 receptors, reduces inflammation and the infiltration of immune cells into atherosclerotic lesions. Nevertheless, these effects are in conflict with the known adverse effects associated with marijuana consumption. Indeed, the bioactive constituents of the marijuana plant and their synthetic and

endogenous analogs cause not only neurobehavioral, but also cardiovascular effects as demonstrated in humans and animal models [75, 76]. In humans, the most consistent cardiovascular effects of marijuana smoking are peripheral vasodilatation and tachycardia. These effects manifest themselves as an increase in cardiac output, increased peripheral blood flow, and variable changes in blood pressure. In anesthetized rats and dogs, THC produces an acute rise in blood pressure followed by long-lasting hypotension and bradycardia. Based on these hypotensive effects, targeting the endocannabinoid system is likely to offer novel therapeutic strategies in the treatment of hypertension. In a multicenter study performed with 3882 patients, marijuana smoking was identified as a rare trigger of acute myocardial infarction [77]. While some of the cardiovascular effects result from activation of CB1 receptors, recent findings indicate that several cannabinoid effects are not mediated by either CB_1 or CB_2 receptors [78].

Besides the risk of unwanted cardiovascular effects, a broad acceptance of cannabinoids as therapeutic agents is hampered by the fact that they exhibit psychotropic effects. Therefore, particular research interest is focusing on the development and characterization of either synthetic or plant derived cannabinoids with therapeutic value that are non-psychotropic. Among the non-psychotropic plant derived drugs, cannabidiol, a major compound of marijuana, has been shown to have potent anti-inflammatory and neuroprotective properties, as discussed above [70]. First clinical trials performed with THC/cannabidiol plant extracts have demonstrated that the study medications were generally well tolerated and associated with only few side effects. However, larger scale and long-term studies are warranted to confirm a clinically relevant improvement of neurological symptoms [79].

More interestingly, several non-psychotropic synthetic cannabinoids with anti-inflammatory properties have recently been developed from plant cannabinoids, such as ajulemic acid (CT3) and HU-320. Of particular interest is the development of agonists that selectively target CB_2 receptors. In preclinical studies, CB2 receptor agonists, such as HU308 and AM-1241, have been shown to be devoid of effects on the central nervous system and show promise for the treatment of acute and

chronic pain [80]. A promising novel compound designated Sch.336, which belongs to a new class of CB_2-specific ligands, the triaryl bissulfones, blocks leukocyte recruitment in vivo [81]. This effect was demonstrated in three different models of inflammation. Their anti-inflammatory properties suggest that CB2 ligands may serve as novel immunomodulatory agents in the treatment of immune disorders such as atherosclerosis. However, little is known about the molecular mode of action of these compounds and requires further investigation. Finally, it remains unclear whether receptor signaling via endocannabinoids plays a modulatory role in chronic inflammation ongoing during atherogenesis. A recent report demonstrates that CB1 receptors mediate intrinsic protective signals that counteract pro-inflammatory responses in a mouse model of colonic inflammation [82]. Additional studies using selective CB_1 and CB_2 receptor antagonists are warranted to investigate a possible role of the endocannabinoid system during atherosclerosis.

Conclusions

Inflammatory processes play a pivotal role in all stages of atherosclerosis. Many risk factors contribute as triggers of inflammatory reactions and injury to the endothelium. Growing evidence suggests that elevated plasma levels of vascular wall inflammation markers may help to predict future risk of plaque rupture. Prevention and current treatments for atherosclerosis are mainly based on drugs that lower plasma cholesterol concentration and high blood pressure. In particular, statins have proven to reduce the risk of cardiovascular events significantly, not only by their cholesterol-lowering properties, but also by their more recently identified anti-inflammatory and immunomodulatory effects. Nevertheless, atherosclerosis remains the primary cause for heart disease and stroke. Thus, a great challenge for future research would be the identification and development of promising novel anti-inflammatory therapies, such as anti-chemokines or non-psychotropic cannabinoids, to reduce the progression of atherosclerosis. A major challenge of contemporary medicine is to break the traditional compartmentalization that frequently separates different fields. The same holds between medical practice and basic biochemical mechanism. Unexpected link-

ages between different areas of medicine are indeed of particular interest. Unsuspected "bridges" across cardiology practice and molecular immunology, as presented here, are good examples of such a linkage.

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LE PRIX CLOËTTA 2007
EST DÉCERNÉ À

MADAME LA PROFESSEURE

NOURIA HERNANDEZ

NÉE EN 1957, DE WINTERTHOUR (ZH),
DIRECTRICE DU CENTRE INTÉGRATIF DE GÉNOMIQUE (CIG)
DE LA FACULTÉ DE BIOLOGIE ET DE MÉDECINE
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POUR SES REMARQUABLES TRAVAUX DANS LE DOMAINE
DE LA TRANSCRIPTION ET DE LA RÉGULATION
DE L'EXPRESSION DES GÈNES.

ZURICH, LE 30 NOVEMBRE 2007

AU NOM DU CONSEIL DE FONDATION:

LE PRÉSIDENT

LE VICE-PRÉSIDENT

UN MEMBRE

Prof. Dr. Nouria Hernandez

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Professional Experience

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Editorial Board

January 1992–October 1993	Editorial Board, Molecular and Cellular Biology
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Scientific review

February 1991	Ad Hoc reviewer for the Molecular Biology Study Section, NIH
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Fellowships, Scholarships and Memberships, Prizes

September 1983– September 1984	Fellowship from the Swiss National Fund
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MECHANISMS OF RNA POLYMERASE III TRANSCRIPTION IN HUMAN CELLS

Nouria Hernandez

If DNA is often referred to as the molecule of life, then gene expression, which leads, ultimately, to execution of the instructions embedded in the DNA, is certainly the process of life. Basal cellular metabolism, cell division, and the intricate processes of cellular differentiation and adaptation to external conditions all depend on the controlled expression of specific genes, starting with the process of transcription. Perhaps not surprisingly, then, the complexity of the machineries involved in gene expression and in particular in transcription increases with the complexity of organisms, and in mammalian genomes, a sizeable percentage of the proteome seems to be involved in the control of transcription (see for example [Waterston et al., 2002]).

Eukaryotes possess three main nuclear DNA-dependent RNA polymerases, RNA polymerases (pol) I, II, and III, each dedicated to the transcription of specific classes of genes. Pol I and III synthesize RNA molecules required for fundamental cellular processes such as RNA processing and protein synthesis; thus, pol I transcribes the 45S gene, generating the 28S, 18S, and 5.5S ribosomal RNAs, and pol III synthesizes structural and catalytic RNA components of the protein synthesis and RNA processing machineries such as, for example, 5S RNA, the tRNAs, and the spliceosomal U6 small nuclear RNA (snRNA), as well as short RNAs of unknown function. Pol III also transcribes micro RNAs as part of some repetitive sequences such as Alu sequences (Borchert et al., 2006). The main task of pol II is the transcription of protein-encoding genes, although it also transcribes some small nuclear RNA genes such as, for example, the U1 and U2 snRNA genes, involved in mRNA splicing. Among the three transcription machineries, the pol II machinery is the most complex, reflecting the highly varied protein constellations present in different cells at different times, and the need for intricate regulation of such protein

patterns, whereas the pol I machinery, which transcribes only one type of gene, is probably the least complex.

The largest effort in the field of transcription has gone toward the study of mechanisms of transcription by pol II. However, there is a growing interest in deciphering how pol I and III transcription is regulated, as this is key to understanding questions as fundamental as how can a cell adapt its protein synthesis capability to its changing needs. In this review, I will summarize what we know about the pol III basal transcription machinery in mammalian cells, and about the regulation of this machinery.

Three main types of pol III promoters

Pol I, being dedicated to transcription of the highly repeated 45S genes, needs to recognize, together with its transcription factors, only one promoter structure. Pol II is at the other extreme; it recognizes promoters that often contain separable core and regulatory regions and that are enormously varied, especially in their regulatory regions. Pol III recognizes a more limited number of promoter structures and thus is, in this respect, intermediate between pol I and pol II. The pol III promoters have been classified into three main types, of which the first two are gene-internal and generally TATA-less, and the third is gene-external and contains a TATA box (see [Schramm and Hernandez, 2002] for a review). These promoters are illustrated in Figure 1. Type 1 and 2 promoters are found in the 5S rRNA genes and in tRNA genes, respectively. The Xenopus Laevis 5S gene promoter, which often serves as the model type 1 promoter, is called internal control region (ICR) and consists of an A box, an intermediate element (IE), and a C box that is conserved in the 5S promoters of different species (Bogenhagen et al., 1980, Sakonju et al., 1980). Most tRNA promoters as well as the Adenovirus VA1 promoter, often used as a model type 2 pol III promoter because of its exceptional strength, consist of an A box and a B box, which can be spaced differently in different genes (Fowlkes and Shenk, 1980, Galli et al., 1981, Hofstetter et al., 1981, Sharp et al., 1981). Type 3 promoters are not found in yeast, and are exemplified by vertebrate

U6 snRNA promoters (Das et al., 1988, Krol et al., 1987, Kunkel and Pederson, 1988). The human U6 promoter consists of a TATA box and a proximal sequence element (PSE), both of which are required for basal transcription in vitro. In addition, the promoter contains a distal sequence element (DSE), which enhances transcription from the basal promoter. The type 3 promoters have the particularity of being very similar to promoters such as the human U1 and U2 promoters, which are recognized by pol II and consist of a PSE and a DSE without a TATA box (see [Hernandez, 2001] for a review). Finally, a number of pol III promoters are mixtures of elements constituting the basic type 1, 2, and 3 promoters. For example, the selenocysteine tRNA promoter from Xenopus laevis combines DSE, PSE and TATA box in the 5' flanking region with a gene-internal B box (Carbon and Krol, 1991).

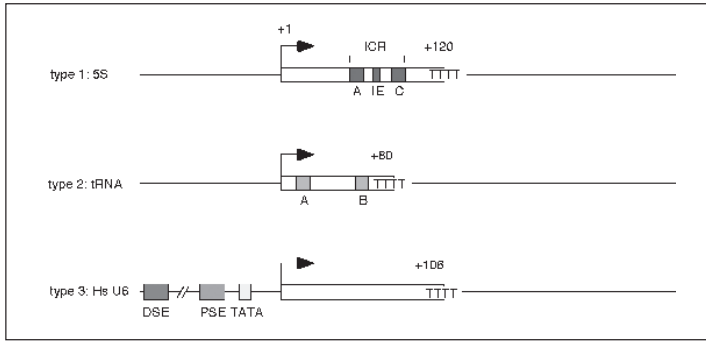

Figure 1
Structure of the three types of pol III promoters.

The various types of pol III promoters recruit different transcription factors

Like other RNA polymerases, pol III cannot recognize its target promoters without the help of accessory factors that bind to promoter elements and in turn recruit other accessory factors and the polymerase. As illustrated in Figure 2, for type 1 promoters, the ICR is recognized by a zinc finger protein referred to as TFIIIA (Engelke et al., 1980, Sakonju et al., 1981). Formation of the TFIIIA-DNA complex then

allows the binding of TFIIIC (Lassar et al., 1983), and then that of Brf1-TFIIIB (Schramm et al., 2000, Teichmann et al., 2000). Once Brf1-TFIIIB is bound, pol III can be recruited to the promoter. For type 2 promoters, TFIIIA is not needed to assemble the preinitiation complex. Instead, TFIIIC binds directly to the A and B boxes and recruit Brf1-TFIIIB and then pol III. In the case of type 3 promoters, a different set of transcription factors is needed. The PSE is recognized by a factor we call the snRNA activating protein complex ($SNAP_c$), also known as PTF, and the TATA box is recognized by Brf2-TFIIIB (see (Geiduschek and Kassavetis, 2001, Hernandez, 2001, Schramm and Hernandez, 2002) for reviews). This then allows the recruitment of the polymerase. Thus, for all pol III promoters, the assembly of the preinitiation complex leads to recruitment of either Brf1- or Brf2-TFIIIB, which then allows pol III recruitment.

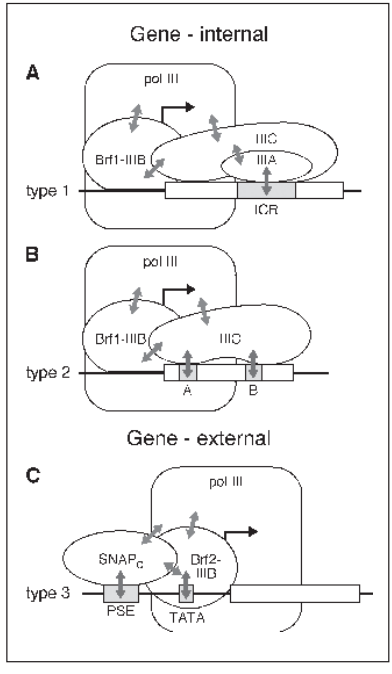

Figure 2
Recruitment of pol III to types 1, 2, and 3 promoters. The arrows indicate either DNA-protein or protein-protein contacts. In the case of type 3 promoters, the contacts between pol III and $SNAP_c$ or Brf2-TFIIIB are putative.

Transcription factors IIIA and IIIC

In the last twenty years or so, a large effort has been devoted to the characterization of the transcription factors mentioned above, which were, originally, uncharacterized activities in different chromatographic fractions. This led to the cloning of cDNAs encoding all of these factors, and thus to a detailed description of the pol III basal transcription machinery. Indeed, for some yeast and human pol III promoters, we can now reconstitute basal pol III transcription with entirely recombinant transcription factors and highly purified pol III. TFIIIA was the first eukaryotic transcription factor to be cloned (Ginsberg et al., 1984), and its characterization then led to the concept of zinc finger proteins (Miller et al., 1985). It indeed contains nine C_2H_2 zinc fingers. In yeast, its only essential role is in the transcription of the 5S RNA gene, because yeast strains engineered to express 5S RNA from a type 2 promoter and lacking TFIIIA are viable (Camier et al., 1995). TFIIIC is a large complex composed of six types of subunits, some of which are only moderately conserved from yeast to human cells (Deprez et al., 1999, Dumay-Odelot et al., 2007, Hsieh et al., 1999a, Hsieh et al., 1999b, Kundu et al., 1999, L'Etoile et al., 1994, Lagna et al., 1994, Lefebvre et al., 1992, Manaud et al., 1998, Marck et al., 1993, Swanson et al., 1991, Willis et al., 1989). A functional yeast TFIIIC complex has recently been reconstituted from recombinant proteins expressed in insect cells with baculovirus vectors (Ducrot et al., 2006).

$SNAP_c$

$SNAP_c$ is found only in metazoans. In mammalian cells, it is composed of five types of subunits, SNAP190, SNAP50, SNAP45, SNAP43, and SNAP19, all of which have been cloned (Bai et al., 1996, Henry et al., 1996, Henry et al., 1998, Henry et al., 1995, Sadowski et al., 1996, Wong et al., 1998, Yoon and Roeder, 1996), and a recombinant complex can be synthesized in insect cells from baculovirus vectors (Henry et al., 1998, Mittal et al., 1999).

Brf1-TFIIIB and Brf2-TFIIIB

In yeast, there is only one TFIIIB activity, which is minimally composed of three polypeptides: the TATA box binding protein TBP, the TFIIB-related factor Brf1, and the SANT domain protein Bdp1 (see

Geiduschek and Kassavetis, 2001, Schramm and Hernandez, 2002, for reviews). In human cells, however, there are two TFIIB-related factors, Brf1 and Brf2, and consequently two TFIIIB activities: Brf1-TFIIIB contains human TBP, Bdp1, and Brf1, whereas Brf2-TFIIIB contains TBP, Bdp1, and Brf2. As described above, Brf1-TFIIIB is recruited to type 1 and 2 promoters, and Brf2 to type 3 promoters(Mital et al., 1996, Schramm et al., 2000, Teichmann et al., 2000).

TBP, Brf1, Brf2, and Bdp1 have all been cloned and can be expressed in E. coli (Mital et al., 1996, Schramm et al., 2000, Teichmann et al., 2000, Wang and Roeder, 1995). Brf1 and Brf2 are of particular interest. As their name indicates, they are related to TFIIB, containing, like TFIIB, a zinc-binding N-terminal domain and a core domain consisting of two repeats. Over most of these regions, the three proteins are approximately 20% identical (Schramm et al., 2000, Teichmann et al., 2000). Brf1 and Brf2 contain, in addition, C-terminal extensions that are absent in TFIIB and that appear unrelated to each other.

At pol II promoters, TFIIB bridges pol II with the promoter-bound preinitiation complex, whereas Brf1 and Brf2 are involved, as part of Brf1-TFIIIB and Brf2-TFIIIB, in the establishment of a pol III transcription initiation complex and in the recruitment of pol III. How do these related factors establish pol II versus pol III specificity? In yeast Brf1, the C-terminal extension is known to interact with the TBP/TATA box complex and to contribute to the recruitment of Bdp1, which presumably leads, in turn, to the recruitment of pol III. Significantly, a structure-function analysis of human Brf2 suggests that the C-terminal extension of Brf2 is required for efficient association of the protein with U6 promoter-bound TBP and $SNAP_c$, and for efficient recruitment of Bdp1 (Saxena et al., 2005). Close inspection of the C-terminal domain of Brf2 reveals a short region that can be aligned with the Brf1 region required for efficient binding to the TBP/TATA box complex. Thus, a common feature among TFIIB family members involved in pol III transcription appears to be the use of their C-terminal extension to associate efficiently with a TBP/TATA box complex and to recruit Bdp1. This in turn suggests that the C-terminal extensions in Brf1 and Brf2 are key to specific recruitment of pol III over pol II (Saxena et al., 2005).

Bdp1

Bdp1 was first cloned in yeast cells by biochemical methods(Kassavetis et al., 1995, Roberts et al., 1996, Rüth et al., 1996), and shown to contain a domain related to a Myb repeat. This domain was identified by comparison of the SWI-SNF and ADA complexes, the transcriptional co-repressor N-Cor, and yeast TFIIIB, and was therefore named the SANT domain (Aasland et al., 1996). The SANT domain of the yeast protein is required for function (Kassavetis et al., 1998), and so human Bdp1 cDNAs were isolated through a combination of database searches for sequences similar to the yeast Bdp1 SANT domain and library screening (Schramm et al., 2000). This led to the identification of Bdp1 splicing variant 1 (Bdp1_v1), which is highly related to the yeast protein within the SANT domain (43% identities) as well as in regions both immediately upstream (21% identities) and downstream (17% identities). Outside of these regions, the two proteins are not conserved, and the human protein differs from the yeast protein by a striking C-terminal extension containing a number of repeats. Other Bdp1 cDNAs corresponding to alternatively spliced mRNAs potentially encode a very large protein in which the last few amino acids of Bdp1_v1 are replaced by a 901 aa extension (Bdp1_v2), and a 725 aa protein (Bdp1_v3) corresponding to Bdp1_v1 sequences up to aa 684, followed by a divergent 47 aa extension (Kelter et al., 2000). Whether all of these alternatively spliced forms of human Bdp1 are involved in pol III transcription in vivo is currently not clear.

Regulation of pol III transcription

Pol III synthesizes RNAs that are often abundant and stable. As described above, these RNA molecules then participate in the processing of other RNA molecules, in protein synthesis, and in other essential metabolic reactions. Thus, in cells that are actively dividing, pol III activity is high such that an entire complement of pol III products can be produced within one cell generation. Indeed, cancer cells are characterized by increased pol III transcription activity. Similarly, in growing cells, pol III activity is high to meet the increased demand for such molecules. On the other hand, in resting cells, pol III activity is mostly

limited to the replacement of the few pol III products that decay over time. Thus, pol III transcription is highly regulated with cell proliferation and growth. Moreover, pol III transcription is very rapidly inhibited after certain stresses such as DNA damage and serum starvation. Accordingly, there is a high interest in understanding the regulation of pol III transcription, the role of such regulation in continued cell division, and the coordination of such regulation with that of pol I transcription and pol II transcription of certain genes involved in, for example, ribosome biogenesis.

Pol III transcription is regulated by at least two very general mechanisms, the first acting through regulatory promoter sequences and the second through the basal transcription machinery. Indeed, although in mammalian cells, the core pol III promoters, which correspond to one of the three types of promoters described in Figure 1 or, in some cases, to a mixture of elements from the different types, are generally thought to direct most of the total transcription activity, there are several examples where flanking sequences are known to modulate the activity of the core promoter (see for example [Howe and Shu, 1989]), and closer examination of natural cellular pol III promoters in human cells would most likely reveal that this is a quite common occurrence. Thus, part of the regulation of pol III transcription is exerted through factors binding to such modulatory sequences, which then activate or, conceivably, repress, pol III transcription. In the second mechanism, regulators act directly on the basal transcription factors described above. Since the basal transcription factors are used by entire classes of pol III promoters, such mechanisms can potentially repress a large collection of pol III genes in a concerted manner.

Transcription activation through regulatory promoters sequences: the human U6 promoter

Perhaps the best studied example of regulation through promoter regulatory sequences is that of the type 3 human U6 snRNA promoter. As described above in Figure 1, type 3 promoters contain a distal sequence element (DSE). The DSE can be composed of various protein binding

sites, but one of them is almost always an octamer sequence that recruits the POU domain transcription factor Oct-1, and the other an SPH (for "*Sph1* postoctamer homology") element that recruits the zinc finger protein Staf (ZNF143) (see [Hernandez, 2001] for a review). How do these factors activate transcription?

In the case of Oct-1, we know that both the activation domain of the protein as well as the DNA binding domain contribute to transcription activation. The mechanism by which the Oct-1 activation domain does so is not known, but the Oct-1 DNA binding domain binds cooperatively with $SNAP_c$ to the U6 promoter and so helps $SNAP_c$ recruitment. The DNA binding domain of Oct-1 is a POU domain, a bipartite DNA binding domain consisting of two helix-turn-helix-containing DNA-binding structures: an amino-terminal POU-specific (POU_S) domain and a carboxy-terminal POU-homeo (POU_H) domain, joined by a flexible linker (Herr and Cleary, 1995). Cooperative binding results from a direct protein-protein contact between the Oct-1 POU_S domain and the largest subunit of $SNAP_c$, contact that is mediated by a nucleosome positioned between the PSE and the DSE in the U6 promoter (Ford et al., 1998, Zhao et al., 2001).

Oct-1 is not capable to bind to pre-assembled chromatin in vitro, suggesting that activation of U6 snRNA gene transcription in vivo requires the prior binding of another factor which can then either recruit Oct-1 directly or somehow modify chromatin to make it accessible to Oct-1. A strong candidate for such a factor is Staf (ZNF143). Indeed, Staf cannot only activate U6 transcription from a chromatin template in vitro like Oct-1, it is in addition capable of binding to preassembled chromatin (Yuan et al., 2007). Moreover, Staf associates with a number of factors that are involved or are likely to be involved in chromatin modification. One of these, chromodomain-helicase-DNA binding protein 8 (CHD8), resides on the human U6- as well as on some pol II promoters in vivo, and contributes to efficient U6 transcription. Thus, pol III transcription is likely to use at least some of the same factors as those used for chromatin remodeling at pol II promoters.

Transcription regulation through the basal pol III transcription machinery

A number of factors have been shown to regulate pol III transcription through the general pol III transcription machinery. These include Rb, c-Myc, PNRC, p53, Maf1, CK2, and the list is growing! All of these factors also regulate transcription of some pol II genes and in some cases of the pol I rRNA genes.

Pol III transcription is regulated with the cell cycle. When Balb/C 3T3 fibroblasts are arrested in G0 by serum deprivation, pol III transcription from class 2 promoters is greatly reduced. It is reactivated shortly after serum addition, well before the G1/S boundary, through a pathway involving the mitogen-activated protein kinase ERK, which binds to and phosphorylates Brf1 (Felton-Edkins et al., 2003). In cycling cells, pol III transcription is low in G1 and high in the S and G2 phases (Scott et al., 2001, White et al., 1995). Consistent with this observation, type 2 pol III promoters are repressed by Rb as well as p107 and p130, which bind to an undefined Brf1-TFIIIB subunit and prevent Brf1-TFIIIB association with promoters (Larminie et al., 1997, Sutcliffe et al., 2000, Sutcliffe et al., 1999, White et al., 1996). Transcription from the type 3 U6 promoter is also inhibited by Rb, which in this case associates with $SNAP_c$ through two of the $SNAP_c$ subunits (Hirsch et al., 2000, Hirsch et al., 2004). Interestingly, Rb repression of U6 transcription requires the Rb A/B pocket as well as the C domain, which is not required for repression of pol II transcription but which is part of the domain required for growth suppression. This suggests that repression of pol III transcription is an important component of growth suppression (Hirsch et al., 2004). During mitosis, pol III transcription is repressed by the cdc2/cyclin B kinase, either through direct phosphorylation of a Brf1-TFIIIB subunit or by activation of secondary kinases, which in turn phosphorylate a Brf1-TFIIIB subunit (Gottesfeld et al., 1994, Leresche et al., 1996). One such secondary kinase is CK2, which can inactivate Bdp1 by direct phosphorylation (Hu et al., 2004). CK2 can also activate transcription, however, through phosphorylation of pol III itself or a pol III-associated factor (Hu et al., 2003). Thus, CK2 has both positive and negative roles in pol III transcription.

A number of positive regulators of pol III transcription have been described. c-Myc binds to Brf1-TFIIIB, activates class 1 and 2 pol III promoters, and can be found on these promoters in vivo by chromatin immunoprecipitation experiments (Gomez-Roman et al., 2003). Similarly, PNRC, a nuclear receptor coactivator that regulates a wide range of pol II-transcribed genes, associates with the RPC30 subunit of pol III and can be localized on pol III promoters by chromatin immunoprecipitation experiments. Further, overexpression of PNRC activates, whereas down-regulation of PNRC by RNA interference decreases, pol III transcription in MCF7 cells, suggesting that one of the protein's function is to stimulate pol III transcription (Zhou et al., 2007).

Pol III transcription is repressed by p53. On type 1 and 2 promoters, p53 inhibits pol III promoter occupancy by targeting the TBP subunit of Brf1-TFIIIB (Cairns and White, 1998, Crighton et al., 2003, Stein et al., 2002). For example, after treatment of cells with methane methylsulfonate (MMS), a DNA damaging agent, tRNA transcription is inhibited, at least in part as a result of p53-mediated effects on TFIIIB; the TFIIIB association with TFIIIC2 and pol III in solution is reduced, as is the TFIIIB association with tRNA promoters in vivo (Crighton et al., 2003). On type 3 promoters, p53 inhibits pol III transcription by association with the promoter itself, probably through protein-protein interactions with members of the transcription initiation complex (Gridasova and Henry, 2005).

A second repressor of pol III transcription is the protein Maf1, which was originally identified in S. *cerevisiae* by the isolation of a temperature-sensitive mutation, *maf1-1* (Murawski et al., 1994). In *maf1-1* cells, tRNA levels were elevated, and pol III transcription was much more active in extracts from such cells than in extracts from wild-type cells, suggesting that Maf1 represses pol III transcription (Pluta et al., 2001). Indeed, yeast Maf1 turns out to be an essential common component of at least three signaling pathways that lead to pol III transcription repression, the secretory defect signaling pathway, the target of rapamycin (TOR) signaling pathway, and the DNA damage signaling pathway (Upadhya et al., 2002), see (Willis et al., 2004) for a review).

In cells lacking Maf1, repression of pol III transcription in response to these signaling pathways fails.

Recent work (Oficjalska-Pham et al., 2006, Roberts et al., 2006) has significantly advanced our understanding of repression by Maf1 in yeast (see [Geiduschek and Kassavetis, 2006] for a review). In actively growing yeast cells, Maf1 is present in both the nucleus and the cytoplasm, and a large fraction of Maf1 is phosphorylated, at least in part by PKA, whose activity counteracts Maf1 repression (Moir et al., 2006). Upon exposure of the cells to various stresses, Maf1 is dephosphorylated in a manner dependent on PP2A and translocates to the nucleus, where it occupies pol III promoters as determined by genome-wide chromatin immunoprecipitations (Oficjalska-Pham et al., 2006, Roberts et al., 2006). The dephosphorylated form of Maf1 can associate with pol III and *in vitro*, Maf1 is capable of preventing assembly of a transcription complex by binding to Brf1. This suggests that in addition to inhibiting transcription through binding to pol III, Maf1 can also prevent the assembly of new transcription complexes (Desai et al., 2005).

Maf1 is conserved in other species (Pluta et al., 2001), raising the important possibility that Maf1 might be involved in pol III repression in mammalian cells. Indeed, recent results show that human Maf1 is a repressor of pol III transcription both *in vitro* and *in vivo* (Reina et al., 2006), down-regulating transcription from type 1, 2, and 3 pol III promoters. Human Maf1 is necessary for efficient down-regulation of pol III transcription after stress, and associates with Brf1 as well as with the pol III subunits RPC1 and RPAC2. Like the yeast protein, human Maf1 is phosphorylated and becomes largely dephosphorylated after stress, and it is the dephosphorylated form of Maf1 that associates with pol III (Reina et al., 2006). Thus, Maf1 is potentially a central regulator of pol III transcription in mammalian cells.

From the brief summary above, it is clear that a large number of factors can individually regulate pol III transcription. However, we are still missing a picture of how these various factors interplay to modulate pol III transcription under various conditions and at different times during

the cell cycle. Indeed, we lack information on how the actions of these factors integrate into complex regulatory pathways, and such pathways might simply be too elaborate to be fully described by traditional reductionist approaches. However, with genomic era techniques, it is possible, for example, to correlate the binding of any factor to all pol III (and other) promoters in the genome with transcription efficiency, and this under a variety of conditions. Combinations of such genome-scale analyses with global proteomic analyses will lead to a comprehensive description of these complex regulatory networks, and in turn to a better understanding of cell proliferation and growth constraints.

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