

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Parametric Determination of Hypoxic Ischemia in Evolution of Atherogenesis

Lawrence M. Agius

*Department of Pathology, Mater Dei Hospital, Tal-Qroqq,
University Of Malta Medical School, Msida,
Malta*

1. Introduction

Atherosclerosis constitutes a primarily destructive phenomenon inherently arising from dynamics of pathobiologic effect within the intima of elastic and muscular arteries. It is significant to view the development of elevated intimal lesions within dimensions of ongoing further injury to the endothelium.

Considerable interactivity evolves within plaques in consequence to neovascularization in particular. The outline evolution of individual atherosclerotic plaques would considerably modulate the dynamics of migration of smooth muscle cells to the intima and as a consequence of various agonists such as hypoxia, growth factors and coagulation-anticoagulation-fibrinolysis systems. Also, insulin appears to exert toxicity on the vascular wall and possibly promote atherogenesis (Nandish et al., 2011).

2. System pathways of injury

System pathways constitute a representative sequence of events that depend on dysfunctional activation of endothelial cells. It is within scope of parameters of permeability and loss of endothelial cells that a full plethora of forms of injury converge as intimal cell proliferation and as deposition of protein matrix proteoglycans. Oxidative stress and chronic inflammation promote diabetes, hypertension and atherosclerosis (Sewon et al., 2011).

The individual roles played by various agonist actions in the definition of the atherosclerotic plaque would evolve within the specificity of focal injury to the intima in particular. The convergence of such injuries appears a constitutive attribute of the variable expression of sequence prototypes in lesion demarcation.

Developmental parameters of modelling include the delineation of individual pathogenic events in terms that integrally reconstitute the modified anatomy of the individual atherosclerotic plaque. In this regard, Ghrelin improves endothelial function, lowers blood pressure and regulates atherosclerosis (Zhang et al., 2011).

Significance in terms of complicated plaques as constitutive pathways in modelling of plaques includes the essential interactivity of endothelium with smooth muscle cell trophic effect. Macrophages in particular implicate a series of converging events that sequentially re-define in repetitive form the dynamics of atherogenesis. Dyslipidemia increases lipid content in foam cells found in atherosclerotic plaques (Wong et al., 2011).

Growth factors are instrumental in terms of the emerging morphologic features of the early atherosclerotic plaque and as derivative phenomena of endothelial injury and permeability. The constitutive parameters of re-distribution of trophic effect particularly interact with neovascularization within the plaque core.

Developmental sequences of multifactorial type in atherogenesis are particularly prone to a staged outline evolution that permeates the intima and sustains injury to the endothelium. Such significant interactivity contributes to outline emergence of new sequences in trophic effect and as proliferation and migration of smooth muscle cells.

The macrophage is central to such interactivity and operates primarily in chemotaxis and trophism, and also in terms that dominantly influence in significant fashion the attributes of lipid foam cells. Plant-derived alpha-linolenic acid, for example, restricts plaque T-cell proliferation, differentiation and inflammatory activity (Winnik et al., 2011).

3. Focality of inflammation

The inflammatory infiltrates include a representative response to injury as atherogenesis further compounds injury to the vascular intima. The role of endothelium is implicated as dysfunctional response with increased permeability to monocytes in particular. Proteoglycans retain lipoproteins subendothelially (Anggraeni et al., (2011).

Such recruitment of novel forms of injury includes the transforming ability of protein matrix proteoglycans as integral constitution of the injurious agents. It is within the dimensional redistribution of such injury that the endothelium plays a prominent role in sequence selectivity and in modulation of parameters of redefinition of activated dysfunctional states of inflammatory cells within the plaque.

The focality of injury is particularly significant within the neovascularized core of the individual plaque and as parameters in the growth and maturation of smooth muscle cells. Reparative processes allow for a sequential remodelling within such system pathways as coagulation and cellular migration within the vascular intima.

The variability of delineation of injurious agents indicates an activation of new parameters as the plaque evolves. The overall confines further extend parameters in plaque modelling that permits responsive elements in the creation of multiple sequence pathways that evolve in their own right; for example, deletion of microsomal prostaglandin E2 synthase-1 retards atherogenesis (Wang et al., 2011).

4. The individual smooth muscle cell/macrophage

The secretory dynamics of smooth muscle cells and of macrophages attribute a central pathogenic role to foam cells within the intima. Both smooth muscle cells and macrophages are recognized source for foam cells that, in turn, predominate in the mature atheromatous plaque. On the other hand, the matrix proteoglycans are also central players in re-defining attributes of the injured endothelium.

The reactivity of macrophages within the protein matrix that accumulate within the intima allows for the emergence of multiple converging agonists that characterize endothelial cell activation. The development of subsequent new forms of injury transforms such endothelial dysfunctionality as parameters of maturation of the plaque. Interleukin 18 is involved in plaque destabilization and regulates the innate immune response (Yamaoka-Tojo et al., 2011).

The central core of the plaque is one dominated by influences exerted by transformations in terms of neovascularization and as compounded maturation leading to lipid core formation within the plaque. Insulin resistance and cardiovascular pathology may share a common genetic background (Bacci et al., 2011).

It is highly significant to view the trophic attributes of injury to the endothelium as source of the evolutionary traits of emerging atherosclerotic plaques; indeed, Insulin-like growth factor-1 stabilizes the atherosclerotic plaque by altering smooth muscle phenotype (von der Thusen et al., 2011). Stages in sequence pathway maturation are central to the outline demarcation of individual plaques in a manner that depends integrally on dynamics of neovascularization of the plaque core.

Hemodynamic shear stress contributes to a redistribution of actin microfilaments within endothelial cells in a manner that modulates dysfunctional issues of activated endothelium.

5. Cellular proliferative kinetics

A proliferative smooth muscle cellular response is further significant in the maturation of the atherosclerotic plaque within such sequence steps as redefined injury to the endothelium.

Stages in preparation for subsequent events in the outline of the atherogenesis process would include the delivery of injurious agents to the intima. The sequence pathways are significant parametric factors in defining the dimensions of the endothelial participation in atherogenesis. Endoplasmic reticulum stress and the unfolded protein response characterize endothelial susceptibility to atherogenesis (Civelek et al., 2011).

It is further to the evolving forms of agonist action that atherogenesis modifies in repeatedly staged sequence the pathways of dysfunctional activation of the endothelium.

6. Low-density lipoproteins

Neovascularization proves to be a centrally operative agonist in the modified development of atheroma formation and deposition. The added parameters of consequence appear to implicate a primarily evolutionary role for hypoxia and ischemia as plaque re-definition, both morphologically and in dysfunctional forms of endothelial activation.

The inflammatory nature of the intimal deposits elicits a responsive panorama that implicates derivative attributes of low density lipoproteins and cholesterol and as extended participation of the neovascularization of the plaque. MicroRNA-29a targets lipoprotein lipase in oxidized low density lipoprotein and modulates cytokines and scavenger receptors (Chen et al., 2011)

Hypoxia is itself essential for the formation of new vessels within the plaque with the production of growth factors and would additionally contribute to the intimal thickening as further evidence for staged representation of injury to the intima.

Directional re-orientation of active dysfunctional states of endothelial cells compounds hypoxia and ischemia within the vascular intima. By-products of matrix proteoglycans and of lipid metabolism indicate the essential staging events in plaque maturation and as derivative phenomenon to further atherogenesis. Chemokines produced by endothelial cells are associated with leukocyte recruitment and angiogenesis in atherosclerosis (Speyer & Ward, 2011).

7. Intimal remodeling

It is as remodelling of the injury to the intima that hypoxia and ischemia further modulate the migration of smooth muscle cells within the intima. The increased permeability of the endothelium is significant as a redefined series of further injuries to the underlying intima.

The orientational redistribution of the agonists in atherogenesis redefine a central plaque contribution to increasing profiles of further hypoxia/ischemia and as evidential remounting of parameters of sequence effect. The multi-factorial injurious events are converging agonists in hypoxic/ischemic core regions of the individual atherosclerotic plaque. In such manner, the multi-staged evolution of plaques correlates with interactive dynamics of further injury within the intima.

Dynamics of action of oxidized lipids correlate closely with emerging new roles for agonist action in developing plaques. The interaction of variably participating agonists contrast with the intimal emergence of incremental hypoxia/ischemia in terms of increasing matrix proteoglycan deposition and cellular proliferation of smooth muscle cells in particular. Atherosclerosis affecting different topographic sites correlate with the type of hyperlipidemia (Van Craeyveld et al., 2011).

The platelet/coagulation systems are incremental sequence events as trophic influence in staged convergence of multiple agonists in intimal injury.

Distributional parameters are particularly significant in the dimensional targeting of the intima in terms of the vasa vasorum supplying the arterial wall.

Component systems of sequential impact would contribute to the emergence of positive feedback effect in agonist action. The endothelial cells participate by the production of various agents such as growth factors, in particular Platelet-Derived Growth Factor. The semblance of such influence dominantly re-characterizes the atherosclerotic plaque that trophically redefines the form of hypoxic/ischemic injury to the intima. miRNA -mediated epigenetic regulation may be implicated in atherogenesis, involving oxidized low-density lipoproteins (Chen et al., 2011).

8. Hemodynamics

Hemodynamics within the neovascularized core of the plaque allows for a developmental evolution in terms of so-called complications such as hemorrhage and rupture of the plaque and as staged representation of the endothelial cell injury. Consequential pathways of significance would confirm the agonist nature of hypoxia/ischemia in terms of further emergence of intimal deposition and of cellular proliferation and migration.

A response to injury permits role redefinition as emerging parameters in pathogenesis of the deposition of proteoglycans within the vascular intima. Matrix metalloproteinases participate in plaque destabilization and rupture. Their overexpression is an independent factor in the pathogenesis of acute coronary syndromes (Kulach et al., 2010). A proliferative response in particular illustrates the nature of the vascular wall injury that incrementally progresses as gradients of hypoxia and ischemia within the vessel wall.

9. Gradient parameters

Consequential involvement of the lipid deposition phenomenon integrally permits the establishment of gradient parameters of hypoxia/ischemia within the operative fields of emerging neovascularization in the plaque core.

Procedural and technical specificity of individual plaques illustrate dynamic turnover within plaques in terms particularly of agonists and cellular parameters in redefinition of atherogenesis. In this regard, Interferon-alpha upregulates expression of scavenger-A in monocytes/macrophages with foam cell formation (Li et al., 2011).

The specificity of the inflammatory response is sequentially consequent to the interchangeability of agonist-induced parameters in creating a microenvironment of hypoxia and ischemia centered on the intima.

10. Cellular endothelial injury

The contributing roles of endothelium especially in cases of trauma to the vessel wall would indicate the prototypical attributes in lesion emergence and of subsequent maturation of the atherogenesis phenomenon. Atherogenesis is contributory phenomenon to an ongoing migratory involvement of the intima. This is well-testified by smooth muscle cells that synthesize and secrete matrix proteoglycans, and oxidative stress also induces production of superoxide by endothelial cells with nitric oxide synthase uncoupling (Zweier et al., 2011).

Significant participation in atherogenesis involves mirror-imaged targeting of multiple component systems within the vessel wall that developmentally integrate as regions of hypoxia and ischemia, including the thioredoxin system that correlates with cellular apoptosis in endothelial cell lines in hypoxic stress (Park et al., 2011). Neovascularization proves a permissive phenomenon in development of gradients of ischemia that redefine the individual plaque as compounding parameters of progression to further injury to the vascular wall.

Permissive dynamics are characteristic of oxidation of lipids and particularly of low-density lipoproteins and as evolution of deposition within the intima. Targeting of subsets of cells indicates a selectivity process of progression within sequential pathways of incremental further injury to the vessel wall. Disrupted endoplasmic reticulum equilibrium engages the unfolded protein response in such cells as monocytes (Carroll et al., 2011).

11. Vulnerability issues

System reproduction indicates vulnerability selectivity in the evolution of atheromatous plaques in terms ranging from cell kinetics to proliferative migration of smooth muscle cells directed to the intima and a sensitivity of endothelial cells to responsive pathway generation and trophic factor production. The macrophage system is especially representative of novel pathway events that induce a sequential series of models in manipulative further compromise of viability of the endothelial cells.

Within such scopes of pathogenic representation, there would emerge a parametric remodelling based on aberrant reconstitution of injury as further projected by responses to injury to the intima and endothelium. Within such context, the unfolded protein response is implicated in all stages of atherogenesis and plaque progression (Lhotak et al., 2011).

12. Pathway activation

The operative essentiality of the intimal involvement in atheroma formation calls into operation the developmental dimensions of both endothelium and also of medial smooth muscle cells. The sequence attributes of multiple different pathways contribute to the subsequent emergence of activation phenomena as well represented by the macrophage and

foam cell systems. Mast cells, macrophages and neutrophils release TNF-alpha, IFN-gamma and IL-6 with expression of adhesion molecules and leukocyte recruitment (Zhang et al., 2011). Synthetic and contractile phenotypes of the individual smooth muscle cell indicate specialized forms of series determination in reconstitution of the damaged or injured subintima and also modelled parametric fashioning of the overlying endothelium. Hemodynamics of blood flow localizes such injured endothelium as representative and constitutive foci of persistent pathway activation that delivers dysfunctional attributes to the multi-components of the early atheromatous plaque.

13. Eventual sequence emergence

Contrasting sequentiality is triggered by an aberrant selectivity for trophic effect reproduction in terms of ongoing creation of hypoxia/ischemic gradients across both the endothelium lining the vascular lumen and also within critical regions of operative effect in the involved vascular intima. Such representation calls into evidence gradient pathways of projected reproduction that specifically induce focality of involvement of the plaque within systems of cascade effect. A complex interaction of genetic and environmental factors operates (Chyu & Shah, 2011)

The platelet and coagulation systems conclusively demonstrate a participating series of roles culminating in organization of adherent thrombus within the plaque as incorporated dynamics of trophic potential.

Incremental attributes of further compromise of the viability of the intima are demonstrable as evidential pathways of increasing impact in terms of enhanced intimal thickness. In this regard, cells proliferate in atherosclerotic lesions and also in vascular tissue bordering the plaque (Zettler et al., 2010).

Scope of representative projection is conclusively constituted by the end-stage plaque with a central atheromatous core that consists of cholesterol lipid, lipoprotein and oxidized molecular entities of variable derivation. Increasing representation of inflammatory dynamics is largely dependent on initiating events within the foci of intima underlying dysfunctionally activated endothelium. The dynamics of spread and of replication of individual endothelial cells constitutes a further pathway model for gradient creation between flowing blood and vascular wall intima. Pancoronary arterial instability implicates multifocal disease in acute coronary syndromes (Puri et al., 2011).

14. Concluding remarks

Re-distribution and retargeting events are primary modelling systems in sequence pathways and as multi-staged involvement of the intima of arterial vessel walls. The intimal thickness and remodelling of pathways allow for incremental redistribution of agonists that target differential systems such as endothelium and smooth muscle cells. Macrophages are constitutive systemic parameters that focally re-orientate the targeting dynamics of hypoxia and ischemia in intimal lesion creation. Oxidation-specific epitopes present on apoptotic cells induce the selection of Pattern Recognition Receptors and damage-associated molecular patterns that may be targeted by innate immunity (Miller et al., 2011).

Only in terms of ensuing neovascularization of the individual atherosclerotic plaque can system specificity in atherogenesis permit the emergence of converging pathways of injury and attempted reconstitution of the vessel wall and endothelium.

Macrophages induce transformational events within micro-environmental conditions of propagated susceptibility patterns that relate in particular to selective sites of vascular involvement such as near-arterial branch points of exit. It is such representation that illustrates the evolving vulnerability of focal sites of intima and endothelium in the generation of multiple atheromatous plaques; these subsequently promote self-involvement in dynamic transformation to the so-called complicated plaque.

Regional pathways of spread and further expansion contrast with the maturation of plaque morphology within such systems as macrophage and endothelial cell activation, with the creation of the synthetic/secretory phenotype of the individual smooth muscle cell within the intima.

Distributional dynamics in generation of the atheromatous plaque are developmental issues as indicated by activation of the proto-oncogenes c-fos and c-myc. The considerable heterogeneity of component cell subpopulations within any atheromatous plaque also permits the emergence of monoclonal groups of smooth muscle cells that trophically sustain growth of the plaque within dimensional confines of the involved intima and of injured overlying endothelium.

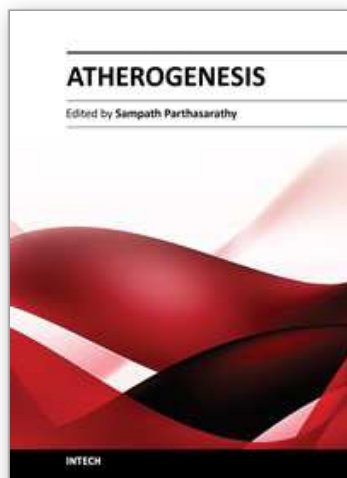
Hypoxia-ischemia is a powerful component series of systems in evolution of the susceptibility pattern determination of plaque localization and remodelling, as well-typified by the marked eventual thickening of the involved intima.

Gradient generation is a key mechanistic system in generation of projected effects of hypoxia-ischemia that coordinate the convergence of injurious agonists in terms of trophic and destructive elements within the intima of the arterial wall.

15. References

- Anggraemi VY, Emoto N, Yagi K, Mayasari DS, Nakayama K, Izumikawa T et al. "Correlation of C4ST-1 and ChGn-2 expression with chondroitin sulphate chain elongation in atherosclerosis" *Biochem Biophys Res Commun* 2011 Jan 29.
- Bacci S, Rizza S, Prudente S, Spoto B, Powers C, Facciorusso A et al. "The ENPPI Q121 variant predicts major cardiovascular events in high-risk individuals: evidence for interaction with obesity in diabetic patients" *Diabetes* 2011 Jan31.
- Carroll TP, Greene CM, McEloaney NG "Measurement of the unfolded protein response (UPR) in monocytes" *Methods Enzymol* 2011;489:83-95.
- Chen KC, Wang YS, Hu CY, Chang WC, Liao YC, Dai CY et al. "OxLDL up-regulates microRNA-29b, leading to epigenetic modifications of MMP-2/MMP-9 genes: a novel mechanism for cardiovascular diseases" *FASEB J* 2011 Jan25.
- Chen T, Li Z, Tu J, Zhu W, Ge J, Zheng X et al. "MicroRNA-29a regulates pro-inflammatory cytokine secretion and scavenger receptor expression by targeting LPL in oxLDL-stimulated dendritic cells" *FEBS Lett* 2011 Jan27.
- Chyu KY, Shah PK "Emerging therapies for atherosclerosis prevention and management" *Cardiol Clin* 2011 Feb;29(1):123-35.
- Civelek M, Manduchi E, Grant GR, Stoeckert CJ Jr, Davies PF "Discovery approaches to UPR in athero-susceptible endothelium in vivo" *Methods Enzymol* 204;489:109-26.
- Kulach A, Dabek J, Glogowska-Ligus J, Garczorz W, Gasior Z "Effects of standard treatment on the dynamics of matrix metalloproteinases gene expression in patients with acute coronary syndromes" *Pharmacol Rep* 2010 Nov-Dec;62(6):1108-16.

- Lee S, Park Y, Zuidema MY, Hannink M, Zhang C "Effects of interventions on oxidative stress and inflammation of cardiovascular diseases" *World J Cardiol* 2011 Jan 26;3(1):18-24.
- Lhotak S, Zhou J, Austin RC "Immunohistochemical detection of the unfolded protein response in atherosclerotic plaques" *Methods Enzymol* 2011;489:23-46.
- Li J, Fu Q, Cui H, Qu B, Pan W, Shen N et al. "Interferon-alpha priming promotes lipid uptake and macrophage-derived foam cell formation: A novel link between interferon-alpha and atherosclerosis in lupus" *Arthritis Rheum* 2011 Feb;63(2):492-502.
- Miller YI, Choi SH, Wiesner P, Fang L, Harkewicz R, Hartvigsen K et al. "Oxidation-specific epitopes are danger-associated molecular patterns recognized by pattern recognition receptors of innate immunity" *Circ Res* 2011 Jan 21; 108(2):235-48.
- Nandish S, Barlon O, Wyatt J, Smith J, Stevens A, Lujan M et al. "Vasculotoxic effects of insulin and its role in atherosclerosis: what is the evidence?" *Curr Atheroscler Rep* 2011 Feb 2.
- Park KJ, Kim YJ, Choi EJ, Park NK, Kim GH, Kim SM et al. "Expression pattern of the thioredoxin system in human endothelial progenitor cells and endothelial cells under hypoxic injury" *Korean Circ J* 2010 Dec;40(12):651-8.
- Puri R, Worthley MI, Nicholls SJ "Intravascular imaging of vulnerable coronary plaque: current and future concepts" *Nat Rev Cardiol* 2011 Jan 25.
- Speyer CL, Ward PA "Role of endothelial chemokines and their receptors during inflammation" *J Invest Surg* 2011;24(1):18-27.
- Van Craeyveld E, Gordts SC, Jacobs F, DeGeest B "Correlation of atherosclerosis between different topographic sites is highly dependent on the type of hyperlipidemia" *Heart Vessels* 2011 Jan 26.
- Von der Thüsen JH, Borensztajn KS, Mormas S, van Heiningen S, Teeling P, van Berkel TJ et al. "IGF-1 has plaque stabilizing effects in atherosclerosis by altering vascular smooth muscle cell phenotype" *Am J Pathol* 2011 Feb;178 | (2):924-34.
- Wang M, Ihida-Stansbury K, Kothapalli D, Tamby MC, Yin Z, Chen L et al. "Microsomal prostaglandin E2 synthase-1 modulates the response to vascular injury" *Circulation* 2011 Jan 31.
- Winnik S, Lohmann C, Richter EK, Schafer N, Song WL, Leiber F et al., "Dietary {alpha}-linolenic acid diminishes experimental atherogenesis and restricts T-cell-driven inflammation" *Eur Heart J* 2011 Jan 31.
- Wong BX, Kyle RA, Croft KD, Quinn CM, Jessup W, Yeap BB "Modulation of macrophage fatty acid content and composition by exposure to dyslipidemia serum in vitro" *Lipids* 2011 Feb 1.
- Yamaoka-Tojo M, Tojo T, Wakaume K, Kameda R, Nemoto S et al. "circulating interleukin-18: A specific biomarker for atherosclerosis-prone patients with metabolic syndrome" *Nutr Metab (Lond)* 2011 Jan 20;8(1):3.
- Zettler ME, Merchant MA, Pierce GN « Augmented cell cycle protein expression and kinase activity in atherosclerotic rabbit vessels » *Exp Clin Cardiol* 2010 Winter ;15(4) :e139-44.
- Zhang G, Yin X, Qi Y, Pendyale L, Chen J, Hou D et al. « Ghrelin and cardiovascular diseases »
- Zhang J, Alcaide P, Liu L, Sun J, He A, Luscinskas FV et al. « Regulation of endothelial cell adhesion molecule expression by mast cells, macrophages, and neutrophils » *PLoS One* 2011 Jan 14 ;6(1) :e14525.
- Zweier J, Chen CA, Druhan LJ "S-Glutathionylation reshapes our understanding of eNOS uncoupling and NO/ROS mediated signaling" *Antioxid Redox Signal* 2011 Jan 24.



Atherogenesis

Edited by Prof. Sampath Parthasarathy

ISBN 978-953-307-992-9

Hard cover, 570 pages

Publisher InTech

Published online 11, January, 2012

Published in print edition January, 2012

This monograph will bring out the state-of-the-art advances in the dynamics of cholesterol transport and will address several important issues that pertain to oxidative stress and inflammation. The book is divided into three major sections. The book will offer insights into the roles of specific cytokines, inflammation, and oxidative stress in atherosclerosis and is intended for new researchers who are curious about atherosclerosis as well as for established senior researchers and clinicians who would be interested in novel findings that may link various aspects of the disease.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Lawrence M. Agius (2012). Parametric Determination of Hypoxic Ischemia in Evolution of Atherogenesis, Atherogenesis, Prof. Sampath Parthasarathy (Ed.), ISBN: 978-953-307-992-9, InTech, Available from: <http://www.intechopen.com/books/atherogenesis/parametric-determination-of-hypoxic-ischemia-in-evolution-of-atherogenesis>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen