

ISSN 1007-9327 (print)
ISSN 2219-2840 (online)



WJG

World Journal of Gastroenterology®

Indexed and Abstracted in:

Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Digital Object Identifier. ISI, Thomson Reuters, 2009 Impact Factor: 2.092 (33/65 Gastroenterology and Hepatology).

Volume 16 Number 48

December 28, 2010

World J Gastroenterol

2010 December 28; 16(48): 6035-6162

Online Submissions

www.wjgnet.com/1007-9327/office

www.wjgnet.com

Printed on Acid-free Paper

世界胃肠病学杂志

Editorial Board

2010-2013

The *World Journal of Gastroenterology* Editorial Board consists of 1144 members, representing a team of worldwide experts in gastroenterology and hepatology. They are from 60 countries, including Albania (1), Argentina (8), Australia (29), Austria (14), Belgium (12), Brazil (10), Brunei Darussalam (1), Bulgaria (2), Canada (20), Chile (3), China (69), Colombia (1), Croatia (2), Cuba (1), Czech (4), Denmark (8), Ecuador (1), Egypt (2), Estonia (2), Finland (8), France (24), Germany (75), Greece (14), Hungary (10), India (26), Iran (6), Ireland (7), Israel (12), Italy (101), Japan (112), Jordan (1), Kuwait (1), Lebanon (3), Lithuania (2), Malaysia (1), Mexico (10), Moldova (1), Netherlands (29), New Zealand (2), Norway (11), Pakistan (2), Poland (11), Portugal (4), Romania (3), Russia (1), Saudi Arabia (3), Serbia (3), Singapore (10), South Africa (2), South Korea (32), Spain (38), Sweden (18), Switzerland (11), Thailand (1), Trinidad and Tobago (1), Turkey (24), United Arab Emirates (2), United Kingdom (82), United States (249), and Uruguay (1).

HONORARY EDITORS-IN-CHIEF

James L Boyer, *New Haven*
Ke-Ji Chen, *Beijing*
Martin H Floch, *New Haven*
Emmet B Keeffe, *Palo Alto*
Geng-Tao Liu, *Beijing*
Lein-Ray Mo, *Tainan*
Eamonn M Quigley, *Cork*
Rafiq A Sheikh, *Sacramento*
Nicholas J Talley, *Rochester*
Ming-Lung Yu, *Kaohsiung*

PRESIDENT AND EDITOR-IN-CHIEF

Lian-Sheng Ma, *Beijing*

ACADEMIC EDITOR-IN-CHIEF

Tauseef Ali, *Oklahoma City*
Mauro Bortolotti, *Bologna*
Tarkan Karakan, *Ankara*
Weekitt Kittisupamongkol, *Bangkok*
Anastasios Koulaouzidis, *Edinburgh*
Bo-Rong Pan, *Xi'an*
Sylvia LF Pender, *Southampton*
Max S Petrov, *Auckland*
George Y Wu, *Farmington*

STRATEGY ASSOCIATE EDITORS-IN-CHIEF

Peter Draganov, *Florida*
Hugh J Freeman, *Vancouver*
Maria C Gutiérrez-Ruiz, *Mexico*
Kazuhiro Hanazaki, *Kochi*
Akio Inui, *Kagoshima*
Kalpesh Jani, *Baroda*
Javier S Martin, *Punta del Este*

Natalia A Osna, *Omaha*
Wei Tang, *Tokyo*
Alan BR Thomson, *Edmonton*
Harry HX Xia, *Hanover*
Jesus K Yamamoto-Furusho, *Mexico*
Yoshio Yamaoka, *Houston*

ASSOCIATE EDITORS-IN-CHIEF

You-Yong Lu, *Beijing*
John M Luk, *Singapore*
Hiroshi Shimada, *Yokohama*

GUEST EDITORIAL BOARD MEMBERS

Chien-Jen Chen, *Taipei*
Yang-Yuan Chen, *Changhua*
Jen-Hwey Chiu, *Taipei*
Seng-Kee Chuah, *Kaohsiung*
Wan-Long Chuang, *Kaohsiung*
Ming-Chih Hou, *Taipei*
Kevin Cheng-Wen Hsiao, *Taipei*
Po-Shiuan Hsieh, *Taipei*
Tsung-Hui Hu, *Kaohsiung*
Wen-Hsin Huang, *Taichung*
Chao-Hung Hung, *Kaohsiung*
I-Rue Lai, *Taipei*
Teng-Yu Lee, *Taichung*
Ching Chung Lin, *Taipei*
Hui-Kang Liu, *Taipei*
Hon-Yi Shi, *Kaohsiung*
Chih-Chi Wang, *Kaohsiung*
Jin-Town Wang, *Taipei*
Cheng-Shyong Wu, *Chia-Yi*
Jaw-Ching Wu, *Taipei*
Jiunn-Jong Wu, *Tainan*
Ming-Shiang Wu, *Taipei*

Ta-Sen Yeh, *Taoyuan*
Hsu-Heng Yen, *Changhua*
Ming-Whei Yu, *Taipei*

MEMBERS OF THE EDITORIAL BOARD



Albania

Bashkim Resuli, *Tirana*



Argentina

Julio H Carri, *Córdoba*
Eduardo de Santibañes, *Buenos Aires*
Bernardo Frider, *Buenos Aires*
Carlos J Pirola, *Buenos Aires*
Bernabe Matias Quesada, *Buenos Aires*
Silvia Sookoian, *Buenos Aires*
Adriana M Torres, *Rosario*
Maria Ines Vaccaro, *Buenos Aires*



Australia

Leon Anton Adams, *Nedlands*
Richard Anderson, *Victoria*
Minoti V Apte, *New South Wales*
Andrew V Biankin, *Sydney*
Filip Braet, *Sydney*
Christopher Christophi, *Melbourne*
Philip G Dinning, *Koagarah*
Guy D Eslick, *Sydney*
Michael A Fink, *Melbourne*

Robert JL Fraser, *Daw Park*
Jacob George, *Westmead*
Mark D Gorrell, *Sydney*
Alexander G Heriot, *Melbourne*
Michael Horowitz, *Adelaide*
John E Kellow, *Sydney*
William Kemp, *Melbourne*
Finlay A Macrae, *Victoria*
Daniel Markovich, *Brisbane*
Vance Matthews, *Melbourne*
Phillip S Oates, *Perth*
Shan Rajendra, *Tasmania*
Rajvinder Singh, *Elizabeth Vale*
Ross C Smith, *Sydney*
Kevin J Spring, *Brisbane*
Nathan Subramaniam, *Brisbane*
Phil Sutton, *Melbourne*
Cuong D Tran, *North Adelaide*
Debbie Trinder, *Fremantle*
David Ian Watson, *Bedford Park*



Austria

Herwig R Cerwenka, *Graz*
Ashraf Dahaba, *Graz*
Peter Ferenci, *Vienna*
Valentin Fuhrmann, *Vienna*
Alfred Gangl, *Vienna*
Alexander M Hirschl, *Wien*
Kurt Lenz, *Linz*
Dietmar Öfner, *Salzburg*
Markus Peck-Radosavljevic, *Vienna*
Markus Raderer, *Vienna*
Stefan Riss, *Vienna*
Georg Roth, *Vienna*
Michael Trauner, *Graz*
Thomas Wild, *Kapellerfeld*



Belgium

Rudi Beyaert, *Gent*
Benedicte Y De Winter, *Antwerp*
Inge I Depoortere, *Leuven*
Olivier Detry, *Liège*
Philip Meuleman, *Ghent*
Marc Peeters, *De Pintelaan*
Freddy Penninckx, *Leuven*
Jean-Yves L Reginster, *Liège*
Mark De Ridder, *Brussels*
Etienne M Sokal, *Brussels*
Kristin Verbeke, *Leuven*
Eddie Wisse, *Keerbergen*



Brazil

José LF Caboclo, *São José do Rio Preto*
Roberto J Carvalho-Filho, *São Paulo*
Jaime Natan Eisig, *São Paulo*
Andre Castro Lyra, *Salvador*
Marcelo Lima Ribeiro, *Braganca Paulista*
Joao Batista Teixeira Rocha, *Santa Maria*
Heitor Rosa, *Goiania*
Damiao C Moraes Santos, *Rio de Janeiro*
Ana Cristina Simões e Silva, *Belo Horizonte*
Eduardo Garcia Vilela, *Belo Horizonte*



Brunei Darussalam

Vui Heng Chong, *Bandar Seri Begawan*



Bulgaria

Zahariy Krastev, *Sofia*
Mihaela Petrova, *Sofia*



Canada

Alain Bitton, *Montreal*
Michael F Byrne, *Vancouver*
Kris Chadee, *Calgary*
Wangxue Chen, *Ottawa*
Ram Prakash Galwa, *Ottawa*
Philip H Gordon, *Montreal*
Waliul Khan, *Ontario*
Qiang Liu, *Saskatoon*
John K Marshall, *Ontario*
Andrew L Mason, *Alberta*
Kostas Pantopoulos, *Quebec*
Nathalie Perreault, *Sherbrooke*
Baljinder Singh Salh, *Vancouver*
Eldon Shaffer, *Calgary*
Martin Storr, *Calgary*
Pingchang Yang, *Hamilton*
Eric M Yoshida, *Vancouver*
Claudia Zwingmann, *Montreal*



Chile

Marcelo A Beltran, *La Serena*
Xabier De Aretxabala, *Santiago*
Silvana Zanlungo, *Santiago*



China

Hui-Jie Bian, *Xi'an*
San-Jun Cai, *Shanghai*
Guang-Wen Cao, *Shanghai*
Xiao-Ping Chen, *Wuhan*
Chi-Hin Cho, *Hong Kong*
Zong-Jie Cui, *Beijing*
Jing-Yuan Fang, *Shanghai*
De-Liang Fu, *Shanghai*
Ze-Guang Han, *Shanghai*
Chun-Yi Hao, *Beijing*
Ming-Liang He, *Hong Kong*
Ching-Lung Lai, *Hong Kong*
Simon Law, *Hong Kong*
Yuk-Tong Lee, *Hong Kong*
En-Min Li, *Shantou*
Fei Li, *Beijing*
Yu-Yuan Li, *Guangzhou*
Zhao-Shen Li, *Shanghai*
Xing-Hua Lu, *Beijing*
Yi-Min Mao, *Shanghai*
Qin Su, *Beijing*
Paul Kwong-Hang Tam, *Hong Kong*
Yuk Him Tam, *Hong Kong*
Ren-Xiang Tan, *Nanjing*
Wei-Dong Tong, *Chongqing*
Eric WC Tse, *Hong Kong*

Fu-Sheng Wang, *Beijing*
Xiang-Dong Wang, *Shanghai*
Nathalie Wong, *Hong Kong*
Justin CY Wu, *Hong Kong*
Wen-Rong Xu, *Zhenjiang*
An-Gang Yang, *Xi'an*
Wei-Cheng You, *Beijing*
Chun-Qing Zhang, *Jinan*
Jian-Zhong Zhang, *Beijing*
Xiao-Peng Zhang, *Beijing*
Xuan Zhang, *Beijing*



Colombia

Germán Campuzano-Maya, *Medellín*



Croatia

Tamara Cacev, *Zagreb*
Marko Duvnjak, *Zagreb*



Cuba

Damian C Rodriguez, *Havana*



Czech

Jan Bures, *Hradec Kralove*
Milan Jirsa, *Praha*
Marcela Kopacova, *Hradec Kralove*
Pavel Trunečka, *Prague*



Denmark

Leif Percival Andersen, *Copenhagen*
Asbjørn M Drewes, *Aalborg*
Morten Frisch, *Copenhagen*
Jan Mollenhauer, *Odense*
Morten Hylander Møller, *Holte*
Søren Rafaelsen, *Vejle*
Jorgen Rask-Madsen, *Skodsborg*
Peer Wille-Jørgensen, *Copenhagen*



Ecuador

Fernando E Sempértegui, *Quito*



Egypt

Zeinab Nabil Ahmed, *Cairo*
Hussein M Atta, *El-Minia*



Estonia

Riina Salupere, *Tartu*
Tamara Vorobjova, *Tartu*



Finland

Saila Kauhanen, *Turku*

Thomas Kietzmann, *Oulu*
Kaija-Leena Kolho, *Helsinki*
Jukka-Pekka Mecklin, *Jyväskylä*
Minna Nyström, *Helsinki*
Pauli Antero Puolakkainen, *Turku*
Juhani Sand, *Tampere*
Lea Veijola, *Helsinki*



France

Claire Bonithon-Kopp, *Dijon*
Lionel Bueno, *Toulouse*
Sabine Colnot, *Paris*
Catherine Daniel, *Lille Cedex*
Alexis Desmoulière, *Limoges*
Thabut Dominique, *Paris*
Francoise L Fabiani, *Angers*
Jean-Luc Faucheron, *Grenoble*
Jean Paul Galmiche, *Nantes cedex*
Boris Guiu, *Dijon*
Paul Hofman, *Nice*
Laurent Huwart, *Paris*
Juan Iovanna, *Marseille*
Abdel-Majid Khatib, *Paris*
Philippe Lehours, *Bordeaux*
Flavio Maina, *Marseille*
Patrick Marcellin, *Paris*
Rene Gerolami Santandera, *Marseille*
Annie Schmid-Alliana, *Nice cedex*
Alain L Servin, *Châtenay-Malabry*
Stephane Supiot, *Nantes*
Baumert F Thomas, *Strasbourg*
Jean-Jacques Tuech, *Rouen*
Frank Zerbib, *Bordeaux Cedex*



Germany

Erwin Biecker, *Siegburg*
Hubert Blum, *Freiburg*
Thomas Bock, *Tuebingen*
Dean Bogoevski, *Hamburg*
Elfriede Bollschweiler, *Köln*
Jürgen Borlak, *Hannover*
Christa Buechler, *Regensburg*
Jürgen Büning, *Lübeck*
Elke Cario, *Essen*
Bruno Christ, *Halle/Saale*
Christoph F Dietrich, *Bad Mergentheim*
Ulrich R Fölsch, *Kiel*
Nikolaus Gassler, *Aachen*
Markus Gerhard, *Munich*
Dieter Glebe, *Giessen*
Ralph Graeser, *Freiburg*
Axel M Gressner, *Aachen*
Nils Habbe, *Marburg*
Thilo Hackert, *Heidelberg*
Wolfgang Hagmann, *Heidelberg*
Dirk Haller, *Freising*
Philip D Hard, *Giessen*
Claus Hellerbrand, *Regensburg*
Klaus R Herrlinger, *Stuttgart*
Eberhard Hildt, *Berlin*
Andrea Hille, *Goettingen*
Joerg C Hoffmann, *Berlin*
Philippe N Khalil, *Munich*
Andrej Khandoga, *Munich*
Jorg Kleeff, *Munich*
Ingmar Königsrainer, *Tübingen*
Peter Konturek, *Erlangen*

Stefan Kubicka, *Hannover*
Joachim Labenz, *Siegen*
Michael Linnebacher, *Rostock*
Jutta Elisabeth Lüttges, *Riegelsberg*
Peter Malfertheiner, *Magdeburg*
Oliver Mann, *Hamburg*
Peter N Meier, *Hannover*
Sabine Mihm, *Göttingen*
Klaus Mönkemüller, *Bottrop*
Jonas Mudter, *Erlangen*
Sebastian Mueller, *Heidelberg*
Robert Obermaier, *Freiburg*
Matthias Ocker, *Erlangen*
Stephan Johannes Ott, *Kiel*
Gustav Paumgartner, *Munich*
Christoph Reichel, *Bad Brückenau*
Markus Reiser, *Bochum*
Steffen Rickes, *Magdeburg*
Elke Roeb, *Giessen*
Christian Rust, *Munich*
Hans Scherubl, *Berlin*
Martin K Schilling, *Homburg*
Joerg F Schlaak, *Essen*
Rene Schmidt, *Freiburg*
Andreas G Schreyer, *Regensburg*
Karsten Schulmann, *Bochum*
Henning Schulze-Bergkamen, *Mainz*
Manfred V Singer, *Mannheim*
Jens Standop, *Bonn*
Jurgen M Stein, *Frankfurt*
Ulrike S Stein, *Berlin*
Wolfgang R Stremmel, *Heidelberg*
Harald F Teutsch, *Ulm*
Hans L Tillmann, *Leipzig*
Christian Trautwein, *Aachen*
Joerg Trojan, *Frankfurt*
Arndt Vogel, *Hannover*
Siegfried Wagner, *Deggendorf*
Frank Ulrich Weiss, *Greifswald*
Fritz von Weizsäcker, *Berlin*
Thomas Wex, *Magdeburg*
Stefan Wirth, *Wuppertal*
Marty Zdichavsky, *Tübingen*



Greece

Helen Christopoulou-Aletra, *Thessaloniki*
T Choli-Papadopoulou, *Thessaloniki*
Tsianos Epameinondas, *Ioannina*
Ioannis Kanellos, *Thessaloniki*
Elias A Kouroumalis, *Heraklion*
Ioannis E Koutroubakis, *Heraklion*
Michael Koutsilieris, *Athens*
Andreas Larentzakis, *Athens*
Emanuel K Manesis, *Athens*
Spilios Manolakopoulos, *Athens*
Konstantinos Mimidis, *Alexandroupolis*
George Papatheodoridis, *Athens*
Spiros Sgouros, *Athens*
Evangelos Tsiambas, *Ag Paraskevi Attiki*



Hungary

György M Buzás, *Budapest*
László Czakó, *Szeged*
Gyula Farkas, *Szeged*
Peter Hegyi, *Szeged*
Peter L Lakatos, *Budapest*

Yvette Mándi, *Szeged*
Zoltan Rakonczay, *Szeged*
Ferenc Sipos, *Budapest*
Zsuzsa Szondy, *Debrecen*
Gabor Veres, *Budapest*



India

Philip Abraham, *Mumbai*
Vineet Ahuja, *New Delhi*
Giriraj Ratan Chandak, *Hyderabad*
Devinder Kumar Dhawan, *Chandigarh*
Radha K Dhiman, *Chandigarh*
Pankaj Garg, *Panchkula*
Pramod Kumar Garg, *New Delhi*
Debidas Ghosh, *Midnapore*
Uday C Ghoshal, *Lucknow*
Bhupendra Kumar Jain, *Delhi*
Ashok Kumar, *Lucknow*
Bikash Medhi, *Chandigarh*
Sri P Misra, *Allahabad*
Gopal Nath, *Varanasi*
Samiran Nundy, *New Delhi*
Jagannath Palepu, *Mumbai*
Vandana Panda, *Mumbai*
Benjamin Perakath, *Tamil Nadu*
Ramesh Roop Rai, *Jaipur*
Nageshwar D Reddy, *Hyderabad*
Barjesh Chander Sharma, *New Delhi*
Virendra Singh, *Chandigarh*
Rupjyoti Talukdar, *Guwahati*
Rakesh Kumar Tandon, *New Delhi*
Jai Dev Wig, *Chandigarh*



Iran

Mohammad Abdollahi, *Tehran*
Peyman Adibi, *Isfahan*
Seyed-Moayed Alavian, *Tehran*
Seyed Mohsen Dehghani, *Shiraz*
Reza Malekzadeh, *Tehran*
Alireza Mani, *Tehran*



Ireland

Billy Bourke, *Dublin*
Ted Dinan, *Cork*
Catherine Greene, *Dublin*
Ross McManus, *Dublin*
Anthony P Moran, *Galway*
Marion Rowland, *Dublin*



Israel

Simon Bar-Meir, *Hashomer*
Alexander Becker, *Afula*
Abraham R Eliakim, *Haifa*
Sigal Fishman, *Tel Aviv*
Boris Kirshtein, *Beer Sheva*
Eli Magen, *Ashdod*
Menachem Moshkowitz, *Tel-Avivo*
Assy Nimer, *Safed*
Shmuel Odes, *Beer Sheva*
Mark Pines, *Bet Dagan*
Ron Shaoul, *Haifa*
Ami D Sperber, *Beer-Sheva*



Italy

Donato F Altomare, *Bari*
 Piero Amodio, *Padova*
 Angelo Andriulli, *San Giovanni Rotondo*
 Paolo Angeli, *Padova*
 Bruno Annibale, *Rome*
 Paolo Aurello, *Rome*
 Salvatore Auricchio, *Naples*
 Antonio Basoli, *Rome*
 Claudio Bassi, *Verona*
 Gabrio Bassotti, *Perugia*
 Mauro Bernardi, *Bologna*
 Alberto Biondi, *Rome*
 Luigi Bonavina, *Milano*
 Guglielmo Borgia, *Naples*
 Roberto Berni Canani, *Naples*
 Maria Gabriella Caruso, *Bari*
 Fausto Catena, *Bologna*
 Giuseppe Chiarioni, *Valeggio*
 Michele Cicala, *Rome*
 Dario Conte, *Milano*
 Francesco Costa, *Pisa*
 Antonio Craxi, *Palermo*
 Salvatore Cucchiara, *Rome*
 Giuseppe Currò, *Messina*
 Mario M D'Elios, *Florence*
 Mirko D'Onofrio, *Verona*
 Silvio Danese, *Milano*
 Roberto de Franchis, *Milano*
 Paola De Nardi, *Milan*
 Giovanni D De Palma, *Naples*
 Giuliana Decorti, *Trieste*
 Gianlorenzo Dionigi, *Varese*
 Massimo Falconi, *Verona*
 Silvia Fargion, *Milan*
 Giammarco Fava, *Ancona*
 Francesco Feo, *Sassari*
 Alessandra Ferlini, *Ferrara*
 Alessandro Ferrero, *Torino*
 Mirella Fraquelli, *Milan*
 Luca Frulloni, *Verona*
 Giovanni B Gaeta, *Napoli*
 Antonio Gasbarrini, *Rome*
 Edoardo G Giannini, *Genoa*
 Alessandro Granito, *Bologna*
 Fabio Grizzi, *Milan*
 Salvatore Gruttadauria, *Palermo*
 Pietro Invernizzi, *Milan*
 Achille Iolascon, *Naples*
 Angelo A Izzo, *Naples*
 Ezio Laconi, *Cagliari*
 Giovanni Latella, *L'Aquila*
 Massimo Leverro, *Rome*
 Francesco Luzzza, *Catanzaro*
 Lucia Malaguarnera, *Catania*
 Francesco Manguso, *Napoli*
 Pier Mannuccio Mannucci, *Milan*
 Giancarlo Mansueto, *Verona*
 Giulio Marchesini, *Bologna*
 Mara Massimi, *Coppito*
 Giovanni Milito, *Rome*
 Giuseppe Montalto, *Palermo*
 Giovanni Monteleone, *Rome*
 Luca Morelli, *Trento*
 Giovanni Musso, *Torino*
 Mario Nano, *Torino*
 Gerardo Nardone, *Napoli*
 Riccardo Nascimbeni, *Brescia*
 Valerio Nobili, *Rome*
 Fabio Pace, *Milan*
 Nadia Peparini, *Rome*

Marcello Persico, *Naples*
 Mario Pescatori, *Rome*
 Raffaele Pezzilli, *Bologna*
 Alberto Piperno, *Monza*
 Anna C Piscaglia, *Rome*
 Piero Portincasa, *Bari*
 Michele Reni, *Milan*
 Vittorio Ricci, *Pavia*
 Oliviero Riggio, *Rome*
 Mario Rizzetto, *Torino*
 Ballarin Roberto, *Modena*
 Gerardo Rosati, *Potenza*
 Franco Roviello, *Siena*
 Cesare Ruffolo, *Treviso*
 Massimo Rugge, *Padova*
 Marco Scarpa, *Padova*
 Carmelo Scarpignato, *Parma*
 Giuseppe Sica, *Rome*
 Marco Silano, *Rome*
 Pierpaolo Sileri, *Rome*
 Vincenzo Stanghellini, *Bologna*
 Fiorucci Stefano, *Perugia*
 Giovanni Tarantino, *Naples*
 Alberto Tommasini, *Trieste*
 Guido Torzilli, *Rozzano Milan*
 Cesare Tosetti, *Porretta Terme*
 Antonello Trecca, *Rome*
 Vincenzo Villanacci, *Brescia*
 Lucia Ricci Vitiani, *Rome*
 Marco Vivarelli, *Bologna*



Japan

Kyoichi Adachi, *Izumo*
 Yasushi Adachi, *Sapporo*
 Takafumi Ando, *Nagoya*
 Akira Andoh, *Otsu*
 Masahiro Arai, *Tokyo*
 Hitoshi Asakura, *Tokyo*
 Kazuo Chijiwa, *Miyazaki*
 Yuichiro Eguchi, *Saga*
 Itaru Endo, *Yokohama*
 Munechika Enjoji, *Fukuoka*
 Yasuhiro Fujino, *Akashi*
 Mitsuhiko Fujishiro, *Tokyo*
 Kouhei Fukushima, *Sendai*
 Masanori Hatakeyama, *Tokyo*
 Keiji Hirata, *Kitakyushu*
 Toru Hiyama, *Higashihiroshima*
 Masahiro Iizuka, *Akita*
 Susumu Ikehara, *Osaka*
 Kenichi Ikejima, *Bunkyo-ku*
 Yutaka Inagaki, *Kanagawa*
 Hiromi Ishibashi, *Nagasaki*
 Shunji Ishihara, *Izumo*
 Toru Ishikawa, *Niigata*
 Toshiyuki Ishiwata, *Tokyo*
 Hajime Isomoto, *Nagasaki*
 Yoshiaki Iwasaki, *Okayama*
 Satoru Kakizaki, *Gunma*
 Terumi Kamisawa, *Tokyo*
 Mototsugu Kato, *Sapporo*
 Naoya Kato, *Tokyo*
 Takumi Kawaguchi, *Kurume*
 Yohei Kida, *Kainan*
 Shogo Kikuchi, *Aichi*
 Tsuneo Kitamura, *Chiba*
 Takashi Kobayashi, *Tokyo*
 Yasuhiro Koga, *Isehara*
 Takashi Kojima, *Sapporo*
 Norihiro Kokudo, *Tokyo*
 Masatoshi Kudo, *Osaka*
 Shin Maeda, *Tokyo*
 Satoshi Mamori, *Hyogo*
 Atsushi Masamune, *Sendai*
 Yasushi Matsuzaki, *Tsukuba*
 Kenji Miki, *Tokyo*
 Toshihiro Mitaka, *Sapporo*
 Hiroto Miwa, *Hyogo*
 Kotaro Miyake, *Tokushima*
 Manabu Morimoto, *Yokohama*
 Yoshiharu Motoo, *Kanazawa*
 Yoshiaki Murakami, *Hiroshima*
 Yoshiki Murakami, *Kyoto*
 Kunihiko Murase, *Tusima*
 Akihito Nagahara, *Tokyo*
 Yuji Naito, *Kyoto*
 Atsushi Nakajima, *Yokohama*
 Hisato Nakajima, *Tokyo*
 Hiroki Nakamura, *Yamaguchi*
 Shotaro Nakamura, *Fukuoka*
 Akimasa Nakao, *Nagoya*
 Shuhei Nishiguchi, *Hyogo*
 Mikio Nishioka, *Niihama*
 Keiji Ogura, *Tokyo*
 Susumu Ohmada, *Maebashi*
 Hirohide Ohnishi, *Akita*
 Kenji Okajima, *Nagoya*
 Kazuichi Okazaki, *Osaka*
 Morikazu Onji, *Ehime*
 Satoshi Osawa, *Hamamatsu*
 Hidetsugu Saito, *Tokyo*
 Yutaka Saito, *Tokyo*
 Naoaki Sakata, *Sendai*
 Yasushi Sano, *Chiba*
 Tokihiko Sawada, *Tochigi*
 Tomohiko Shimatan, *Hiroshima*
 Yukihiko Shimizu, *Kyoto*
 Shinji Shimoda, *Fukuoka*
 Yoshio Shirai, *Niigata*
 Masayuki Sho, *Nara*
 Shoichiro Sumi, *Kyoto*
 Hidekazu Suzuki, *Tokyo*
 Masahiro Tajika, *Nagoya*
 Yoshihisa Takahashi, *Tokyo*
 Toshinari Takamura, *Kanazawa*
 Hiroaki Takeuchi, *Kochi*
 Yoshitaka Takuma, *Okayama*
 Akihiro Tamori, *Osaka*
 Atsushi Tanaka, *Tokyo*
 Shinji Tanaka, *Hiroshima*
 Satoshi Tanno, *Hokkaido*
 Shinji Togo, *Yokohama*
 Hitoshi Tsuda, *Tokyo*
 Hiroyuki Uehara, *Osaka*
 Masahito Uemura, *Kashihara*
 Yoshiyuki Ueno, *Sendai*
 Mitsuyoshi Urashima, *Tokyo*
 Takuya Watanabe, *Niigata*
 Satoshi Yamagiwa, *Niigata*
 Taketo Yamaguchi, *Chiba*
 Mitsunori Yamakawa, *Yamagata*
 Takayuki Yamamoto, *Yokkaichi*
 Yutaka Yata, *Maebashi*
 Hiroshi Yoshida, *Tokyo*
 Norimasa Yoshida, *Kyoto*
 Yuichi Yoshida, *Osaka*
 Kentaro Yoshika, *Toyoake*
 Hitoshi Yoshiji, *Nara*
 Katsutoshi Yoshizato, *Higashihiroshima*
 Tomoharu Yoshizumi, *Fukuoka*



Jordan

Ismail Matalka, *Irbid*

**Kuwait**Islam Khan, *Safat***Lebanon**Bassam N Abboud, *Beirut*
Ala I Sharara, *Beirut*
Rita Slim, *Beirut***Lithuania**Giedrius Barauskas, *Kaunas*
Limas Kupcinskas, *Kaunas***Malaysia**Andrew Seng Boon Chua, *Ipah***Mexico**Richard A Awad, *Mexico*
Aldo Torre Delgadillo, *Mexico*
Diego Garcia-Compean, *Monterrey*
Paulino M Hernández Magro, *Celaya*
Miguel Angel Mercado, *Distrito Federal*
Arturo Panduro, *Jalisco*
Omar Vergara-Fernandez, *Tlalpan*
Saúl Villa-Trevio, *Mexico***Moldova**Igor Mishin, *Kishinev***Netherlands**Ulrich Beuers, *Amsterdam*
Lee Bouwman, *Leiden*
Albert J Bredenoord, *Nieuwegein*
Lodewijk AA Brosens, *Utrecht*
J Bart A Crusius, *Amsterdam*
Wouter de Herder, *Rotterdam*
Pieter JF de Jonge, *Rotterdam*
Robert J de Knegt, *Rotterdam*
Wendy W Johanna de Leng, *Utrecht*
Annemarie de Vries, *Rotterdam*
James CH Hardwick, *Leiden*
Frank Hoentjen, *Haarlem*
Misha Luyer, *Sittard*
Jeroen Maljaars, *Maastricht*
Gerrit A Meijer, *Amsterdam*
Servaas Morré, *Amsterdam*
Chris JJ Mulder, *Amsterdam*
John Plukker, *Groningen*
Albert Frederik Pull ter Gunne, *Tilburg*
Paul E Sijens, *Groningen*
BW Marcel Spanier, *Arnhem*
Shiri Sverdlov, *Maastricht*
Maarten Tushuizen, *Amsterdam*
Jantine van Baal, *Heidelberglaan*
Astrid van der Velde, *The Hague*
Karel van Erpecum, *Utrecht*
Loes van Keimpema, *Nijmegen*Robert Christiaan Verdonk, *Groningen*
Erwin G Zoetendal, *Wageningen***New Zealand**Andrew S Day, *Christchurch***Norway**Olav Dalgard, *Oslo*
Trond Peder Flaten, *Trondheim*
Reidar Fossmark, *Trondheim*
Rasmus Goll, *Tromso*
Ole Høie, *Arendal*
Asle W Medhus, *Oslo*
Espen Melum, *Oslo*
Trine Olsen, *Tromso*
Eyvind J Paulssen, *Tromso*
Jon Arne Søreide, *Stavanger*
Kjetil Søreide, *Stavanger***Pakistan**Shahab Abid, *Karachi*
Syed MW Jafri, *Karachi***Poland**Marek Bebenek, *Wroclaw*
Tomasz Brzozowski, *Cracow*
Halina Cichoż-Lach, *Lublin*
Andrzej Dabrowski, *Bialystok*
Hanna Gregorek, *Warsaw*
Marek Hartleb, *Katowice*
Beata Jolanta Jabłońska, *Katowice*
Stanislaw J Konturek, *Krakow*
Jan Kulig, *Krakow*
Dariusz M Lebensztejn, *Bialystok*
Julian Swierczynski, *Gdansk***Portugal**Raquel Almeida, *Porto*
Ana Isabel Lopes, *Lisboa Codex*
Ricardo Marcos, *Porto*
Guida Portela-Gomes, *Estoril***Romania**Dan L Dumitrascu, *Cluj*
Adrian Saftoiu, *Craiova*
Andrada Seicean, *Cluj-Napoca***Russia**Vasiliy I Reshetnyak, *Moscow***Saudi Arabia**Ibrahim A Al Mofleh, *Riyadh*
Abdul-Wahed Meshikhes, *Qatif*
Faisal Sanai, *Riyadh***Serbia**Tamara M Alempijevic, *Belgrade*
Dusan M Jovanovic, *Sremska Kamenica*
Zoran Krivokapic, *Belgrade***Singapore**Madhav Bhatia, *Singapore*
Kong Weng Eu, *Singapore*
Brian Kim Poh Goh, *Singapore*
Khek-Yu Ho, *Singapore*
Kok Sun Ho, *Singapore*
Fock Kwong Ming, *Singapore*
London Lucien Ooi, *Singapore*
Nagarajan Perumal, *Singapore*
Francis Seow-Choen, *Singapore***South Africa**Rosemary Joyce Burnett, *Pretoria*
Michael Kew, *Cape Town***South Korea**Sang Hoon Ahn, *Seoul*
Sung-Gil Chi, *Seoul*
Myung-Gyu Choi, *Seoul*
Hoon Jai Chun, *Seoul*
Yeun-Jun Chung, *Seoul*
Young-Hwa Chung, *Seoul*
Kim Donghee, *Seoul*
Ki-Baik Hahm, *Incheon*
Sun Pyo Hong, *Geonggi-do*
Seong Gyu Hwang, *Seongnam*
Hong Joo Kim, *Seoul*
Jae J Kim, *Seoul*
Jin-Hong Kim, *Suwon*
Nayoung Kim, *Seongnam-si*
Sang Geon Kim, *Seoul*
Seon Hahn Kim, *Seoul*
Sung Kim, *Seoul*
Won Ho Kim, *Seoul*
Jeong Min Lee, *Seoul*
Kyu Taek Lee, *Seoul*
Sang Kil Lee, *Seoul*
Sang Yeoup Lee, *Gyeongsangnam-do*
Yong Chan Lee, *Seoul*
Eun-Yi Moon, *Seoul*
Hyoung-Chul Oh, *Seoul*
Seung Woon Paik, *Seoul*
Joong-Won Park, *Goyang*
Ji Kon Ryu, *Seoul*
Si Young Song, *Seoul*
Marie Yeo, *Suwon*
Byung Chul Yoo, *Seoul*
Dae-Yeul Yu, *Daejeon***Spain**Maria-Angeles Aller, *Madrid*
Raul J Andrade, *Málaga*
Luis Aparisi, *Valencia*
Gloria González Aseguinolaza, *Navarra*
Matias A Avila, *Pamplona*

Fernando Azpiroz, *Barcelona*
 Ramon Bataller, *Barcelona*
 Belén Beltrán, *Valencia*
 Adolfo Benages, *Valencia*
 Josep M Bordas, *Barcelona*
 Lisardo Boscá, *Madrid*
 Luis Bujanda, *San Sebastián*
 Juli Busquets, *Barcelona*
 Matilde Bustos, *Pamplona*
 José Julián calvo Andrés, *Salamanca*
 Andres Cardenas, *Barcelona*
 Antoni Castells, *Barcelona*
 Fernando J Corrales, *Pamplona*
 JEDomínguez-Muñoz, *Santiago de Compostela*
 Juan Carlos Laguna Egea, *Barcelona*
 Isabel Fabregat, *Barcelona*
 Antoni Farré, *Barcelona*
 Vicente Felipo, *Valencia*
 Laureano Fernández-Cruz, *Barcelona*
 Luis Grande, *Barcelona*
 Angel Lanas, *Zaragoza*
 Juan-Ramón Larrubia, *Guadalajara*
 María IT López, *Jaén*
 Juan Macías, *Seville*
 Javier Martin, *Granada*
 José Manuel Martin-Villa, *Madrid*
 Julio Mayol, *Madrid*
 Mireia Miquel, *Sabadell*
 Albert Parés, *Barcelona*
 Jesús M Prieto, *Pamplona*
 Pedro L Majano Rodriguez, *Madrid*
 Joan Roselló-Catafau, *Barcelona*
 Eva Vaquero, *Barcelona*



Sweden

Lars Erik Agréus, *Stockholm*
 Mats Andersson, *Stockholm*
 Roland Andersson, *Lund*
 Mauro D'Amato, *Huddinge*
 Evangelos Kalaitzakis, *Gothenburg*
 Greger Lindberg, *Stockholm*
 Annika Lindblom, *Stockholm*
 Sara Lindén, *Göteborg*
 Hanns-Ulrich Marschall, *Stockholm*
 Pär Erik Myreliid, *Linköping*
 Åke Nilsson, *Lund*
 Helena Nordenstedt, *Stockholm*
 Kjell Öberg, *Uppsala*
 Lars A Pahlman, *Uppsala*
 Stefan G Pierzynowski, *Lund*
 Sara Regnér, *Malmö*
 Bobby Tingstedt, *Lund*
 Zongli Zheng, *Stockholm*



Switzerland

Pascal Bucher, *Geneva*
 Michelangelo Foti, *Geneva*
 Jean L Frossard, *Geneva*
 Andreas Geier, *Zürich*
 Pascal Gervaz, *Geneva*
 Gerd A Kullak-Ublick, *Zürich*
 Fabrizio Montecucco, *Geneva*
 Paul M Schneider, *Zürich*
 Felix Stickel, *Berne*
 Bruno Stieger, *Zürich*
 Inti Zlobec, *Basel*



Trinidad and Tobago

Shivananda Nayak, *Mount Hope*



Turkey

Sinan Akay, *Tekirdag*
 Metin Basaranoglu, *Istanbul*
 Yusuf Bayraktar, *Ankara*
 A Mithat Bozdayi, *Ankara*
 Hayrullah Derici, *Balikesir*
 Eren Ersoy, *Ankara*
 Mukaddes Esrefoglu, *Malatya*
 Can Goen, *Kutahya*
 Selin Kapan, *Istanbul*
 Aydin Karabacakoglu, *Konya*
 Cuneyt Kayaalp, *Malatya*
 Kemal Kismet, *Ankara*
 Seyfettin Köklü, *Ankara*
 Mehmet Refik Mas, *Etilik-Ankara*
 Osman C Ozdogan, *Istanbul*
 Bülent Salman, *Ankara*
 Orhan Sezgin, *Mersin*
 Ilker Tasci, *Ankara*
 Müge Tecder-Ünal, *Ankara*
 Ahmet Tekin, *Mersin*
 Mesut Tez, *Ankara*
 Ekmel Tezel, *Ankara*
 Özlem Yilmaz, *Izmir*



United Arab Emirates

Fikri M Abu-Zidan, *Al-Ain*
 Sherif M Karam, *Al-Ain*



United Kingdom

Simon Afford, *Birmingham*
 Navneet K Ahluwalia, *Stockport*
 Mohamed H Ahmed, *Southampton*
 Basil Ammori, *Salford*
 Lesley A Anderson, *Belfast*
 Chin Wee Ang, *Liverpool*
 Yeng S Ang, *Wigan*
 Anthony TR Axon, *Leeds*
 Kathleen B Bamford, *London*
 Jim D Bell, *London*
 John Beynon, *Swansea*
 Chris Briggs, *Sheffield*
 Geoffrey Burnstock, *London*
 Alastair D Burt, *Newcastle*
 Jeff Butterworth, *Shrewsbury*
 Jeremy FL Cobbold, *London*
 Jean E Crabtree, *Leeds*
 Tatjana Crnogorac-Jurcevic, *London*
 William Dickey, *Londonderry*
 Sunil Dolwani, *Cardiff*
 Emad M El-Omar, *Aberdeen*
 A M El-Tawil, *Birmingham*
 Charles B Ferguson, *Belfast*
 Andrew Fowell, *Southampton*
 Piers Gatenby, *London*
 Daniel R Gaya, *Edinburgh*
 Anil George, *London*
 Rob Glynne-Jones, *Northwood*
 Jason CB Goh, *Birmingham*
 Gianpiero Gravante, *Leicester*

Brian Green, *Belfast*
 William Greenhalf, *Liverpool*
 Indra N Guha, *Nottingham*
 Stefan G Hübscher, *Birmingham*
 Robin Hughes, *London*
 Pali Hungin, *Stockton*
 Nawfal Hussein, *Nottingham*
 Clement W Imrie, *Glasgow*
 Janusz AZ Jankowski, *Oxford*
 Sharad Karandikar, *Birmingham*
 Peter Karayiannis, *London*
 Shahid A Khan, *London*
 Patricia F Lalor, *Birmingham*
 John S Leeds, *Sheffield*
 Ian Lindsey, *Oxford*
 Hong-Xiang Liu, *Cambridge*
 Dileep N Lobo, *Nottingham*
 Graham MacKay, *Glasgow*
 Mark Edward McAlindon, *Sheffield*
 Anne McCune, *Bristol*
 Donald Campbell McMillan, *Glasgow*
 Giorgina Mieli-Vergani, *London*
 Jamie Murphy, *London*
 Guy Fairbairn Nash, *Poole*
 James Neuberger, *Birmingham*
 Patrick O'Dwyer, *Glasgow*
 Christos Paraskeva, *Bristol*
 Richard Parker, *North Staffordshire*
 Thamara Perera, *Birmingham*
 Kondragunta Rajendra Prasad, *Leeds*
 D Mark Pritchard, *Liverpool*
 Alberto Quaglia, *London*
 Akhilesh B Reddy, *Cambridge*
 Kevin Robertson, *Glasgow*
 Sanchoy Sarkar, *Liverpool*
 John B Schofield, *Kent*
 Marco Senzolo, *Padova*
 Venkatesh Shanmugam, *Derby*
 Paul Sharp, *London*
 Chew Thean Soon, *Manchester*
 Aravind Suppiah, *East Yorkshire*
 Noriko Suzuki, *Middlesex*
 Simon D Taylor-Robinson, *London*
 Frank I Tovey, *London*
 A McCulloch Veitch, *Wolverhampton*
 Vamsi R Velchuru, *Lowestoft*
 Sumita Verma, *Brighton*
 Catherine Walter, *Cheltenham*
 Julian RF Walters, *London*
 Roger Williams, *London*



United States

Kareem M Abu-Elmagd, *Pittsburgh*
 Sami R Achem, *Florida*
 Golo Ahlenstiel, *Bethesda*
 Bhupinder S Anand, *Houston*
 M Ananthanarayanan, *New York*
 Balamurugan N Appakalal, *Minneapolis*
 Dimitrios V Avgerinos, *New York*
 Shashi Bala, *Worcester*
 Anthony J Bauer, *Pittsburgh*
 Kevin E Behrns, *Gainesville*
 Roberto Bergamaschi, *New York*
 Henry J Binder, *New Haven*
 Edmund J Bini, *New York*
 Wojciech Blonski, *Philadelphia*
 Mark Bloomston, *Columbus*
 Edward L Bradley III, *Sarasota*
 Carla W Brady, *Durham*

David A Brenner, *San Diego*
Adeel A Butt, *Pittsburgh*
Shi-Ying Cai, *New Haven*
Justin MM Cates, *Nashville*
Eugene P Ceppa, *Durham*
Jianyuan Chai, *Long Beach*
Ronald S Chamberlain, *Livingston*
Fei Chen, *Morgantown*
Xian-Ming Chen, *Omaha*
Ramsey Chi-man Cheung, *Palo Alto*
Denesh Chitkara, *East Brunswick*
Clifford S Cho, *Madison*
Parimal Chowdhury, *Arkansas*
John David Christein, *Birmingham*
Thomas Clancy, *Boston*
Ana J Coito, *Los Angeles*
Ricardo Alberto Cruciani, *New York*
Joseph J Cullen, *Iowa City*
Mark J Czaja, *New York*
Mariana D Dabeva, *Bronx*
Jessica A Davila, *Houston*
Conor P Delaney, *Cleveland*
Laurie DeLeve, *Los Angeles*
Anthony J Demetris, *Pittsburgh*
Sharon DeMorrow, *Temple*
Bijan Eghtesad, *Cleveland*
Yoram Elitsur, *Huntington*
Mohamad A Eloubeidi, *Alabama*
Wael El-Rifai, *Nashville*
Sukru H Emre, *New Haven*
Giamila Fantuzzi, *Chicago*
Ashkan Farhadi, *Irvine*
Ronnie Fass, *Tucson*
Martín E Fernández-Zapico, *Rochester*
Alessandro Fichera, *Chicago*
Josef E Fischer, *Boston*
Piero Marco Fisichella, *Maywood*
Fritz Francois, *New York*
Glenn T Furuta, *Aurora*
T Clark Gamblin, *Pittsburgh*
Henning Gerke, *Iowa City*
Jean-Francois Geschwind, *Baltimore*
R Mark Ghobrial, *Texas*
John F Gibbs, *Buffalo*
Shannon S Glaser, *Temple*
Ajay Goel, *Dallas*
Jon C Gould, *Madison*
Eileen F Grady, *San Francisco*
James H Grendell, *New York*
John R Grider, *Richmond*
Anna S Gukovskaya, *Los Angeles*
Chakshu Gupta, *St. Joseph*
Grigoriy E Gurvits, *New York*
Hai-Yong Han, *Phoenix*
Yuan-Ping Han, *Los Angeles*
Imran Hassan, *Springfield*
Charles P Heise, *Madison*
Lisa J Herrinton, *Oakland*
Oscar Joe Hines, *Los Angeles*
Samuel B Ho, *San Diego*
Steven Hochwald, *Gainesville*
Richard Hu, *Los Angeles*
Eric S Hungness, *Chicago*
Jamal A Ibdah, *Columbia*
Atif Iqbal, *Omaha*
Hartmut Jaeschke, *Tucson*
Donald M Jensen, *Chicago*
Robert Jensen, *Bethesda*
Leonard R Johnson, *Memphis*
Andreas M Kaiser, *Los Angeles*
JingXuan Kang, *Charlestown*
John Y Kao, *Michigan*
Randeep Singh Kashyap, *New York*
Rashmi Kaul, *Tulsa*
Jonathan D Kaunitz, *Los Angeles*
Stephen M Kavic, *Baltimore*
Ali Keshavarzian, *Chicago*
Amir Maqbul Khan, *Marshall*
Kusum K Kharbanda, *Omaha*
Chang Kim, *West Lafayette*
Dean Y Kim, *Detroit*
Miran Kim, *Providence*
Burton I Korelitz, *New York*
Josh Korzenik, *Boston*
Richard A Kozarek, *Seattle*
Alyssa M Krasinskas, *Pittsburgh*
Shiu-Ming Kuo, *Buffalo*
Michelle Lai, *Boston*
Michael Leitman, *New York*
Dong-Hui Li, *Houston*
Ming Li, *New Orleans*
Zhiping Li, *Baltimore*
Gary R Lichtenstein, *Philadelphia*
Chen Liu, *Gainesville*
Zhang-Xu Liu, *Los Angeles*
Craig D Logsdon, *Houston*
Kaye M Reid Lombardo, *Rochester*
Michael R Lucey, *Madison*
Kirk Ludwig, *Wisconsin*
James D Luketich, *Pittsburgh*
Patrick M Lynch, *Houston*
John S Macdonald, *New York*
Willis C Maddrey, *Dallas*
Mercedes Susan Mandell, *Aurora*
Christopher Mantyh, *Durham*
Wendy M Mars, *Pittsburgh*
John Marshall, *Columbia*
Robert CG Martin, *Louisville*
Laura E Matarese, *Pittsburgh*
Craig J McClain, *Louisville*
Lynne V McFarland, *Washington*
David J McGee, *Shreveport*
Valentina Medici, *Sacramento*
Stephan Menne, *New York*
Didier Merlin, *Atlanta*
George Michalopoulos, *Pittsburgh*
James M Millis, *Chicago*
Pramod K Mistry, *New Haven*
Emiko Mizoguchi, *Boston*
Huanbiao Mo, *Denton*
Robert C Moesinger, *Ogden*
Smruti R Mohanty, *Chicago*
John Morton, *Stanford*
Peter L Moses, *Burlington*
Sandeep Mukherjee, *Omaha*
Million Mulugeta, *Los Angeles*
Michel M Murr, *Tampa*
Pete Muscarella, *Columbus*
Ece A Mutlu, *Chicago*
Masaki Nagaya, *Boston*
Laura E Nagy, *Cleveland*
Aejaz Nasir, *Tampa*
Udayakumar Navaneethan, *Cincinnati*
Stephen JD O'Keefe, *Pittsburgh*
Robert D Odze, *Boston*
Giuseppe Orlando, *Winston Salem*
Pal Pacher, *Rockville*
Georgios Papachristou, *Pittsburgh*
Jong Park, *Tampa*
William R Parker, *Durham*
Mansour A Parsi, *Cleveland*
Marco Giuseppe Patti, *Chicago*
Zhiheng Pei, *New York*
CS Pitchumoni, *New Brunswick*
Parviz M Pour, *Omaha*
Xiaofa Qin, *Newark*
Florencia Georgina Que, *Rochester*
Massimo Raimondo, *Jacksonville*
Raymund R Razonable, *Minnesota*
Kevin Michael Reavis, *Orange*
Robert V Rege, *Dallas*
Douglas K Rex, *Indianapolis*
Victor E Reyes, *Galveston*
Basil Rigas, *New York*
Richard A Rippe, *Chapel Hill*
Alexander S Rosemurgy, *Tampa*
Philip Rosenthal, *San Francisco*
Raul J Rosenthal, *Weston*
Joel H Rubenstein, *Ann Arbor*
Shawn D Safford, *Norfolk*
Rabih M Salloum, *Rochester*
Bruce E Sands, *Boston*
Tor C Savidge, *Galveston*
Michael L Schilsky, *New Haven*
Beat Schnüriger, *California*
Robert E Schoen, *Pittsburgh*
Matthew James Schuchert, *Pittsburgh*
Ekihiro Seki, *La Jolla*
Le Shen, *Chicago*
Perry Shen, *Winston-Salem*
Stuart Sherman, *Indianapolis*
Mitchell L Shiffman, *Richmond*
Shivendra Shukla, *Columbia*
Bronislaw L Slomiany, *Newark*
Scott Steele, *Fort Lewis*
Branko Stefanovic, *Tallahassee*
Lygia Stewart, *San Francisco*
Luca Stocchi, *Cleveland*
Daniel S Straus, *Riverside*
Robert Todd Striker, *Madison*
Jonathan Strosberg, *Tampa*
Christina Surawicz, *Seattle*
Patricia Sylla, *Boston*
Wing-Kin Syn, *Durham*
Yvette Taché, *Los Angeles*
Kazuaki Takabe, *Richmond*
Kam-Meng Tchou-Wong, *New York*
Klaus Thaler, *Columbia*
Charles Thomas, *Oregon*
Natalie J Torok, *Sacramento*
George Triadafilopoulos, *Stanford*
Chung-Jyi Tsai, *Lexington*
Thérèse Tuohy, *Salt Lake City*
Andrew Ukleja, *Florida*
Santhi Swaroop Vege, *Rochester*
Aaron Vinik, *Norfolk*
Dinesh Vyas, *Washington*
Arnold Wald, *Wisconsin*
Scott A Waldman, *Philadelphia*
Jack R Wands, *Providence*
Jiping Wang, *Boston*
Irving Waxman, *Chicago*
Wilfred M Weinstein, *Los Angeles*
Steven D Wexner, *Weston*
John W Wiley, *Ann Arbor*
Jackie Wood, *Ohio*
Jian Wu, *Sacramento*
Wen Xie, *Pittsburgh*
Guang-Yin Xu, *Galveston*
Fang Yan, *Nashville*
Radha Krishna Yellapu, *New York*
Anthony T Yeung, *Philadelphia*
Zobair M Younossi, *Virginia*
Liqing Yu, *Winston-Salem*
Run Yu, *Los Angeles*
Ruben Zamora, *Pittsburgh*
Michael E Zenilman, *New York*
Mark A Zern, *Sacramento*
Lin Zhang, *Pittsburgh*
Martin D Zielinski, *Rochester*
Michael A Zimmerman, *Colorado*

EDITORIAL

- 6035 Oxidative stress and antioxidants in hepatic pathogenesis
Ha HL, Shin HJ, Feitelson MA, Yu DY
- 6044 Hepatic organ protection: From basic science to clinical practice
Schmidt R

TOPIC HIGHLIGHT

- 6046 Regulation of hepatic blood flow: The hepatic arterial buffer response revisited
Eipel C, Abshagen K, Vollmar B
- 6058 Molecular mechanisms of liver preconditioning
Alchera E, Dal Ponte C, Imarisio C, Albano E, Carini R
- 6068 Heme oxygenase system in hepatic ischemia-reperfusion injury
Richards JA, Wigmore SJ, Devey LR
- 6079 Role of nitric oxide in hepatic ischemia-reperfusion injury
Siriussawakul A, Zaky A, Lang JD
- 6087 Hepatoprotective actions of melatonin: Possible mediation by melatonin receptors
Mathes AM
- 6098 Current protective strategies in liver surgery
Gurusamy KS, Gonzalez HD, Davidson BR

ORIGINAL ARTICLE

- 6104 Promoter polymorphism of MRP1 associated with reduced survival in hepatocellular carcinoma
Zhao J, Yu BY, Wang DY, Yang JE

- 6111 Impaired PI3K/Akt signal pathway and hepatocellular injury in high-fat fed rats

Han JW, Zhan XR, Li XY, Xia B, Wang YY, Zhang J, Li BX

BRIEF ARTICLE

- 6119 High prevalence of nonalcoholic fatty liver in patients with idiopathic venous thromboembolism

Di Minno MND, Tufano A, Rusolillo A, Di Minno G, Tarantino G

- 6123 Extrahepatic portal vein thrombosis in children and adolescents: Influence of genetic thrombophilic disorders

Pietrobattista A, Luciani M, Abraldes JG, Candusso M, Pancotti S, Soldati M, Monti L, Torre G, Nobili V

- 6128 Tissue factor in predicted severe acute pancreatitis

Andersson E, Axelsson J, Eckerwall G, Ansari D, Andersson R

- 6135 Role of serotonin in development of esophageal and gastric fundal varices

Rudić JS, Čulafić DM, Mirković DS, Ješić RS, Krstić MN

- 6139 Value of duplex doppler ultrasonography in non-invasive assessment of children with chronic liver disease

El-Shabrawi MHF, El-Raziky M, Sheiba M, El-Karakasy HM, El-Raziky M, Hassanin F, Ramadan A

- 6145 Pegylated interferon α -2b up-regulates specific CD8⁺ T cells in patients with chronic hepatitis B

Chen J, Wang Y, Wu XJ, Li J, Hou FQ, Wang GQ

- 6151 Short-segment Barrett's esophagus and cardia intestinal metaplasia: A comparative analysis

Chang Y, Liu B, Liu GS, Wang T, Gong J

- 6155 Increasing the frequency of CIK cells adoptive immunotherapy may decrease risk of death in gastric cancer patients

Jiang JT, Shen YP, Wu CP, Zhu YB, Wei WX, Chen LJ, Zheng X, Sun J, Lu BF, Zhang XG

ACKNOWLEDGMENTS I Acknowledgments to reviewers of *World Journal of Gastroenterology*

APPENDIX I Meetings
I-VI Instructions to authors

AIM AND SCOPE *World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, DOI: 10.3748) is a weekly, open-access, peer-reviewed journal supported by an editorial board of 1144 experts in gastroenterology and hepatology from 60 countries.

The major task of *WJG* is to report rapidly the most recent results in basic and clinical research on esophageal, gastrointestinal, liver, pancreas and biliary tract diseases, *Helicobacter pylori*, endoscopy and gastrointestinal surgery, including: gastroesophageal reflux disease, gastrointestinal bleeding, infection and tumors; gastric and duodenal disorders; intestinal inflammation, microflora and immunity; celiac disease, dyspepsia and nutrition; viral hepatitis, portal hypertension, liver fibrosis, liver cirrhosis, liver transplantation, and metabolic liver disease; molecular and cell biology; geriatric and pediatric gastroenterology; diagnosis and screening, imaging and advanced technology.

FLYLEAF I-VII Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiao-Fang Liu*
Responsible Electronic Editor: *Yin-Ping Lin*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Zhong-Fang Shi*
Proofing Editorial Office Director: *Jian-Xia Cheng*

NAME OF JOURNAL
World Journal of Gastroenterology

LAUNCH DATE
October 1, 1995

RESPONSIBLE INSTITUTION
Department of Science and Technology of Shanxi Province

SPONSOR
Taiyuan Research and Treatment Center for Digestive Diseases, 77 Shuangta Xijie, Taiyuan 030001, Shanxi Province, China

EDITING
Editorial Board of *World Journal of Gastroenterology*, Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-5908-0039
Fax: +86-10-8538-1893
E-mail: wjg@wjgnet.com
<http://www.wjgnet.com>

PUBLISHING
Baishideng Publishing Group Co., Limited, Room 1701, 17/F, Henan Building, No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
<http://www.wjgnet.com>

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
<http://www.wjgnet.com>

PRINT SUBSCRIPTION
RMB 245 Yuan for each issue, RMB 11760 Yuan for one year.

ONLINE SUBSCRIPTION
One-Year Price 864.00 USD

PUBLICATION DATE
December 28, 2010

CSSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

HONORARY EDITORS-IN-CHIEF
James L. Boyer, *New Haven*
Ke-Ji Chen, *Beijing*
Martin H Floch, *New Haven*
Geng-Tao Liu, *Beijing*
Emmet B Keefe, *Palo Alto*
Lein-Ray Mo, *Tainan*
Eamonn M Quigley, *Cork*
Rafiq A Sheikh, *Sacramento*
Nicholas J Talley, *Rochester*
Ming-Lung Yu, *Kaohsiung*

PRESIDENT AND EDITOR-IN-CHIEF
Lian-Sheng Ma, *Beijing*

ACADEMIC EDITOR-IN-CHIEF
Tauseef Ali, *Oklahoma*
Mauro Bortolotti, *Bologna*
Tarkan Karakan, *Ankara*
Weekitt Kittisupamongkol, *Bangkok*
Anastasios Koulaouzidis, *Edinburgh*
Gerd A Kullak-Ublick, *Zürich*
Bo-Rong Pan, *Xi'an*
Sylvia LF Pender, *Southampton*
Max S Petrov, *Auckland*
George Y Wu, *Farmington*

STRATEGY ASSOCIATE EDITORS-IN-CHIEF
Peter Draganov, *Florida*
Hugh J Freeman, *Vancouver*
María Concepción Gutiérrez-Ruiz, *México*
Kazuhiro Hanazaki, *Kochi*

Akio Inui, *Kagoshima*
Kalpesh Jani, *Baroda*
Javier S Martin, *Punta del Este*
Natalia A Osna, *Omaha*
Wei Tang, *Tokyo*
Alan BR Thomson, *Edmonton*
Harry HX Xia, *Hanover*

ASSOCIATE EDITORS-IN-CHIEF
You-Yong Lu, *Beijing*
John M Luk, *Pokfulam*
Hiroshi Shimada, *Yokohama*

EDITORIAL OFFICE
Jian-Xia Cheng, Director
World Journal of Gastroenterology
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-5908-0039
Fax: +86-10-8538-1893
E-mail: wjg@wjgnet.com
<http://www.wjgnet.com>

COPYRIGHT
© 2010 Baishideng. All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior permission of Baishideng. Authors are required to grant *World Journal of Gastroenterology* an exclusive license to publish.

SPECIAL STATEMENT
All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1007-9327/g_info_20100315215714.htm. If you do not have web access please contact the editorial office.

ONLINE SUBMISSION
<http://www.wjgnet.com/1007-9327office>

Pegylated interferon α -2b up-regulates specific CD8+ T cells in patients with chronic hepatitis B

Ji Chen, Yan Wang, Xue-Jie Wu, Jun Li, Feng-Qin Hou, Gui-Qiang Wang

Ji Chen, Yan Wang, Xue-Jie Wu, Jun Li, Feng-Qin Hou, Gui-Qiang Wang, Department of Infectious Diseases, Center for Liver Diseases, Peking University First Hospital, Beijing 100034, China

Author contributions: Chen J and Wang Y contributed equally to this work; Chen J performed the laboratory work and wrote the paper; Wang Y collected the clinical samples and data, joined part in writing; Wu XJ performed the laboratory work; Li J and Hou FQ collected the samples and the data; Wang GQ designed the project and prepared the writing and supported all the work.

Supported by National Natural Science Foundation of China, No. 30771905; National Basic Research Program of China (973 Program), No. 2007CB512800; Mega-projects of Science Research, No. 008ZX10002-008; Beijing Municipal Science & Technology Commission, No. D08050700650803

Correspondence to: Gui-Qiang Wang, MD, Professor of Medicine, Chairman of Department of Infectious Diseases, Center for Liver Diseases, Peking University First Hospital, No. 8, Xishiku Street, Xicheng District, Beijing 10034, China. wangqg@hotmail.com

Telephone: +86-10-66551122 Fax: +86-10-66551680

Received: July 7, 2010 Revised: September 26, 2010

Accepted: October 3, 2010

Published online: December 28, 2010

Abstract

AIM: To investigate the effect of pegylated interferon (IFN) α -2b on specific CD8+ T lymphocytes in patients with chronic hepatitis B (CHB).

METHODS: Twenty-one patients with CHB were treated with pegylated IFN α -2b. Periphery blood mononuclear cells were isolated from fresh heparinized blood by Ficoll-Hypaque density gradient centrifugation (density: 1.077 g/L, Pharmingen) at weeks 0, 4, 8, 12, and 24, respectively. Frequency of circulating hepatitis B virus (HBV) epitope-specific CD8 T cells was detected by flow cytometry. Cytokines were detected by cytometric bead assay.

RESULTS: The frequency of circulating HBV core or env-specific CD8 T cells was higher ($P < 0.05$), the number of HBV core specific CD8 T cells was greater

at week 24 ($P < 0.05$), the level of Th1-type cytokines [interleukin (IL)-12, tumor necrosis factor- α , and IFN- γ] was higher, while that of Th2-type cytokines (IL-4, IL-6, and IL-10) was lower in responders than in non-responders ($P < 0.05$) after pegylated IFN α -2b treatment. The IL-6 level was correlated with HBV DNA ($r = 0.597$, $P = 0.04$), while the inducible protein-10 (IP-10) level was correlated with serum alanine aminotransferase (ALT) ($r = 0.545$, $P = 0.005$). The IP-10 level at week 8 after pegylated IFN α -2b treatment could predict the normalization of ALT in CHB patients (positive predict value = 56%, negative predict value = 92%).

CONCLUSION: Pegylated IFN α -2b can enhance the immune response of CHB patients by increasing the frequency of HBV specific CD8+ T cells and regulating the Th1/Th2 cytokines.

© 2010 Baishideng. All rights reserved.

Key words: Chronic hepatitis B; Pegylated interferon α -2b therapy; Immune response; Cytokine

Peer reviewer: Dr. Jeff Butterworth, MB, FRCP, Department of Gastroenterology, Shrewsbury and Telford Hospital NHS Trust, Mytton Oak Road, Shrewsbury, Shropshire, SY3 8XQ, United Kingdom

Chen J, Wang Y, Wu XJ, Li J, Hou FQ, Wang GQ. Pegylated interferon α -2b up-regulates specific CD8+ T cells in patients with chronic hepatitis B. *World J Gastroenterol* 2010; 16(48): 6145-6150 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i48/6145.htm> DOI: <http://dx.doi.org/10.3748/wjg.v16.i48.6145>

INTRODUCTION

More than two billion people have been infected with hepatitis B virus (HBV) and chronic HBV infection affects about 400 million people worldwide^[1,2]. Chronic hepatitis B (CHB) is a chronic inflammatory liver disease,

which can progress to end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma.

Adaptive immunity plays a central role in the pathogenesis of chronic HBV infection, and it is crucial to understanding the behavior of T cell response for the design of effective strategies for the control of HBV infection^[3-5]. Different studies in chronic and early acute phases of HBV infection suggested that the functional impairment of HBV-specific cell-mediated immune response plays an important role in HBV persistence^[6-14]. Moreover, recent studies showed that both positive and negative signals regulate the antigen-specific T cell function and are important for the better outcome of patients with HBV infections^[15-17].

Pegylated interferon (IFN) α -2b can modulate and reduce antiviral function of CHB patients by enhancing their immune responses. However, the exact effect of pegylated IFN α -2b on the immune responses of patients with HBV infections remains unclear. The present study was designed to investigate the effect of pegylated IFN α -2b on HBV specific CD8+ T cells and secretion of cytokines in CHB patients.

MATERIALS AND METHODS

Patients and study design

Twenty-one consecutive CHB patients (17 males and 4 females) at the age of 20-39 years (mean 25 years), admitted to our hospital from January 2008 to May 2009 were included in this study. Diagnosis of HBV infection was established as previously described^[18]. Clinical data and characteristics of the patients are summarized in Table 1. The patients were treated with pegylated IFN α -2b (PegIntron from Schering-Plough), at the dose of 0.5-1 μ g/kg of body weight, once a week for 24 wk. Clinical and laboratory data about the patients were detected before treatment, or at weeks 4, 8, 12, and 24 after treatment. Patients co-infected with HBV and HCV or with detectable antibodies against hepatitis delta virus or against human immunodeficiency virus were excluded, as were those with other causes of liver disease, including alcohol abuse. No patient had decompensated liver disease (evidence or history of ascites, variceal bleeding, hepatic encephalopathy or jaundice).

Isolation of peripheral blood mononuclear cells

Peripheral blood mononuclear cells (PBMC) were isolated from fresh heparinized blood by Ficoll-Hypaque density gradient centrifugation (density: 1.077 g/L, Pharmingen). Blood was two-fold diluted with RPMI 1640 medium containing 300 μ g/mL L-glutamin, 100 U/mL penicillin, 100 μ g/mL streptomycin and 10% fetal calf serum, then added into the isovolumic Ficoll, centrifuged for 400 \times g at 21°C for 35 min. The cells were washed twice with phosphate buffered saline (PBS).

Human leukocyte antigen-A2 typing

One hundred microliters of fresh heparinized blood (100) was incubated with human leukocyte antigen-A2 primary antibody for 30 min. Erythrocytes were lysed with an erythrocyte lysate at 37°C, washed with PBS, and then incubated

with secondary antibody, washed again and analyzed on Becton Dickinson FACS (Becton Dickinson, USA).

Analysis of HBV epitope-specific CD8+ T cells

Frequency of HBV epitope-specific CD8 T cells was detected by flow cytometry after incubated with HBV core18-27 tetramers (ProImmune, Oxford, UK) and HBV env 335-343 pentamers (ProImmune, Oxford, UK). Freshly isolated PBMC were incubated with PE-labeled tetramer or pentamer in PBS (10% FCS) for 15 min at 37°C, washed once with PBS (1% FCS) and then incubated on ice for 30 min with FITC-anti-CD8 (ProImmune, Oxford, UK), washed twice with PBS, adjusted to 1×10^6 cells/vial, and fixed in 2% paraformaldehyde for analysis. About 1×10^6 PBMC were harvested and analyzed within the CD8 gate on Becton Dickinson FACS using the CELLQuest™ software.

Secretion of cytokines

Serum levels of interleukin (IL)-2, IL-4, IL-5, IL-6, IL-10, IL-12, IFN- γ and inducible protein-10 (IP-10) in CHB patients were measured by cytometric bead assay (BD, USA) according to its manufacturer's instructions.

Serological assessment

Fasting serum levels of liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase] were measured with a Hitachi-7180 automatic biochemistry analyzer (Hitachi Inc., Japan) following the standard laboratory methods. HBV DNA was detected by real time polymerase chain reaction (Amplicor, Roche).

Statistical analysis

All data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Descriptive baseline data were expressed as mean \pm SD for continuous variables. Differences between groups were assessed using Kruskal-Wallis H for continuous variables. Spearman *P* test was performed for correlation analysis. The accuracy of serum factors for predicting virologic response was assessed using the receiver operating characteristic curve. *P* < 0.05 was considered statistically significant.

RESULTS

Frequency of circulating HBV epitope-specific CD8 T cells in CHB patients after pegylated IFN α -2b treatment

Circulating HBV epitope-specific CD8 T cells were detected 13 out of the 21 CHB patients (Table 1). The frequency of HBV core 18-27 tetramers+/CD8+ T cells at week 0 was 0.013 ± 0.002 , which increased to 0.026 ± 0.015 , 0.029 ± 0.019 , 0.036 ± 0.025 , and 0.045 ± 0.027 , respectively, at weeks 4, 8, 12, and 24 after IFN α -2b treatment (Figure 1), with a significant difference between weeks 8 and 0, and between weeks 24 and 0 (*P* < 0.05). The frequency of HBV env 335-343 pentamers+/CD8+ T cells began to increase at week 8 with a significant difference between weeks 24 and 0 (*P* < 0.05). No significant difference was observed in frequency of HBV core and HBV env specific CD8 T cells.

Table 1 Clinical characteristics of chronic hepatitis B patients included in this study

Patient	Age (yr)/sex	HBV DNA (IU/L)	ALT (U/L)	Total bilirubin (mg/dL)	Albumin (g/dL)	Platelets ($\times 10^9/L$)	HBeAg	HBeAb	HBsAg	HBsAb	Genotype
1	27/M	201 000 000	143	9.1	43.7	113	+	-	+	-	C
2	25/M	160 000 000	147	12.9	47.4	167	+	+	+	-	C
3	30/M	471 000 000	205	11.9	44.3	127	+	-	+	-	C
4	21/M	32 200 000	123	10.8	45.8	181	+	-	+	-	C
5	21/M	186 000 000	148	14.2	44.1	110	+	-	+	-	C
6	38/F	30 800 000	347	18.1	45.5	126	+	-	+	-	C
7	20/F	29 000 000	171	10.0	44.9	284	+	-	+	-	C
8	20/M	143 000 000	-	13.6	48.0	248	+	-	+	-	B
9	20/F	621 000 000	112	13.4	48.5	170	+	-	+	-	C
10	23/M	597 000 000	196	18.9	43.2	201	-	+	+	-	C
11	20/F	2 910 000	98	15.6	48.0	137	+	+	+	-	C
12	38/M	63 700 000	206	11.1	51.2	142	+	+	+	-	C
13	28/M	134 000 000	138	9.0	45.9	174	+	+	+	-	C
14	25/M	237 000 000	93	16.9	51.3	130	+	-	+	-	B
15	39/M	1 190 000 000	122	18.2	50.6	166	+	-	+	-	C
16	36/M	8 820 000	170	22.9	47.1	169	+	-	+	-	C
17	25/M	655 000 000	90	20.9	46.8	161	+	-	+	-	B
18	25/M	157 000 000	164	24.3	47.3	209	-	+	+	-	C
19	20/M	290 000 000	124	11.9	47.8	140	+	-	+	-	B
20	23/M	655 000 000	19.9	19.9	44.6	194	+	-	+	-	B
21	28/M	15 300 000	237	14.5	45.3	154	+	-	+	-	C

HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBeAb: Hepatitis B e antibody; HBsAg: Hepatitis B surface antigen; HBsAb: Hepatitis B surface antibody.

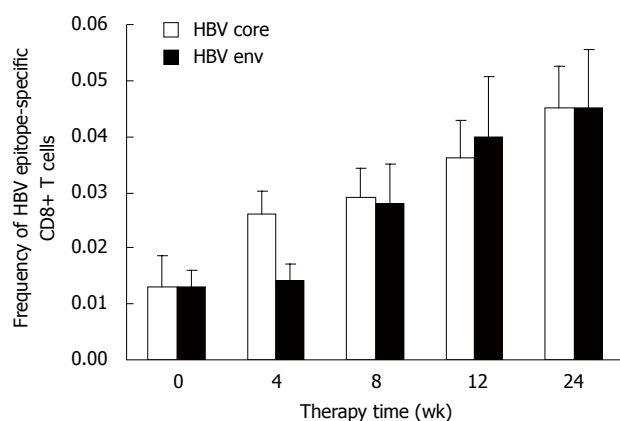


Figure 1 Frequency of hepatitis B virus epitope tetramer+/CD8+ T cell after pegylated interferon α -2b treatment. The frequency of hepatitis B virus (HBV) specific CD8+ T cells was increased connectively at weeks 4, 8, 12 and 24 after pegylated interferon α -2b treatment with no difference in frequency of HBV core specific CD8+ T cells and HBV env specific T cells.

To further analyze the effect of pegylated IFN α -2b on HBV-specific CD8 T cells, 13 patients were divided into responders ($n = 7$) and non-responders ($n = 6$). Responders were defined as their ALT returned to its normal level and their HBV DNA was decreased to over 2log, and/or their serum HBeAg was converted. The frequency of HBV core18-27 tetramers+/CD8+ T cells was 0.014 ± 0.011 , 0.029 ± 0.022 , 0.029 ± 0.021 , 0.067 ± 0.029 , and 0.05 ± 0.025 , respectively, in responders at weeks 0, 4, 8, 12 and 24 after treatment, which was higher than that in non-responders (0.012 ± 0.007 , 0.018 ± 0.009 , 0.028 ± 0.019 , 0.025 ± 0.021 and 0.030 ± 0.01 , respectively). No significant difference was found in frequency of HBV core specific CD8 T cells between responders and non-re-

sponders at baseline, even at weeks 4, 8, and 12 after treatment (Figure 2), with a significant difference observed at week 24 ($P < 0.05$, Figure 3). The frequency of HBV env specific CD8 T cells was higher in responders than in non-responders ($P < 0.05$, Figure 2).

Secretion of cytokines after pegylated IFN treatment and its correlation with virologic responses

The serum levels of IL-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)- α , IFN- γ , IL-12, and IP-10 were measured at baseline, during the treatment and follow-up. The serum IL-2 level was very low in CHB patients, which was almost undetectable. The levels of Th1-type cytokines including IL-12, TNF- α and IFN- γ were increased while those of Th2-type cytokines including IL-4, IL-6 and IL-10 were decreased at week 48 after treatment (Figure 4). The baseline IP-10 level was increased from week 4 and decreased from week 48 after treatment.

The baseline IL-6 level was correlated with HBV DNA in responders ($r = 0.597$, $P < 0.05$) but not with HBV DNA in non-responders. IL-10 was correlated with IL-6 ($r = 0.762$, $P = 0.002$), and IL-12 was correlated with IFN- γ ($r = 0.485$, $P = 0.026$).

The IP-10 level was closely correlated with the serum ALT level not only in responders but also in non-responders ($r = 0.545$, $P = 0.005$, Figure 5), indicating that IP-10 level fluctuates with serum ALT level. The baseline IP-10 level was lower in patients with their ALT < 40 U/L than in those with their ALT > 40 U/L.

Predictability of IP-10

To determine whether IP-10 can predict the normalization of ALT (< 40 U/L) after peg-IFN α -2b treatment, receiver operating characteristic curve was plotted for IP-10. The

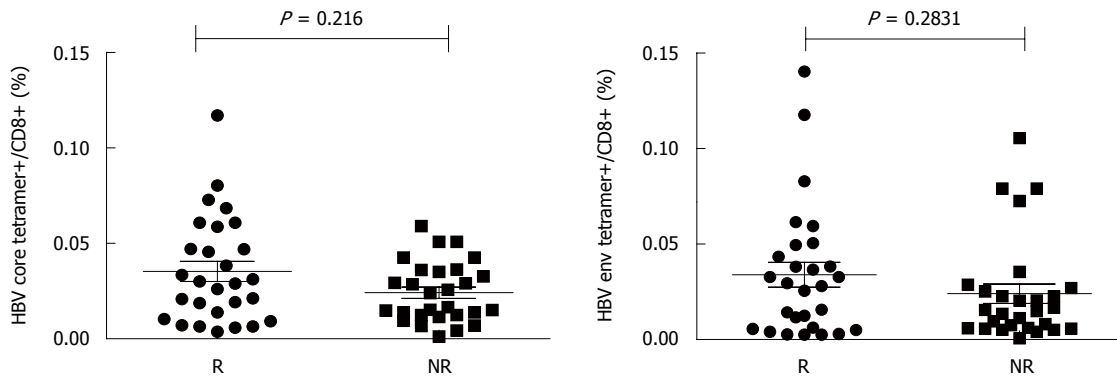


Figure 2 No correlation between increased hepatitis B virus epitope-specific CD8+ T cells and treatment outcome. The frequency of hepatitis B virus (HBV) core or env epitope-specific CD8+ T cells was higher in non-responders (NR) than in responders (R).

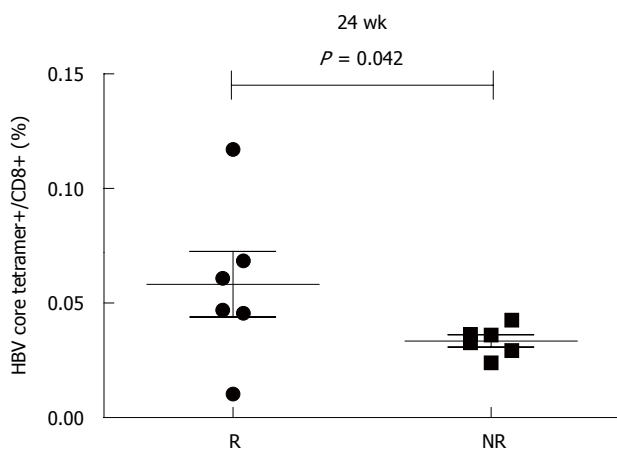


Figure 3 Correlation between increased hepatitis B virus specific T cells and treatment response 24 wk after therapy. The frequency of hepatitis B virus (HBV) core epitope-specific CD8+ T cells at week 24 was higher in responders (R) than in non-responders (NR).

IP-10 level at week 8 after treatment was predictable. The area under the curve was 0.741 ($P = 0.065$). A cutoff value of 437.78 was chosen. Correspondingly, the positive and negative predictive value was 56% and 92%, respectively (Table 2).

DISCUSSION

HBV has a high propensity to persist and several strategies have been developed for control of its evading from T cell responses, including the direct inhibitory effect of viral proteins on T cell responses and the emergence of escape mutations^[19-21]. Moreover, HBV infection is more common in immune deficient individuals, such as infants, patients with cancer and those treated with steroid hormone, thereby can interfere with viral clearance by the innate immune system^[22,23]. Inefficient innate responses and rapid spread of HBV may in turn delay and impair adaptive responses because of inefficient promotion of T cell priming by innate immunity and through T cell exhaustion induced by a rapidly increased viral load. However, the actual impact of exhaustion by persistent exposure to high antigen concentrations on virus persistence has only been partially defined.

Furthermore, two kinds of drugs (nucleoside analogs and IFN) are usually used in antiviral treatment of CHB

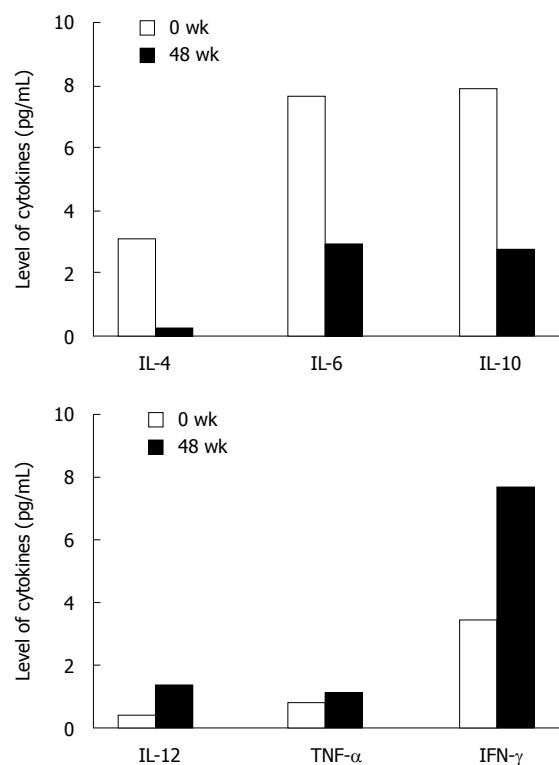


Figure 4 Level of cytokines after treatment. The levels of Th1-type cytokines [interleukin (IL)-12, tumor necrosis factor (TNF)- α and interferon (IFN)- γ] were higher, while the levels of Th2-type cytokines (IL-4, IL-6 and IL-10) were lower at week 48 after treatment.

patients. IFN is involved in numerous immune interactions during viral infection, as an inducer, regulator, and effector of both innate and adaptive antiviral systems. IFN- α and beta are produced rapidly due to viral factors, such as envelope glycoprotein, CpG DNA or dsRNA, and interact with cellular pattern-recognition receptors, such as mannose receptors, toll-like receptors, and cytosolic receptors^[24]. In addition, IFN modulates both innate and adaptive immunity, ultimately resulting in an enhanced antiviral effector function.

In the present study, the frequency of HBV epitope-specific CD8+ T cells in peripheral blood was persistently increased at weeks 4, 8, 12 and 24 after peg-IFN α -2a treatment, while the number of HBV epitope-specific CD8+ T cells in HBV core 18-27 tetramers and HBV env 335-343

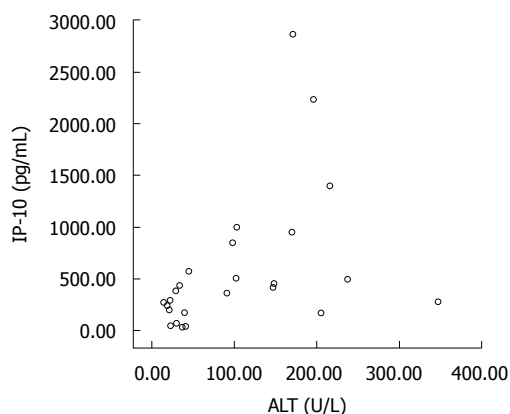


Figure 5 Positive correlation between alanine aminotransferase and inducible protein-10 levels ($r = 0.545$, $P = 0.005$). ALT: Alanine aminotransferase; IP-10: Inducible protein-10.

Table 2 Predictive value of serum inducible protein-10 levels 8 wk after treatment

IP-10 (pg/mL)	ALT < 40 U/L	ALT \geq 40 U/L	Predictive value
< 437.78	5	4	PPV = 56%
\geq 437.78	1	11	NPV = 92%

IP-10: Inducible protein-10; ALT: Alanine aminotransferase; PPV: Positive predict value; NPV: Negative predict value.

pentamers was greater in responders than in non-responders after pegylated IFN α -2b treatment, suggesting that the therapeutic effect of pegylated IFN α -2b on HBV infection may be attributed to the elevated HBV-specific CD8 T cells, and that the immune response mediated by HBV-specific cells plays an important role in control of HBV. However, the frequency of HBV core 18-27 tetramers+/CD8+ T cells was higher than that of HBV env 335-343 pentamers+/CD8+ T cells after pegylated IFN treatment, suggesting that the HBV core epitope plays a more critical role in induction of a stronger immune response to HBV infection than to HBV env epitope. Pegylated IFN α -2b could enhance specific immune response of CHB patients. Further study should be performed with a large sample size.

Cytokines play an important role in immune modulation. Clearance of HBV infection is mediated by a strong polyclonal cellular response of both CTL and Th1 cells. Chronic HBV infection is caused mainly by an increased response of Th2 cells and impaired production of type 1 cytokines. IL-10, a Th2-type cytokine secreted by T-cells, activated B cells and monocytes, is a powerful inhibitor of Th1 activation and suppresses cell-mediated immunity in mice and humans^[25,26]. Of the detected cytokines, Th2-type cytokines such as IL-4, IL-6 and IL-10, were altered conspicuously. After treatment, the level of Th2-type cytokines (IL-4 and IL-10) was down-regulated, thus confirming the immune recover potential of pegylated IFN α -2b, the level of IL-12 which can promote the differentiation of Th1-type cytokines was low, and the production of Th1-type cytokines was increased, indicating that the immune function of pegylated IFN α -2b can be achieved by regulating the balance of Th1/Th2 cytokines.

IL-6 is a multifunctional cytokine with both differentiation and growth-promoting effects for a variety of target cells. IL-6 is generally considered an important cytokine in the network of cytokines that regulate immune reactions and acute phase responses^[27]. It was reported that IL-6 is correlated with liver fibrosis/cirrhosis^[28] and is a cell attachment site for HBV^[29]. In the present study, the IL-6 level was correlated with HBV DNA plasma only in responders.

IP-10, a chemotactic CXC chemokine of 77 aa in its mature form^[30,31], can be produced by a variety of cells, including hepatocytes^[32,33]. The correlation between IP-10 levels and necroinflammatory activity, as well as the high and low IP-10 levels before and after pegylated IFN α -2b treatment, may imply that IP-10 plays a role in the natural pathogenesis of HBV-induced liver damage^[34]. It was reported that the baseline IP-10 level can predictive the response of CHB patients to HCV treatment, and is correlated with liver inflammation and fibrosis^[35,36]. In this study, the baseline IP-10 level in CHB patients could predict the normalization of ALT after pegylated IFN α -2b treatment.

In conclusion, given the importance of protective T cell responses in control of HBV, the correlation between immunomodulatory molecules and pegylated IFN α -2b treatment in restoration of the immune responses of antiviral T cells are highly desirable. Pegylated IFN α -2b therapy can enhance the immune response of CHB patients by influencing the production of cytokines. IP-10 can potentially predict the normalization of ALT, which is correlated with liver damage. Further study is needed with a large sample size.

ACKNOWLEDGMENTS

The authors thank Dr. Ming Yu and Hong-Li Xi for their technical support help in this study.

COMMENTS

Background

More than two billion people have been infected with hepatitis B virus (HBV) and chronic HBV infection affects about 400 million people worldwide. Two kinds of drugs [nucleoside analogs and interferon (IFN)] are mainly used in treatment of chronic hepatitis B (CHB) patients. IFN is involved in numerous immune interactions as an inducer, regulator, and effector in treatment of viral infections. Cytokines play an important role in immune modulation. Clearance of HBV infection is mediated by a strong polyclonal cellular response of both CTL and Th1 cells. Chronic HBV infection is caused mainly by an increased response of Th2 cells and impaired production of type 1 cytokines. Inducible protein 10 (IP-10) is a chemotactic CXC chemokine of 77 aa in its mature form.

Research frontiers

IFN- α and β are produced rapidly due to viral factors, such as envelope glycoproteins, CpG DNA or dsRNA, and interact with cellular pattern-recognition receptors, such as mannose receptors, toll-like receptors, and cytosolic receptors. IP-10 can be produced by a variety of cells, including hepatocytes. The results of this study show that the baseline IP-10 level can predict the response of patients with HBV infection to its treatment with pegylated IFN α -2b.

Innovations and breakthroughs

The present study demonstrated the correlation between pegylated IFN α -2b treatment and HBV-specific T lymphocytes. In addition, the effect of pegylated IFN α -2b on HBV infection could be achieved by balancing the production of Th1/Th2 cytokines and IP-10 could predict the outcome of patients with HBV infection after pegylated IFN α -2b treatment.

Applications

In this study, pegylated IFN α -2b could up-regulate HBV epitope specific CD8+ T cells. The specific cellular immune response could control HBV. IP-10 serum

level could predict the outcome of patients with HBV infection after pegylated IFN α -2b treatment, thus providing a new index for the treatment of HBV infection. Pegylated IFN α -2b may be used as a novel strategy for the treatment of HBV infection by regulating the cytokines.

Terminology

Human leukocyte antigen (HLA) typing is a method to define the HLA+ and HLA- blood for studied subjects. Flow cytometry is used to define the HBV epitope specific CD8+ T lymphocytes. Cytometric bead assay is a new technique for detecting serum concentration of cytokines.

Peer review

This is a very interesting study, showing that pegylated IFN α -2b therapy can increase the frequency of specific CD8+ T lymphocytes in CHB patients. This may contribute to the better control of HBV replication and to the recovery of CHB patients, thus having a promise for therapeutic interventions. The experiments support the claim of the authors.

REFERENCES

- Kane M. Global programme for control of hepatitis B infection. *Vaccine* 1995; **13** Suppl 1: S47-S49
- Dienstag JL. Hepatitis B virus infection. *N Engl J Med* 2008; **359**: 1486-1500
- Webster GJ, Reigat S, Maini MK, Whalley SA, Ogg GS, King A, Brown D, Amlot PL, Williams R, Vergani D, Dusheiko GM, Bertolotti A. Incubation phase of acute hepatitis B in man: dynamic of cellular immune mechanisms. *Hepatology* 2000; **32**: 1117-1124
- Thimme R, Wieland S, Steiger C, Ghayeb J, Reimann KA, Purcell RH, Chisari FV. CD8(+) T cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection. *J Virol* 2003; **77**: 68-76
- Grady GF, Lee VA, Prince AM, Gitnick GL, Fawaz KA, Vyas GN, Levitt MD, Senior JR, Galambos JT, Bynum TE, Singleton JW, Clowdus BF, Akdamar K, Aach RD, Winkelman EI, Schiff GM, Hersh T. Hepatitis B immune globulin for accidental exposures among medical personnel: final report of a multicenter controlled trial. *J Infect Dis* 1978; **138**: 625-638
- Ferrari C, Penna A, Bertolotti A, Valli A, Antoni AD, Giuberti T, Cavalli A, Petit MA, Fiaccadori F. Cellular immune response to hepatitis B virus-encoded antigens in acute and chronic hepatitis B virus infection. *J Immunol* 1990; **145**: 3442-3449
- Jung MC, Spengler U, Schraut W, Hoffmann R, Zachoval R, Eisenburg J, Eichenlaub D, Riethmüller G, Paumgartner G, Ziegler-Heitbrock HW. Hepatitis B virus antigen-specific T-cell activation in patients with acute and chronic hepatitis B. *J Hepatol* 1991; **13**: 310-317
- Penna A, Artini M, Cavalli A, Levrero M, Bertolotti A, Pilli M, Chisari FV, Rehermann B, Del Prete G, Fiaccadori F, Ferrari C. Long-lasting memory T cell responses following self-limited acute hepatitis B. *J Clin Invest* 1996; **98**: 1185-1194
- Penna A, Del Prete G, Cavalli A, Bertolotti A, D'Elis MM, Sorrentino R, D'Amato M, Boni C, Pilli M, Fiaccadori F, Ferrari C. Predominant T-helper 1 cytokine profile of hepatitis B virus nucleocapsid-specific T cells in acute self-limited hepatitis B. *Hepatology* 1997; **25**: 1022-1027
- Rehermann B, Fowler P, Sinden J, Person J, Redeker A, Brown M, Moss B, Sette A, Chisari FV. The cytotoxic T lymphocyte response to multiple hepatitis B virus polymerase epitopes during and after acute viral hepatitis. *J Exp Med* 1995; **181**: 1047-1058
- Penna A, Chisari FV, Bertolotti A, Missale G, Fowler P, Giuberti T, Fiaccadori F, Ferrari C. Cytotoxic T lymphocytes recognize an HLA-A2-restricted epitope within the hepatitis B virus nucleocapsid antigen. *J Exp Med* 1991; **174**: 1565-1570
- Jung MC, Hartmann B, Gerlach JT, Diepolder H, Gruber R, Schraut W, Grüner N, Zachoval R, Hoffmann R, Santantonio T, Wächter M, Pape GR. Virus-specific lymphokine production differs quantitatively but not qualitatively in acute and chronic hepatitis B infection. *Virology* 1999; **261**: 165-172
- Böcher WO, Herzog-Hauff S, Schlaak J, Meyer zum Büschenfeld KH, Löhr HF. Kinetics of hepatitis B surface antigen-specific immune responses in acute and chronic hepatitis B or after HBs vaccination: stimulation of the in vitro antibody response by interferon gamma. *Hepatology* 1999; **29**: 238-244
- Sobao Y, Tomiyama H, Sugi K, Tokunaga M, Ueno T, Saito S, Fujiyama S, Morimoto M, Tanaka K, Takiguchi M. The role of hepatitis B virus-specific memory CD8 T cells in the control of viral replication. *J Hepatol* 2002; **36**: 105-115
- Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, Iwai Y, Long AJ, Brown JA, Nunes R, Greenfield EA, Bourque K, Boussiotis VA, Carter LL, Carreno BM, Malenkovich N, Nishimura H, Okazaki T, Honjo T, Sharpe AH, Freeman GJ. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol* 2001; **2**: 261-268
- Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, Horton HF, Fouser L, Carter L, Ling V, Bowman MR, Carreno BM, Collins M, Wood CR, Honjo T. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000; **192**: 1027-1034
- Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, Freeman GJ, Ahmed R. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature* 2006; **439**: 682-687
- Chinese Society of Infectious disease and Parasitology and Chinese Society of Hepatology of Chinese medical association. The programme of prevention and cure for viral hepatitis. *Zhonghua Ganzangbing Zazhi* 2000; **8**: 324-329
- Baumert TF, Barth H, Blum HE. Genetic variants of hepatitis B virus and their clinical relevance. *Minerva Gastroenterol Dietol* 2005; **51**: 95-108
- Tong S. Mechanism of HBV genome variability and replication of HBV mutants. *J Clin Virol* 2005; **34** Suppl 1: S134-S138
- Milich D, Liang TJ. Exploring the biological basis of hepatitis B e antigen in hepatitis B virus infection. *Hepatology* 2003; **38**: 1075-1086
- Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol* 2005; **5**: 215-229
- Chisari FV, Ferrari C. Hepatitis B virus immunopathogenesis. *Annu Rev Immunol* 1995; **13**: 29-60
- Malmgaard L. Induction and regulation of IFNs during viral infections. *J Interferon Cytokine Res* 2004; **24**: 439-454
- Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol* 2001; **19**: 683-765
- Akdis CA, Blaser K. Mechanisms of interleukin-10-mediated immune suppression. *Immunology* 2001; **103**: 131-136
- Le JM, Vilcek J. Interleukin 6: a multifunctional cytokine regulating immune reactions and the acute phase protein response. *Lab Invest* 1989; **61**: 588-602
- Devriere J, Content J, Denys C, Vandebussche P, Schandene L, Wybran J, Dupont E. High interleukin-6 serum levels and increased production by leucocytes in alcoholic liver cirrhosis. Correlation with IgA serum levels and lymphokines production. *Clin Exp Immunol* 1989; **77**: 221-225
- Neurath AR, Strick N, Sproul P. Search for hepatitis B virus cell receptors reveals binding sites for interleukin 6 on the virus envelope protein. *J Exp Med* 1992; **175**: 461-469
- Luster AD, Unkeless JC, Ravetch JV. Gamma-interferon transcriptionally regulates an early-response gene containing homology to platelet proteins. *Nature* 1985; **315**: 672-676
- Neville LF, Mathiak G, Bagasra O. The immunobiology of interferon-gamma inducible protein 10 kD (IP-10): a novel, pleiotropic member of the C-X-C chemokine superfamily. *Cytokine Growth Factor Rev* 1997; **8**: 207-219
- Hua LL, Lee SC. Distinct patterns of stimulus-inducible chemokine mRNA accumulation in human fetal astrocytes and microglia. *Glia* 2000; **30**: 74-81
- Harvey CE, Post JJ, Palladinetti P, Freeman AJ, French RA, Kumar RK, Marinos G, Lloyd AR. Expression of the chemokine IP-10 (CXCL10) by hepatocytes in chronic hepatitis C virus infection correlates with histological severity and lobular inflammation. *J Leukoc Biol* 2003; **74**: 360-369
- Wang J, Zhao JH, Wang PP, Xiang GJ. Expression of CXC chemokine IP-10 in patients with chronic hepatitis B. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 45-50
- Romero AI, Lagging M, Westin J, Dhillon AP, Dustin LB, Pawlotsky JM, Neumann AU, Ferrari C, Missale G, Haagsmans BL, Schalm SW, Zeuzem S, Negro F, Verheij-Hart E, Hellstrand K. Interferon (IFN)-gamma-inducible protein-10: association with histological results, viral kinetics, and outcome during treatment with pegylated IFN-alpha 2a and ribavirin for chronic hepatitis C virus infection. *J Infect Dis* 2006; **194**: 895-903
- Zeremski M, Petrovic LM, Chiriboga L, Brown QB, Yee HT, Kinkhabwala M, Jacobson IM, Dimova R, Markatou M, Talal AH. Intrahepatic levels of CXCR3-associated chemokines correlate with liver inflammation and fibrosis in chronic hepatitis C. *Hepatology* 2008; **48**: 1440-1450