Els 10 articles de major factor d'impacte del 1er semestre 2015

1. Mlynarski EE; Sheridan MB; Xie M; Guo T; Racedo SE; McDonald-McGinn DM; Gai X; Chow EW; Vorstman J; Swillen A; Devriendt K; Breckpot J; Digilio MC; Marino B; Dallapiccola B; Philip N; Simon TJ; Roberts AE; Piotrowicz M; Bearden CE; Eliez S; Gothelf D; Coleman K; Kates WR; Devoto M; Zackai E; **Heine-Suñer D**; Shaikh TH; Bassett AS; Goldmuntz E; Morrow BE; Emanuel BS. *Copy-Number Variation of the Glucose Transporter Gene SLC2A3 and Congenital Heart Defects in the 22q11.2 Deletion Syndrome.* **AM J HUM GENET** 2015 May 7;96(5):753-64. doi: 10.1016/j.ajhg.2015.03.007. Epub 2015 Apr 16.

   FACTOR D'IMPACTE: 10,931 (Q1; D1)

AJHG

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Article

Copy-Number Variation of the Glucose Transporter Gene *SLC2A3* and Congenital Heart Defects in the 22q11.2 Deletion Syndrome

Elisabeth E. Mlynarski[1], Molly B. Sheridan[1], Michael Xie[2], Tingwei Guo[3], Silvia E. Racedo[3], Donna M. McDonald-McGinn[1,4], Xiaowu Gai[5], Eva W.C. Chow[6], Jacob Vorstman[7], Ann Swillen[8], Koen Devriendt[8], Jeroen Breckpot[8], Maria Cristina Digilio[9], Bruno Marino[10], Bruno Dallapiccola[9], Nicole Philip[11], Tony J. Simon[12], Amy E. Roberts[13], Małgorzata Piotrowicz[14], Carrie E. Bearden[15], Stephan Eliez[16], Doron Gothelf[17], Karlene Coleman[18], Wendy R. Kates[19], Marcella Devoto[1,4,20,21], Elaine Zackai[1,4], Damian Heine-Suñer[22], Tamim H. Shaikh[23], Anne S. Bassett[6], Elizabeth Goldmuntz[4,24],

2. Zugna D; Galassi C; Annesi-Maesano I; Baïz N; Barros H; Basterrechea M; Correia S; Duijts L; Esplugues A; Fantini MP; Forastiere F; Gascon M; Gori D; Inskip H; Larsen PS; Mommers M; Nybo Andersen AM; Penders J; Petersen MS; Pike K; Porta D; Sonnenschein-van der Voort A; Steuerwald U; Sunyer J; **Torrent M**; Vrijheid M; Richiardi L; Rusconi F. *Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts.* **INT J EPIDEMIOL** 2015 Feb;44(1):199-208. doi: 10.1093/ije/dyu260. Epub 2015 Jan 27.

FACTOR D'IMPACTE: 9,176 (Q1; D1)

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Original article

Early Life

Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts

Daniela Zugna,[1] Claudia Galassi,[1] Isabella Annesi-Maesano,[2] Nour Baïz,[2] Henrique Barros,[3] Mikel Basterrechea,[4] Sofia Correia,[3] Liesbeth Duijts,[5] Ana Esplugues,[6] Maria Pia Fantini,[7] Francesco Forastiere,[8] Mireia Gascon,[9] Davide Gori,[7] Hazel Inskip,[10] Pernille S Larsen,[11] Monique Mommers,[12] Anne-Marie Nybo Andersen,[11] John Penders,[12,13] Maria S Petersen,[14] Katharine Pike,[15] Daniela Porta,[8] Agnes Sonnenschein-van der Voort,[5] Ulrike Steuerwald,[14] Jordi Sunyer,[9] Maties Torrent,[16] Martine Vrijheid,[9] Lorenzo Richiardi[1] and Franca Rusconi[17]*

3. Peña C; **Cabot G**; Gómez-Zorrilla S; **Zamorano L**; Ocampo-Sosa A; **Murillas J**; Almirante B; Pomar V; Aguilar M; Granados A; Calbo E; Rodríguez-Baño J; Rodríguez-López F; Tubau F; Martínez-Martínez L; **Oliver A**. *Influence of Virulence Genotype and Resistance Profile in the Mortality of Pseudomonas aeruginosa Bloodstream Infections*. **CLIN INFECT DIS** 2015 Feb 15;60(4):539-48. doi: 10.1093/cid/ciu866. Epub 2014 Nov 6.

FACTOR D'IMPACTE: 8,886 (Q1; D1)

Clinical Infectious Diseases Advance Access published November 21, 2014

MAJOR ARTICLE

Influence of Virulence Genotype and Resistance Profile in the Mortality of *Pseudomonas aeruginosa* Bloodstream Infections

Carmen Peña,[1] Gabriel Cabot,[2] Silvia Gómez-Zorrilla,[1] Laura Zamorano,[2] Alain Ocampo-Sosa,[3] Javier Murillas,[2] Benito Almirante,[4] Virginia Pomar,[5] Manuela Aguilar,[6] Ana Granados,[7] Esther Calbo,[8] Jesús Rodríguez-Baño,[9] Fernando Rodríguez-López,[10] Fe Tubau,[1] Luis Martínez-Martínez,[3,11] and Antonio Oliver[2]; for the Spanish Network for Research in Infectious Diseases (REIPI)

[1]Servicio de Enfermedades Infecciosas, Hospital Universitario de Bellvitge-IDIBELL, Barcelona, [2]Unidad de Investigación, Servicio de Microbiología y Servicio de Medicina Interna, Hospital Universitario de Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, [3]Servicio de Microbiología, Hospital Universitario Marqués de Valdecilla-IFIMAV, Santander, [4]Servicio de Enfermedades Infecciosas, Hospital Universitario Vall d'Hebrón, [5]Unidad de Enfermedades Infecciosas, Hospital Santa Creu i Sant Pau, Barcelona, [6]Servicio de Enfermedades Infecciosas, Hospital Universitario Virgen del Rocío, Sevilla, [7]Sección de Enfermedades Infecciosas, Consorci Hospitalari Parc Taulí, Sabadell, [8]Sección de Enfermedades Infecciosas, Hospital Mutua de Terrasa, [9]Sección de Enfermedades Infecciosas, Hospital Universitario Virgen Macarena, Sevilla, [10]Servicio de Microbiología Infecciosas, Hospital Universitario Reina Sofía-IMIBIC, Córdoba, and [11]Departamento de Biología Molecular, Universidad de Cantabria, Santander, Spain

Background. The type III secretion system (TTSS) is a major virulence determinant of *Pseudomonas aeruginosa*. The objective of this study was to determine whether the TTSS genotype is a useful prognostic marker of *P. aeruginosa* bacteremia mortality. We also studied the potential association between TTSS genotypes and multidrug-resistant (MDR) profiles, and how this interaction impacts the outcome of bloodstream infections.

Methods. We performed a post hoc analysis of a published prospective multicenter cohort of *P. aeruginosa* bloodstream infections. The impact in mortality of TTSS genotypes (*exoS*, *exoT*, *exoU*, *and exoY* genes) and resistance profiles was investigated. Cox regression analysis was used to control for confounding variables.

Results. Among 590 patients, the 30-day mortality rate was 30% (175 patients), and 53% of them died in the first 5 days (early mortality). The unadjusted probabilities of survival until 5 days was 31.4% (95% confidence interval [CI], 17.4%–49.4%) for the patients with *exoU*-positive isolates and 53.2% (95% CI, 44.6%–61.5%) for *exoU*-negative isolates (log rank $P = .005$). After adjustment for confounders, *exoU* genotype (adjusted hazard ratio [aHR], 1.90 [95% CI, 1.15–3.14]; $P = .01$) showed association with early mortality. In contrast, late (30-day) mortality was not influenced by TTSS genotype but was independently associated with MDR profiles (aHR,1.40 [95% CI, 1.01–1.94]; $P = .04$). Moreover, the *exoU* genotype (21% of all isolates) was significantly less frequent (13%) among MDR strains (particularly among extensively drug-resistant isolates, 5%), but was positively linked to moderately resistant (1–2 antipseudomonals) phenotypes (34%).

Conclusions. Our results indicate that the *exoU* genotype, which is associated with specific susceptibility profiles, is a relevant independent marker of early mortality in *P. aeruginosa* bacteremia.

4. Tischer C; Casas L; Wouters IM; Doekes G; Garcia-Esteban R; Gehring U; Hyvärinen A; Oldenwening M; Kerkhof M; Sunyer J; Standl M; Thiering E; **Torrent M**; Heinrich J. *Early exposure to bio-contaminants and asthma up to 10 years of age: results of the HITEA study*. **EUR RESPIR J** 2015 Feb;45(2):328-37. doi: 10.1183/09031936.00060214. Epub 2014 Sep 3.

FACTOR D'IMPACTE: 7,636 (Q1; D1)

Early exposure to bio-contaminants and asthma up to 10 years of age: results of the HITEA study

Christina Tischer[1†], Lidia Casas[2,3,4,5], Inge M. Wouters[6], Gert Doekes[6], Raquel Garcia-Esteban[3,4,5], Ulrike Gehring[6], Anne Hyvärinen[7], Marieke Oldenwening[6], Marjan Kerkhof[8], Jordi Sunyer[3,4,5,9], Marie Standl[1], Elisabeth Thiering[1,10], Maties Torrent[11] and Joachim Heinrich[1] for the HITEA study group

Author Affiliations

Christina Tischer, Institute of Epidemiology I, Helmholtz Zentrum München, German Research Centre for Environmental Health, Ingolstaedter Landstrasse 1, D-85764 Neuherberg, Germany. E-mail: christina.tischer@helmholtz-muenchen.de

Abstract

Inverse associations have been found between exposure to bio-contaminants and asthma and allergies. The aim of this study was to prospectively assess whether early exposure to bio-contaminants in dust is associated with asthma and allergy later in childhood among children from (sub)-urban areas.

In subsets of three European birth cohorts (PIAMA: n=553; INMA: n=481; and LISAplus: n=395), endotoxin, (1,3,)-β-D-glucan and extracellular polysaccharide were measured in dust from living rooms shortly after birth. Current asthma at 6 years and 10 years of age and ever asthma up to 10 years of age were assessed by parental questionnaires. Specific IgE levels at 8 years (PIAMA) and 10 years (LISAplus) were available. Adjusted, cohort-specific logistic regression analyses were performed.

Higher endotoxin concentrations were positively associated with current asthma at 6 years of age in PIAMA (adjusted OR 1.96, 95% CI 1.07-3.58), but were inversely related with ever asthma up to 10 years of age in INMA (adjusted OR 0.39, 95% CI 0.16-0.94). No associations with asthma were found for LISAplus. No associations were observed with atopic sensitisation in all cohorts. All associations with (1,3)-β-D-glucan and extracellular polysaccharide were statistically nonsignificant.

The suggested immunological mechanisms of early exposure to bio-contaminants with regards to asthma and allergy might be different for children growing up in (sub)-urban environments.

5. Barbé F; Sánchez-de-la-Torre A; Abad J; Durán-Cantolla J; Mediano O; Amilibia J; Masdeu MJ; Florés M; **Barceló A**; **de la Peña M**; Aldomá A; Worner F; Valls J; Castellà G; Sánchez-de-la-Torre M. *Effect of obstructive sleep apnoea on severity and short-term prognosis of acute coronary syndrome.* **EUR RESPIR J** 2015 Feb;45(2):419-27. doi: 10.1183/09031936.00071714. Epub 2015 Jan 8.

FACTOR D'IMPACTE: 7,636 (Q1; D1)

Effect of obstructive sleep apnoea on severity and short-term prognosis of acute coronary syndrome

Ferran Barbé[1,2]†, Alicia Sánchez-de-la-Torre[1,2], Jorge Abad[3], Joaquin Durán-Cantolla[2,4], Olga Mediano[5], Jose Amilibia[6], Maria José Masdeu[7], Marina Florés[1], Antonia Barceló[2,8], Mónica de la Peña[2,8], Albina Aldomá[9], Fernando Worner[9], Joan Valls[10], Gerard Castellà[10] and Manuel Sánchez-de-la-Torre[1,2] on behalf of the Spanish Sleep Network

Author Affiliations

Ferran Barbé, Respiratory Dept, Hospital Univ Arnau de Vilanova, Rovira Roure, 80, 25198 Lleida, Spain. E-mail: febarbe.lleida.ics@gencat.cat

Abstract

The goal of this study was to evaluate the influence of obstructive sleep apnoea on the severity and short-term prognosis of patients admitted for acute coronary syndrome.

Obstructive sleep apnoea was defined as an apnoea-hypopnoea index (AHI) >15 h^{-1}. We evaluated the acute coronary syndrome severity (ejection fraction, Killip class, number of diseased vessels, and plasma peak troponin) and short-term prognosis (length of hospitalisation, complications and mortality).

We included 213 patients with obstructive sleep apnoea (mean±SD AHI 30±14 h^{-1}, 61±10 years, 80% males) and 218 controls (AHI 6±4 h^{-1}, 57±12 years, 82% males). Patients with obstructive sleep apnoea exhibited a higher prevalence of systemic hypertension (55% *versus* 37%, p<0.001), higher body mass index (29±4 kg·m^{-2} *versus* 26±4 kg·m^{-2}, p<0.001), and lower percentage of smokers (61% *versus* 71%, p=0.04). After adjusting for smoking, age, body mass index and hypertension, the plasma peak troponin levels were significantly elevated in the obstructive sleep apnoea group (831±908 ng·L^{-1} *versus* 987±884 ng·L^{-1}, p=0.03) and higher AHI severity was associated with an increased number of diseased vessels (p=0.04). The mean length of stay in the coronary care unit was higher in the obstructive sleep apnoea group (p=0.03).

This study indicates that obstructive sleep apnoea is related to an increase in the peak plasma troponin levels, number of diseased vessels, and length of stay in the coronary care unit.

6. De Majumdar S; Yu J; Fookes M; McAteer SP; **Llobet E**; Finn S; Spence S; Monaghan A; Kissenpfennig A; Ingram RJ; Bengoechea J; Gally DL; Fanning S; Elborn JS; Schneiders T. *Elucidation of the RamA Regulon in Klebsiella pneumoniae Reveals a Role in LPS Regulation.* **PLOS PATHOG** 2015 Jan 29;11(1):e1004627. doi: 10.1371/journal.ppat.1004627. eCollection 2015.

FACTOR D'IMPACTE: 7,562 (Q1; D1)

PLOS | PATHOGENS

RESEARCH ARTICLE

Elucidation of the RamA Regulon in *Klebsiella pneumoniae* Reveals a Role in LPS Regulation

Shyamasree De Majumdar[1,2], Jing Yu[1], Maria Fookes[3], Sean P. McAteer[4], Enrique Llobet[5], Sarah Finn[6], Shaun Spence[1], Avril Monaghan[1], Adrien Kissenpfennig[1], Rebecca J. Ingram[1], José Bengoechea[1,5], David L. Gally[4], Séamus Fanning[6], Joseph S. Elborn[1], Thamarai Schneiders[1,2]*

1 Centre for Infection and Immunity, Belfast, United Kingdom, 2 Division of Pathway and Infection Medicine, Edinburgh, United Kingdom, 3 Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, United Kingdom, 4 Division of Immunity and Infection, The Roslin Institute and R(D) SVS, The University of Edinburgh, Easter Bush, Midlothian, United Kingdom, 5 Laboratory Microbial Pathogenesis, Fundació d'Investigació Sanitària de les Illes Balears (FISIB) Recinto Hospital Joan March, Bunyola, Spain, 6 UCD Centre for Molecular Innovation and Drug Discovery, School of Public Health, Physiotherapy & Population Science, University College Dublin, Dublin, Ireland

* thamarai.schneiders@ed.ac.uk

Abstract

Klebsiella pneumoniae is a significant human pathogen, in part due to high rates of multi-drug resistance. RamA is an intrinsic regulator in *K. pneumoniae* established to be important for the bacterial response to antimicrobial challenge; however, little is known about its possible wider regulatory role in this organism during infection. In this work, we demonstrate that RamA is a global transcriptional regulator that significantly perturbs the transcriptional landscape of *K. pneumoniae*, resulting in altered microbe-drug or microbe-host response. This is largely due to the direct regulation of 68 genes associated with a myriad of cellular functions. Importantly, RamA directly binds and activates the *lpxC*, *lpxL-2* and *lpxO* genes associated with lipid A biosynthesis, thus resulting in modifications within the lipid A moiety of the lipopolysaccharide. RamA-mediated alterations decrease susceptibility to colistin E, polymyxin B and human cationic antimicrobial peptide LL-37. Increased RamA levels reduce *K. pneumoniae* adhesion and uptake into macrophages, which is supported by *in vivo* infection studies, that demonstrate increased systemic dissemination of ramA overexpressing *K. pneumoniae*. These data establish that RamA-mediated regulation directly perturbs microbial surface properties, including lipid A biosynthesis, which facilitate evasion from the innate host response. This highlights RamA as a global regulator that confers pathoadaptive phenotypes with implications for our understanding of the pathogenesis of *Enterobacter*, *Salmonella* and *Citrobacter* spp. that express orthologous RamA proteins.

Author Summary

Bacteria can rapidly evolve under antibiotic pressure to develop resistance, which occurs when target genes mutate, or when resistance-encoding genes are transferred. Alternatively, microbes can simply alter the levels of intrinsic proteins that allow the organism to

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Competing Interests: The authors have declared that no competing interests exist.

7. **Romaguera D**; Ward H; Wark PA; Vergnaud AC; Peeters PH; van Gils CH; Ferrari P; Fedirko V; Jenab M; Boutron-Ruault MC; Dossus L; Dartois L; Hansen CP; Dahm CC; Buckland G; Sánchez MJ; Dorronsoro M; Navarro C; Barricarte A; Key TJ; Trichopoulou A; Tsironis C; Lagiou P; Masala G; Pala V; Tumino R; Vineis P; Panico S; Bueno-de-Mesquita HB; Siersema PD; Ohlsson B; Jirström K; Wennberg M; Nilsson LM; Weiderpass E; Kühn T; Katzke V; Khaw KT; Wareham NJ; Tjønneland A; Boeing H; Quirós JR; Gunter MJ; Riboli E; Norat T. *Pre-diagnostic concordance with the WCRF/AICR guidelines and survival in European colorectal cancer patients: a cohort study*. **BMC MED** 2015 May 7;13:107. doi: 10.1186/s12916-015-0332-5.

FACTOR D'IMPACTE: 7,249 (Q1; D1)

Romaguera *et al. BMC Medicine* (2015) 13:107
DOI 10.1186/s12916-015-0332-5

BMC Medicine

RESEARCH ARTICLE Open Access

Pre-diagnostic concordance with the WCRF/AICR guidelines and survival in European colorectal cancer patients: a cohort study

Dora Romaguera[1,2,3*], Heather Ward[1], Petra A Wark[4], Anne-Claire Vergnaud[1], Petra H Peeters[1,5], Carla H van Gils[5], Pietro Ferrari[6], Veronika Fedirko[7,8], Mazda Jenab[6], Marie-Christine Boutron-Ruault[9,10,11], Laure Dossus[9,10,11], Laureen Dartois[9,10,11], Camilla Plambeck Hansen[12], Christina Catherine Dahm[12], Genevieve Buckland[13], María José Sánchez[14,15], Miren Dorronsoro[15,16], Carmen Navarro[15,17,18], Aurelio Barricarte[15,19], Timothy J Key[20], Antonia Trichopoulou[21,22], Christos Tsironis[21], Pagona Lagiou[22,23,24], Giovanna Masala[25], Valeria Pala[26], Rosario Tumino[27], Paolo Vineis[1,28], Salvatore Panico[29], H Bas Bueno-de-Mesquita[1,30,31,32], Peter D Siersema[31], Bodil Ohlsson[33], Karin Jirström[34], Maria Wennberg[35], Lena M Nilsson[36], Elisabete Weiderpass[37,38,39,40], Tilman Kühn[41], Verena Katzke[41], Kay-Tee Khaw[42], Nick J Wareham[43], Anne Tjønneland[44], Heiner Boeing[45], José R Quirós[46], Marc J Gunter[1], Elio Riboli[1] and Teresa Norat[1]

Abstract

Background: Cancer survivors are advised to follow lifestyle recommendations on diet, physical activity, and body fatness proposed by the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) for cancer prevention. Previous studies have demonstrated that higher concordance with these recommendations measured using an index score (the WCRF/AICR score) was associated with lower cancer incidence and mortality. The aim of this study was to evaluate the association between pre-diagnostic concordance with WCRF/AICR recommendations and mortality in colorectal cancer (CRC) patients.

Methods: The association between the WCRF/AICR score (score range 0–6 in men and 0–7 in women; higher scores indicate greater concordance) assessed on average 6.4 years before diagnosis and CRC-specific (n = 872) and overall mortality (n = 1,113) was prospectively examined among 3,292 participants diagnosed with CRC in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (mean follow-up time after diagnosis 4.2 years). Multivariable Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality.
(Continued on next page)

8. Calvete O; Reyes J; Zuñiga S; Paumard-Hernández B; Fernández V; Bujanda L; Rodriguez-Pinilla MS; Palacios J; **Heine-Suñer D**; Banka S; Newman WG; Cañamero M; Pritchard DM; Benítez J. *Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour*. **HUM MOL GENET** 2015 May 15;24(10):2914-22. doi: 10.1093/hmg/ddv054. Epub 2015 Feb 11.

   FACTOR D'IMPACTE: 6,393 (Q1; D1)

Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour

Oriol Calvete[1-3], Jose Reyes[4], Sheila Zuñiga[5], Beatriz Paumard-Hernández[1], Victoria Fernández[1], Luis Bujanda[6], María S. Rodriguez-Pinilla[7], Jose Palacios[8], Damian Heine-Suñer[9], Siddharth Banka[10], William G. Newman[10], Marta Cañamero[2,†], D. Mark Pritchard[11] and Javier Benítez[1-3,*]

+ Author Affiliations

* To whom correspondence should be addressed at: Spanish National Cancer Research Center, (CNIO), Melchor Fernández Almagro, 3. 28029, Madrid, Spain. Tel: +34 912246911; Fax: +34 912246911; Email: jbenitez@cnio.es

† Present address: Roche Pharmaceutical Research and Early Development, Translational Medicine Oncology Roche Innovation Center. 82377 Penzberg, Germany.

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Abstract

Gastric neuroendocrine tumours (NETs) arise from enterochromaffin-like cells, which are located in oxyntic glands within the stomach. Type I tumours represent 70–80% of gastric NETs and are associated with hypergastrinaemia, chronic atrophic gastritis and achlorhydria. Gastrin is involved in the endocrine regulation of gastric acid production. Most type I gastric NETs are sporadic, have a good prognosis and their genetic basis are unknown. We performed an **exome sequencing** study in a family with consanguineous parents and 10 children, five of whom were affected by type I gastric NET. Atypical clinical traits included an earlier age of onset (around 30 years), aggressiveness (three had nodal infiltration requiring total gastrectomy and one an adenocarcinoma) and iron-deficiency rather than megaloblastic anaemia. We identified a homozygous missense mutation in the 14th exon of the *ATP4A* gene (c.2107C>T), which encodes the proton pump responsible for acid secretion by gastric parietal cells. The amino acid p.Arg703Cys is highly conserved across species and originates a change of one of the transmembrane domains that avoids the liberation of protons from cells to stomach. This is consistent with the achlorhydria that was observed in the affected individuals. No germline or somatic mutations in the *ATP4A* gene were found in sporadic gastric NET patients. Based on the results of this large family, it seems that this atypical form of gastric NET has an earlier age of onset, behaves more aggressively and has atypical clinical traits that differentiated from other studied cases.

9. **Córdoba A**; **Satué M**; **Gómez-Florit M**; Hierro-Oliva M; Petzold C; Lyngstadaas SP; González-Martín ML; **Monjo M**; **Ramis JM**. *Flavonoid-Modified Surfaces: Multifunctional Bioactive Biomaterials with Osteopromotive, Anti-Inflammatory, and Anti-Fibrotic Potential.* **ADV HEALTHC MATER** 2015 Mar 11;4(4):540-9. doi: 10.1002/adhm.201400587. Epub 2014 Oct 21.

FACTOR D'IMPACTE: 5,797 (Q1; D1)

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Flavonoid-Modified Surfaces: Multifunctional Bioactive Biomaterials with Osteopromotive, Anti-Inflammatory, and Anti-Fibrotic Potential

Alba Córdoba, María Satué, Manuel Gómez-Florit, Margarita Hierro-Oliva, Christiane Petzold, Staale P. Lyngstadaas, María Luisa González-Martín, Marta Monjo, and Joana M. Ramis**

Flavonoids are small polyphenolic molecules of natural origin with antioxidant, anti-inflammatory, and antibacterial properties. Here, a bioactive surface based on the covalent immobilization of flavonoids taxifolin and quercitrin on titanium substrates is presented, using (3-aminopropyl)triethoxysilane (APTES) as coupling agent. FTIR and XPS measurements confirm the grafting of the flavonoids to the surfaces. Using 2-aminoethyl diphenylborinate (DPBA, a flavonoid-specific dye), the modified surfaces are imaged by fluorescence microscopy. The bioactivity of the flavonoid-modified surfaces is evaluated in vitro with human umbilical cord derived mesenchymal stem cells (hUC-MSCs) and human gingival fibroblasts (HGFs) and compared to that of simple flavonoid coatings prepared by drop casting. Flavonoid-modified surfaces show anti-inflammatory and anti-fibrotic potential on HGF. In addition, Ti surfaces covalently functionalized with flavonoids promote the differentiation of hUC-MSCs to osteoblasts—enhancing the expression of osteogenic markers, increasing alkaline phosphatase activity and calcium deposition; while drop-casted surfaces do not. These findings could have a high impact in the development of advanced implantable medical devices like bone implants. Given the broad range of bioactivities of flavonoid compounds, these surfaces are ready to be explored for other biomedical applications, e.g., as stent surface or tumor-targeted functionalized nanoparticles for cardiovascular or cancer therapies.

1. Introduction

Many implantable medical devices fail due to a bad tissue integration, infection procedures or inflammatory responses. Surface modification is a common strategy for solving these drawbacks that aims to tailor cell-material interactions.[1] Much of the current effort to achieve bioactive surfaces is focused on modifying the implant surface chemistry, e.g., by immobilization of bioactive molecules such as growth factors, or other proteins or peptides.[2] However, the use of growth factors in biomedical devices entails some serious drawbacks regarding stability, administration, bioactivity, and bioavailability. Growth factors are unstable and short-lived proteins. Therefore, they have to be handled with care. In addition, growth factors have very limited regulatory approval due to unwanted side effects and might even impede the magnitude of tissue-material response.[2] Furthermore, growth factors are commercially produced using recombinant technology, which makes

10. Høiby N; Bjarnsholt T; Moser C; Bassi GL; Coenye T; Donelli G; Hall-Stoodley L; Holá V; Imbert C; Kirketerp-Møller K; Lebeaux D; **Oliver A**; Ullmann AJ; Williams C. *ESCMID guideline for the diagnosis and treatment of biofilm infections 2014.* **CLIN MICROBIOL INFEC** 2015 May;21 Suppl 1:S1-25. doi: 10.1016/j.cmi.2014.10.024. Epub 2015 Jan 14.

FACTOR D'IMPACTE: 5,768 (Q1; D1)

ESCMID GUIDELINES

ESCMID* guideline for the diagnosis and treatment of biofilm infections 2014

N. Høiby[1,2], T. Bjarnsholt[1,2], C. Moser[1], G. L. Bassi[3], T. Coenye[4], G. Donelli[5], L. Hall-Stoodley[6], V. Holá[7], C. Imbert[8], K. Kirketerp-Møller[9], D. Lebeaux[10], A. Oliver[11], A. J. Ullmann[12] and C. Williams[13], for the ESCMID Study Group for Biofilms (ESGB) and Consulting External Expert Werner Zimmerli[14]

1) Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark, 2) Department of International Health, Immunology and Microbiology, University of Copenhagen, Denmark, 3) Department of Pulmonary and Critical Care Medicine, Thorax Institute, Hospital Clinic, Barcelona; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona; Centro de Investigación Biomedica En Red- Enfermedades Respiratorias (CIBERES), Barcelona; and University of Barcelona, Barcelona, Spain, 4) Laboratory of Pharmaceutical Microbiology, Ghent University, Ghent, Belgium, 5) Microbial Biofilm Laboratory, IRCCS Fondazione Santa Lucia, Rome, Italy, 6) Department of Microbial Infection and Immunity, Center for Microbial Interface Biology, Ohio State University, Columbus, OH, USA, 7) Institute for Microbiology, Masaryk University and St Anne's University Hospital, Brno, Czech Republic, 8) Laboratoire Ecologie et Biologie des Interactions, Université de Poitiers, Poitiers, France, 9) Department of Orthopaedic Surgery, Hvidovre University Hospital, Hvidovre, Denmark, 10) Institut Pasteur, Unité de Génétique des Biofilms, Paris; Université Paris Descartes, Sorbonne Paris Cité, Hôpital Necker Enfants Malades, Centre d'Infectiologie Necker-Pasteur; and Institut Imagine, Paris, France, 11) Servicio de Microbiología, Hospital Universitario Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain, 12) Department of Internal Medicine II, Julius-Maximilians-University, Würzburg, Germany, 13) Institute of Healthcare Associated Infection, University of the West of Scotland, Paisley, UK and 14) Basel University Medical Clinic, Liestal, Switzerland

Abstract

Biofilms cause chronic infections in tissues or by developing on the surfaces of medical devices. Biofilm infections persist despite both antibiotic therapy and the innate and adaptive defence mechanisms of the patient. Biofilm infections are characterized by persisting and progressive pathology due primarily to the inflammatory response surrounding the biofilm. For this reason, many biofilm infections may be difficult to diagnose and treat efficiently. It is the purpose of the guideline to bring the current knowledge of biofilm diagnosis and therapy to the attention of clinical microbiologists and infectious disease specialists. Selected hallmark biofilm infections in tissues (e.g. cystic fibrosis with chronic lung infection, patients with chronic wound infections) or associated with devices (e.g. orthopaedic alloplastic devices, endotracheal tubes, intravenous catheters, indwelling urinary catheters, tissue fillers) are the main focus of the guideline, but experience gained from the biofilm infections included in the guideline may inspire similar work in other biofilm infections. The clinical and laboratory parameters for diagnosing biofilm infections are outlined based on the patient's history, signs and symptoms, microscopic findings, culture-based or culture-independent diagnostic techniques and specific immune responses to identify microorganisms known to cause biofilm infections. First, recommendations are given for the collection of appropriate clinical samples, for reliable methods to specifically detect biofilms, for the evaluation of antibody responses to biofilms, for antibiotic susceptibility testing and for improvement of laboratory reports of biofilm findings in the clinical microbiology laboratory. Second, recommendations are given for the prevention and treatment of biofilm infections and for monitoring treatment effectiveness. Finally, suggestions for future research are given to improve diagnosis and treatment of biofilm infections.