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| NAMEBenedetta Bussolati, MD, PhD | POSITION TITLEAssociate Professor of Nephrology, Molecular and Biotechnology Center, University of Torino |
| eRACOMMONS USER NAME (credential, e.g., agency login)BBUSSOLATI |
| EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)* |
| INSTITUTION AND LOCATION | DEGREE*(if applicable)* | MM/YY | FIELD OF STUDY |
| University of Torino | M.D. | 07/1994 |  Medicine |

 University of Parma PhD 10/1998 Nephrology

University of Birmingham, UK Post-Doc 1999 Vascular Physiopathology University of Torino Post-Doc 2001 Nephrology

1. **Personal Statement**

During my first years of research, I acquired a strong background on renal pathophysiology, working on mediators of glomerular and tubular inflammation, on angiogenesis and on the mechanisms of renal damage and progression. In addition, I have extensive experience in studies of stem cell biology and regenerative medicine that include characterization of various stem cell types and their potential use for tissue regeneration. I also investigated the role of extracellular vesicles (EVs) in regenerative medicine. I’m actually focusing on the role of renal progenitors and derived extracellular vesicles as therapeutic tools. In addition, I’m interested in the molecular mechanisms exploited by stem cell-derived extracellular vesicles to induce cell reprogramming and modulate angiogenesis and renal repair. I work with a highly skilled and dedicated research group and we have the technology to carrying out all of the proposed work.

1. ***Positions and Honors***

*Positions*

-1998-1999: Research Visiting Fellow at the Laboratory of Vascular and Reproductive Physiopathology, directed by Prof. Asif. Ahmed, University of Birmingham, UK;
- 1999-2001: post-Doc position at the Laboratory of Renal Immunopathology, University of Torino

- 2001-2006: position of Assistant Professor in Pharmacology, Department of Biological and Clinical Sciences, University of Torino;

-2006-present: Associate Professor of Nephrology, Department of Molecular Biotechnology and Health Sciences, Molecular and Biotechnology Center, University of Torino

*Awards*

- “Young investigator award” at the “ 4ht Word Congress on Inflammation”. Paris, July 1999.

- Wyeth-Ayerst award from the Society for Gynecologic Investigation,: Nitric oxide released via VEGFR-1 suppresses VEGFR-2 mediated endothelial cell growth and regulates angiogenesis. Chicago, March 2000.

-Award of the Medical Research Society: “Science and Medicine Conference”, Royal College of Physicians, November 2000.

-Investigator award of the ERA-EDTA. CD133+ renal progenitor cells contribute to development and angiogenesis of renal carcinoma. Glasgow, July 2006.

-Investigator award of the ’ERA-EDTA. Functional and molecular characterization of adult renal resident stem cells of autosomal dominant polycystic kidney disease patients. Stockholm, May 2008.

-Investigator award of the ’ERA-EDTA. The plasticity of human renal CD133+ progenitors is modulated by hypoxia through Oct4/miR-145 balance Prague, June 2011.

*Other experience and professional memberships*

-Council Member of the European Vascular Biology Organization (EVBO)

-Member of the Italian Society of Nephrology

-Member of the ERA-EDTA

-Co-Editor of J. Nephrology

-Accademic Editor of Plos One

-Editorial board of ISRN Stem Cells
-Editorial Board of Nephrology Dialysis and Transplantation

1. **Contributions to Science**

Dr. Bussolati is author of 127 articles on PubMED. (<http://www.ncbi.nlm.nih.gov/pubmed/?term=Bussolati+B>)

**Main recent contributions:**

***Isolation and characterization of CD133+ cells with a progenitor phenotype in normal and pathologic renal tissue.***

I was the first to identify in the human adult kidney a population of resident cells expressing CD133+. When isolated, these cells were able to differentiate *in vitro* and *in vivo* into epithelial cells and promoted renal repair in a model of acute injury (1). I also showed that CD133 cells were located in different nephron segments, including the Henle’s loop, and demonstrated the role of the microRNA145/Oct4 balance in the modulation of a progenitor phenotype (2). Finally, I showed that CD133+ cells from the inner medulla are able to produce erythropoietin under hypoxia or prolyl-hydroxylase inhibition (3). While the presence of CD133+ cells appears related to a reparative/regenerative process, we showed that the increase of cells presenting a progenitor phenotype is linked to cyst formation and proliferation in patients with polycystic kidney disease (4). These studies provide the basis for further characterization of the regenerative processes undergoing in human renal tissue, and on the other side on those mechanisms leading to impaired regeneration.

Selected references

1. Bussolati B, Bruno S, Grange C, Buttiglieri S, Deregibus MC, Cantino D, Camussi G. Isolation of renal progenitor cells from adult human kidney. Am J Pathol. 2005 Feb;166(2):545-55.

2: Bussolati B, Moggio A, Collino F, Aghemo G, D'Armento G, Grange C, Camussi G. Hypoxia modulates the undifferentiated phenotype of human renal inner medullary CD133+ progenitors through Oct4/miR-145 balance. Am J Physiol Renal Physiol. 2012 Jan 1;302(1):F116-28.

3: Bussolati B, Lauritano C, Moggio A, Collino F, Mazzone M, Camussi G. Renal CD133(+)/CD73(+) progenitors produce erythropoietin under hypoxia and prolyl hydroxylase inhibition. J Am Soc Nephrol. 2013 Jul;24(8):1234-41.

4. Carvalhosa R, Deambrosis I, Carrera P, Pasquino C, Rigo F, Ferrari M, Lasaponara F, Ranghino A, Biancone L, Segoloni G, Bussolati B, Camussi G. Cystogenic potential of CD133+ progenitor cells of human polycystic kidneys. J Pathol. 2011 Sep;225(1):129-41.

***Stem cells isolation from kidney, liver and endometriotic tissue***.

Different populations of stem cells with a mesenchymal phenotype are known to exist in tissue. We isolated and characterized populations of mesenchymal-like multipotent progenitor cells from human glomeruli (1) and human liver (2). These cells could be exploited in regenerative medicine. For instance, a Phase 1 study of intra-parenchymal hepatic injection of these liver stem cells is undergoing at the Giovanni Battista Hospital of Torino in patients suffering from liver-based inborn metabolic diseases. I am also inventor on two related patents: (“Liver progenitor cells” International Patent Application N. PCT/IT2005/000303; and “Isolated Multipotent Mesenchymal Stem Cell From Human Adult Glomeruli, A Method Of Preparing Thereof And Uses Thereof In The Regenerative Medicine Of The Kidney, pat. App. N. 20110256111”).

In addition, we isolated from the ectopic lesions of patients with endometriosis a population of mesenchymal stem cell with an altered phenotype and angiogenic properties (3). Indeed, cell treatment with anti-angiogenic therapy reverted the pathologic phenotype, suggesting a novel therapeutic approach for this pathology (4).

Selected references

1: Bruno S, Bussolati B, Grange C, Collino F, di Cantogno LV, Herrera MB, Biancone L, Tetta C, Segoloni G, Camussi G. Isolation and characterization of resident mesenchymal stem cells in human glomeruli. Stem Cells Dev. 2009 Jul-Aug;18(6):867-80.

2: Herrera MB, Bruno S, Buttiglieri S, Tetta C, Gatti S, Deregibus MC, Bussolati B, Camussi G. Isolation and characterization of a stem cell population from adult human liver. Stem Cells. 2006 Dec;24(12):2840-50.

3. Moggio A, Pittatore G, Cassoni P, Marchino GL, Revelli A, Bussolati B. Sorafenib inhibits growth, migration, and angiogenic potential of ectopic endometrial mesenchymal stem cells derived from patients with endometriosis. Fertil Steril. 2012 Dec;98(6):1521-30.e2.

4. Pittatore G, Moggio A, Benedetto C, Bussolati B, Revelli A. Endometrial adult/progenitor stem cells: pathogenetic theory and new antiangiogenic approach or endometriosis therapy. Reprod Sci. 2014 Mar;21(3):296-304.

***Regenerative medicine***

I investigated the effect of cell therapy in acute kidney injury, as well as the mechanisms involved in cell recruitment and bio-distribution, as they are crucial information for Regenerative therapies. We showed that murine mesenchymal stem cells home to injured kidney and contribute to the repair of the local damage in a model of acute renal failure (1). Moreover, comparing the localization of mesenchymal stem cells and CD133+ progenitors in a model of acute kidney injury, I showed a preferential renal distribution of the cells of renal origin in respect to bone-marrow derived mesenchymal stem cells (2). Finally, we showed the therapeutic effect of stem cells derived from human amniotic fluid in acute renal damage, and studied their secretome in respect to mesenchymal stem cells (3). Finally, we showed the therapeutic effect of CD133+ cell administration in model of acute kidney injury, and the paracrine effects involved with a particular focus on erythropoietin production (4).

Selected references

1: Herrera MB, Bussolati B, Bruno S, Fonsato V, Romanazzi GM, Camussi G.Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. Int J Mol Med. 2004 Dec;14(6):1035-41.

2: Grange C, Moggio A, Tapparo M, Porta S, Camussi G, Bussolati B. Protective effect and localization by optical imaging of human renal CD133+ progenitor cells in an acute kidney injury model. Physiol Rep. 2014 May 2;2(5):e12009.

3: Hauser PV, De Fazio R, Bruno S, Sdei S, Grange C, Bussolati B, Benedetto C, Camussi G. Stem cells derived from human amniotic fluid contribute to acute kidney injury recovery. Am J Pathol. 2010 Oct;177(4):2011-21.

4: Aggarwal S, Grange C, Iampietro C, Camussi G, Bussolati B. Human CD133(+)Renal Progenitor Cells Induce Erythropoietin Production and Limit Fibrosis After Acute Tubular Injury. Sci Rep. 2016 Nov 17;6:37270.

***Extracellular vesicles***

I investigated the relative contribution of stem-cell derived EVs in the therapeutic effect of the cell therapy, and the relative mechanisms. We first showed that EVs mediated the benefit of mesenchymal stem cell administration in acute renal damage, and that the removal of RNA prevented this effect, indicating a role for the transfer of genetic information. (1) We also first showed that EVs from endothelial progenitor cells reprogram target cells through delivery of genetic material (2). The transfer of microRNA also mediated the pro-angiogenic effect of EVs derived from tumor stem cells (3).

Finally, in recent studies, I showed that EVs present in urine may represent useful markers of renal damage/regeneration. We showed the presence of vesicles expressing CD133 in normal subjects but not in patients with end stage renal disease, and we correlated their number with the presence of graft dysfunction in transplanted patients (4).

Selected references

1. Bruno S, Grange C, Deregibus MC, Calogero RA, Saviozzi S, Collino F, Morando L, Busca A, Falda M, Bussolati B, Tetta C, Camussi G. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. J Am Soc Nephrol. 2009 May;20(5):1053-67.

2. Deregibus MC, Cantaluppi V, Calogero R, Lo Iacono M, Tetta C, Biancone L, Bruno S, Bussolati B, Camussi G. Endothelial progenitor cell derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. Blood. 2007 Oct 1;110(7):2440-8.

3: Grange C, Tapparo M, Collino F, Vitillo L, Damasco C, Deregibus MC, Tetta C, Bussolati B, Camussi G. Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche. Cancer Res. 2011 Aug 1;71(15):5346-56.

4: Dimuccio V, Ranghino A, Praticò Barbato L, Fop F, Biancone L, Camussi G, Bussolati B. Urinary CD133+ extracellular vesicles are decreased in kidney transplanted patients with slow graft function and vascular damage. PLoS One. 2014 Aug 6;9(8):e104490.

***Angiogenesis***

I first described a new role for the VEGF receptor-1 as a negative modulator of angiogenesis (1). I showed that VEGF-induced activation of heme-oxygenase possess a dual role in angiogenesis, inhibiting the inflammatory angiogenesis while favoring the endothelial angiogenesis necessary for the tissue repair.
I identified a population of CD105+ bipotent renal tumor stem cells in renal carcinomas, with tumor-initiating properties and ability to generate vessels (3). This observation demonstrated that tumor stem cells might also contribute to tumor vasculogenesis, thus representing a new target for anti-angiogenic therapy). Finally, I investigated the VEGF dependent and independent mechanisms of endothelial differentiation of tumor stem cells and their involvement in anti-angiogenic treatment resistance (4).

Selected references

1. Bussolati B, Dunk C, Grohman M, Kontos CD, Mason J, Ahmed A. Vascular endothelial growth factor receptor-1 modulates vascular endothelial growth factor-mediated angiogenesis via nitric oxide. Am J Pathol. 2001 Sep;159(3):993-1008.

2: Bussolati B, Ahmed A, Pemberton H, Landis RC, Di Carlo F, Haskard DO, Mason JC. Bifunctional role for VEGF-induced heme oxygenase-1 in vivo: induction of angiogenesis and inhibition of leukocytic infiltration. Blood. 2004 Feb 1;103(3):761-6.

3: Bussolati B, Bruno S, Grange C, Ferrando U, Camussi G. Identification of a tumor-initiating stem cell population in human renal carcinomas. FASEB J. 2008 Oct;22(10):3696-705.

4: Brossa A, Grange C, Mancuso L, Annaratone L, Satolli MA, Mazzone M, Camussi G, Bussolati B. Sunitinib but not VEGF blockade inhibits cancer stem cell endothelial differentiation. Oncotarget. 2015 Feb 28. [Epub ahead of print]

**C. Research Support.**

In the last 3 years, Dr. Bussolati has been the principal investigator in research projects funded by both national funding agencies: Italian Ministry of Education, University, and Research (MIUR) and Piedmont Region as well as European funding agencies. Moreover, she is supported by a Grant of the Unicyte EV AG company for the study of stem cell-derived EVs in oncology.

1- FP7 Nephro-Tools - People – Research Training Network 2011-2015 Ga N. 289754. www.nephrotools.com

Overall goals of the project: to generate stem/progenitor cell lines from different types of human renal tissue, and evaluate their potential for use in drug discovery programmes and cell-based therapies.

Responsibilities: PI in WP1: Generation and characterisation of human adult kidney stem/progenitor cell and PI in WP3: Identification of the pharmacological properties of kidney stem/progenitor cell-derived podocytes

2- Grant AIM (Advanced in Medicine)- 2013-2015 Effect of LifeInside on regenerative medicine.

Overall goal: Identify new sources of growth factors for regenerative medicine.

Responsibility: PI, analysis of the content of colostrum-derived exosomes/extracellular vesicles.

3-MIUR 60% 2014 National Grant: Evaluation of microRNA and surface markers in urinary exosomes as markers of renal damage and regeneration.

Overall goal: Discovery of markers of renal damage/regeneration.

Responsibilities: PI, Study on transplanted patient-derived urinary extracellular vesicles.

4--Biotechnology Platform, UE/RegionePiemonte, 2010-2014;MBC consortium PiStem project

Overall goal: Biotechnological platform for the use of stem cells in the Piedmont Region.

Responsibility: PI of WP9: Differentiation of stem cells from different origin into renal cells.

5- Unicyte EG AV “Pre-clinical development of stem cell-derived EVs for treatment of Renal Carcinomas” 01/01/16 - 31/12/17

This project aims to establish preclinical models for development of stem cell-derived miRNA therapeutic strategies for renal carcinomas.