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Editoriale

Editorial

New insights into biological targets and therapeutic management of infectious diseases

Approfondimenti in tema di target biologici e gestione terapeutica delle malattie infettive

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New acquisitions on pathogen receptor-mediated interactions with host target cells and on pathogen induced host cell signaling events, have allowed a better understanding of mechanisms facilitating pathogen survival and replication within its host as well as their escape from immune control. In this issue, emphasis has been placed on membrane receptors playing a major role in pathogen interaction with host cells and immune system and representing new promising targets in the therapy of infectious diseases.

The urokinase-type plasminogen activator receptor (uPAR) is a cell-surface receptor largely expressed on leukocytes [1-3]. A soluble uPAR form (suPAR) is increased in sera of individuals suffering from viral, bacterial or parasitical infections as well as autoimmune diseases and cancer. suPAR levels are thought to reflect the state of immune activation of the individual and, in all of these conditions, the higher concentration of serum suPAR correlates with a worse prognosis of the disease. Here, Montuori et al. review the expression and possible functions of the various forms of uPAR in infectious diseases [4].

The 37/67 kDa laminin receptor precursor/laminin receptor (37LRP/67LR) represents a multifunctional protein located on the cell surface, in the cytosol and the nucleus [5]. The receptor mediates laminin-dependent cell adhesion, migration and proliferation, major functions during tumor invasion and metastasis. 37LRP/67LR also acts as a receptor for viruses, bacteria and yeasts and is involved in the binding and internalization of prion proteins. In this issue, Rea et al. review the structure and function of this molecule, its role in cancer and prion diseases and its importance as a new therapeutic target [6].

Formyl peptide receptors (FPRs) are a seven-transmembrane domain, G protein-coupled receptors, expressed mainly by phagocytic leukocytes and involved in host defense and inflammation. *Helicobacter pylori* (*H. pylori*) infection affects more than half of the world's population and peptides produced by *H. pylori* are involved in inflammation associated with the infection, conferring the risk of serious diseases [7]. Here, Rossi et al. comment on some advances in the elucidation of specific interactions between the Hp(2-20) peptide, derived from H. pylori, and FPRs, providing new insights into inflammatory carcinogenesis that could then be targeted for therapeutic intervention [8].

Such interactions between host and pathogens may provide new insights to further understand viral, fungal and bacterial virulence in malignant and non malignant hematological diseases. Clinical relationships between acute and chronic infections and hematological malignancies are not well known. During the last three decades, targeted immunosuppressive and anticancer treatments, diagnostic techniques, broad-spectrum antimicrobials, supportive care, surveillance and prevention of specific nosocomial infections as well as several other prevention measures have greatly im-

proved the outcome of hematological malignancies and non [9-11]. Despite these improvements, bacterial, fungal and viral infections remain a leading cause of morbidity and mortality especially in hematological patients undergoing potent immunosuppressive (e.g. alemtuzumab, eculizumab) and chemotherapy treatments [12-16]. The most important risk factor for the development of infections in such patients is the depth and duration of neutropenia with bacterial infections occurring more commonly during the early stage of neutropenia and yeast, mould, and viral infections occurring later [9-11]. Although neutropenia remains of critical importance in establishing the risk of infection, it is only one of the risks. Beyond neutropenia, several other variables have been documented associated with an high risk of infectious complications, including the dosage of immunosuppressive and anticancer agents, the type and phase of disease, gastrointestinal mucositis, the use of indwelling medical devices, epidemiologic exposures, and increasing length of hospitalization [17-21]. Thus, neutropenic patients represent an heterogeneous population with different rates of infection-related morbidity and mortality depending on different combination of the risk factors described above. Allogeneic stem cell transplanted (HSCT) recipients tend to be at the highest risk of infections. Moreover, such patients experience varying immune derangements based on stem cell source, donor-recipient matching, type and dosage of drugs used for conditioning regimen and graft-versus-host disease (GVHD) prophylaxis, as well as the occurrence and severity of acute and chronic GVHD [9-11].

Invasive fungal infections (IFI) and cytomegalovirus (CMV) infection are the most common life threatening complications in patients with hematological malignancies and in HSCT recipients. Currently, in neutropenic febrile patients with hematologic malignancies empirical antifungal treatment have been documented to decrease the incidence of IFIs and their related mortality with respect to pre-emptive antifungal approach. Mucormycosis is the third most frequent opportunistic mycosis in patients with neoplastic diseases. In this issue Serio et al. show a successful management of pulmonary mucormycosis with liposomal amphotericin B and surgical curettage [22].

Both prophylaxis and preemptive therapy are used to manage CMV infection in the HSCT setting. Preemptive therapy is most commonly used, but prophylaxis is performed by some centers for high-risk patients such as recipients of CMV positive, unrelated, HLA-mismatched, or cord blood stem cell products. In this issue, Serio ea al. provide evidence that low-dose oral valgancyclovir is safe and effective as CMV reactivation prophylaxis in HSCT recipients [23].

In addition to new molecular laboratory tests and imaging techniques, recently fine-needle aspiration cytology (FNAC) has been proposed for infections site evaluation [24-26]. Lymphoadenopaties, due to several opportunistic pathogens, may frequently occur in HIV patients with long-lasting fever during antiretroviral therapy. Cozzolino et al. document in some of such HIV patients the presence of non lymphomatous clonal B-cell populations in enlarged lymph nodes [27].

In conclusion, recent insights into molecular cross-talk between pathogens and host cells may help to the development of novel drug targets for infectious disease. The better understanding of epidemiology, risk factors as well as the early detection of infections are fundamental to establish effective prophylactic and prevention strategies for patients receiving antineoplastic therapy. A multidisciplinary team consisting of specialists in hemato-oncology, pathology, microbiology, radiology, infectious disease and, if needed, a surgeon, can be useful to promptly establish diagnosis of infection diseases and to choice their correct therapeutic management.

Keywords: Viral infections, fungal infections, hematological malignancies.

Conflict of interest disclosure
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REFERENCES

[1] Ragno P. The urokinase receptor: a ligand or a receptor? Story of a sociable molecule. *Cell. Mol. Life Sci.* 63, 1028-1037, 2006.

[2] Selleri C., Montuori N., Ricci P., et al. In vivo activity of the cleaved form of soluble urokinase receptor: a new hematopoietic stem/progenitor cell mobilizer. *Cancer Res.* 66, 10885-10890, 2006.

[3] Selleri C., Montuori N., Ricci P., et al. Involvement of the urokinase-type plasminogen activator receptor in hematopoietic stem cell mobilization. *Blood* 105, 2198-2205, 2005.

[4] Montuori N., Selleri C., Ragno P. The urokinase-receptor in infectious diseases. *Infez. Med.* 20, suppl. 2, 13-18, 2012.
[5] Selleri C., Ragno P., Ricci P., et al. The metastasis-associated 67-kDa laminin receptor is involved in G-CSF-induced hematopoietic stem cell mobilization. *Blood* 108, 2476-2484, 2006.
[6] Rea V.E.A., Rossi F.W., De Paulis A, et al. 67 kDa laminin receptor: structure, function and role in cancer and infection. *Infez. Med.* 20, suppl. 2, 8-12, 2012.
[7] De Paulis A., Prevete N., Rossi F.W., et al. Helicobacter pylori Hp(2-20) promotes migration and proliferation of gastric epithelial cells by interacting with formyl peptide receptors in vitro and accelerates gastric mucosal healing in vivo. *J. Immun.* 183, 3761-3769, 2009.
[8] Rossi F.W., Prevete N., Montuori N., et al. Hp(2-20) peptide of Helicobacter pylori and the Innate Immune Receptors: Specific Role(s) of the Formyl Peptide Receptors. *Infez. Med.* 20, suppl. 2, 19-25, 2012.
[9] Pagano L., Akova M., Dimopoulos G., Herbrecht R., Drgona L., Blijlevens N. Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. *J. Antimicrob. Chemother.* 66, Suppl 1, 5-14, 2011.
[10] Viscoli C., Varnier O., Machetti M. Infections in patients with febrile neutropenia: epidemiology, microbiology, and risk stratification. *Clin. Infect. Dis.* 40, Suppl 4, 240-245, 2005.
[11] Angarone M. Epidemiology and prevention of viral infections in patients with hematologic malignancies. *Infect. Disord. Drug Targets* 11, 27-33, 2011.
[12] Selleri C., Serio B., Risitano A.M. Novel immunosuppressive strategies for bone marrow failure syndromes: a focus on alemtuzumab. *Mini Rev. Med. Chem.* 11, 536-543, 2011.
[13] Risitano A.M., Selleri C., Serio B., et al. Alemtuzumab is safe and effective as immunosuppressive treatment for aplastic anaemia and single-lineage marrow failure: a pilot study and a survey from the EBMT WPSAA. *Br. J. Haematol.* 148, 791-796, 2010.
[14] Risitano A.M., Serio B., Selleri C., Rotoli B. Valganciclovir as CMV reactivation prophylaxis in patients receiving alemtuzumab for marrow failure syndromes. *Ann. Hematol.* 88, 1261-1262, 2009.
[15] Risitano A.M., Perna F., Selleri C. Achievements and limitations of complement inhibition by eculizumab in paroxysmal nocturnal hemoglobinuria: the role of complement component 3. *Mini Rev. Med. Chem.* 11, 528-535, 2011.
[16] Risitano A.M., Notaro R., Pascariello C., et al. The complement receptor 2/factor H fusion protein TT30 protects paroxysmal nocturnal hemoglobinuria erythrocytes from complement-mediated hemolysis and C3 fragment. *Blood* 119, 6307-6316, 2012.
[17] Esposito S., Esposito I., Leone S. Considerations of antibiotic therapy duration in community- and hospital-acquired bacterial infections. *J. Antimicrob. Chemother*. Jul 24, 2012. [Epub ahead of print].
[18] Esposito S., Leone S. Antimicrobial treatment for Intensive Care Unit (ICU) infections including the role of the infectious diseases specialist. *Int. J. Antimicrob. Agents*. 29, 494-500, 2007 I.F. 3.67
[19] Gould I.M., Cauda R., Esposito S., Gudiol F., Mazzei T. Garau management of serious meticillin-resistant *Staphylococcus aureus* infections: what are the limits? *Int. J. Antimicrob. Agents.* 37, 3, 202-209, 2011.
[20] Dryden M., Andrasevic A.T., Bassetti M., Bouza E., Chastre J., Cornaglia G., Esposito S., French G., Giamarellou H., Gyssens I.C., Nathwani D., Unal S., Voss A. A European survey of antibiotic management of methicillin-resistant *Staphylococcus aureus* infection: current clinical opinion and practice. *Clin. Microbiol. Infect.* 16, Suppl 1, 3-30, 2010.
[21] Gould I.M., David M.Z., Esposito S., Garau J., Lina G., Mazzei T., Peters G. New insights into meticillin-resistant *Staphylococcus aureus* (MRSA) pathogenesis, treatment and resistance. *Int. J. Antimicrob. Agents* 39, 2, 96-104, 2012.
[22] Serio B., Rosamilio R., Giudice V., et al. Successful management of pulmonary mucormycosis with liposomal amphotericin B and surgery treatment: a case report. *Infez. Med.* 20, suppl. 2, 43-47, 2012.
[23] Serio B., Rosamilio R., Giudice V., et al. Low-dose valgancyclovir as cytomegalovirus reactivation prophylaxis in allogeneic haematopoietic stem cell transplantation. *Infez. Med.* 20, suppl. 2, 26-34, 2012.
[24] Zeppa P. Haematocytopathology: why? *Cytopathology*. 23, 73-75, 2012.
[25] Schmitt F., Vielh P., Zeppa P. Cytology for pathologists: two sides of the same coin or different views of the same side? *Cytopathology*. 23, 345-346, 2012.
[26] Vigliar E., Cozzolino I., Fernandez L.V., et al. Fine-needle cytology and flow cytometry assessment of reactive and lymphoproliferative processes of the breast. *Acta Cytol.* 56, 130-138, 2012.
[27] Cozzolino I., Vigliar L., Fernandez L.V.S., et al. Non lymphomatous clonal B-Cell populations in enlarged lymph nodes in acquired immunodeficiency syndrome. *Infez. Med.* 20, suppl. 2, 35-42, 2012.