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Impact of DAMPs, and specifically HMGB1, on the biology of mesenchymal stromal cells within injured/necrotic tissue

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Necrosis and hypoxic conditions are characteristic features of advanced solid tumors, regardless of the origin of neoplastic tissue. Released necrotic factors, also referred to as damage associated molecular patterns (DAMPs), are known to critically impact the tumor microenvironment by enhancing angiogenesis or influencing the immune response.

Acting as nurse-like cells within injured tissue mesenchymal stromal cells (MSCs) provide optimal microenvironmental conditions for would healing and suppress local immune response partly by virtue of the expression of indoleamine-2,3-dioxygenase (IDO). As a "never healing wound", tumor cells may harness host's regenerative capacities to favor their own proliferation. The presence of tumor-infiltrating-MSCs is associated with tumor progression and metastasis.

We demonstrate that necrotic material from both neoplastic and non-neoplastic/normal cells promotes proliferation and chemotaxis of human mesenchymal stem cells (MSCs) and characterize high mobility group box 1 (HMGB1) as a crucial member of DAMPs within necrotic material responsible for observed effects. In addition, we show that DAMPs interfere with the expression of indoleamine 2,3-dioxygenase (IDO) in MSCs. The biological activity of necrotic material on MSCs is abolished once these DAMPs are oxidized.

Here, we reveal DAMPs to be crucial factors in the setting of MSC biology within injured/necrotic tissue and specifically within tumor micro-milieu. The tumor microenvironment is characterized by reducing and hypoxic conditions that protect DAMPs from oxidation. Based on our results, oxidizing conditions should be considered for therapeutic approaches targeting tumor microenvironment.

Biography

R. Lotfi finished his Medical School at the University of Muenster (Germany) in 1998. After 2 ½ years of Pediatrics he went to the University Hospital of Tuebingen (Germany) where he specialized in Transfusion Medicine. From 2005 to 2007 he worked as a Post-Doc in Dr. Michael T. Lotze's laboratory at the University of Pittsburgh (PA), where he focused on tumor immunology and the impact of oxidative conditions and eosinophilia within tumor microenvironment. Since 2007 he is back to Germany and is presently the head of the Department of Innovative Cellular Therapeutics in the Institute for Transfusion Medicine of the University Hospital Ulm.

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