Institute for Pancreatic Islet Research / Paul Langerhans Institute Dresden
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Highlight / Publication:
DEL-1 promotes macrophage efferocytosis and clearance of inflammation.
Kourtzelis I, Li X, Mitroulis I, Grosser D, Kajikawa T, Wang B, Grzybek M, von Renesse J, Czogalla A, Troullinaki M, Ferreira A, Doreth C, Ruppova K, Chen LS, Hosur K, Lim JH, Chung KJ, Grossklaus S, Tausche AK, Joosten LAB, Moutsopoulos NM, Wielockx B, Castrillo A, Korostoff JM, **Coskun Ü**, Hajishengallis G, Chavakis T.
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Inflammation resolution, Del-1, efferocytosis, immunometabolism, periodontitis

Central statement of the highlight in one sentence:
We identified Developmental endothelial locus-1 (DEL-1) as a novel component of the inflammation resolution program that promotes the clearance of apoptotic material and subsequently induces a reparative, pro-resolving phenotype in macrophages.

Text of the highlight:
Resolution of inflammation following a sterile or microbial inflammatory stimulus is a well-coordinated, active process aiming to restore tissue integrity and homeostasis. Persistent inflammation due to failure of its resolution leads to chronic inflammatory disease, for instance metabolic-inflammatory and cardiometabolic disease. Recognition and removal of dying cells by macrophages, a process termed as efferocytosis, is central in the process of inflammation resolution. Despite significant advances in resolution of inflammation in recent years, the network of molecules and mechanisms that coordinate efferocytosis is incompletely understood. By using two different inflammation models and multiple complementary genetic and pharmacologic approaches, we have demonstrated that DEL-1 promotes inflammation resolution by facilitating efferocytosis and by reprograming macrophages toward a pro-resolving/reparative phenotype. Specifically, we showed that in human and murine periodontitis, a common inflammatory disease of the oral mucosa, inflammation resolution correlated with DEL-1 upregulation. DEL-1 deficiency resulted in non-resolving inflammation and persistent inflammatory bone loss in experimental periodontitis. The pro-resolving function of DEL-1 was also demonstrated in a model of acute peritoneal inflammation and could be attributed to effective efferocytosis. We also showed that DEL-1 binds with high affinity to the 'eat-me' signal phosphatidylserine that is present in dying cells and interacts with the macrophage receptor αvβ3 integrin, thereby acting as a „bridge" between apoptotic cell and efferocytic macrophage. Importantly, by generating different transgenic mice with cell-specific overexpression of DEL-1, we could ascribe the anti-leukocyte recruitment action

to endothelial cell-derived DEL-1 and the efferocytic/pro-resolving action to macrophage-derived DEL-1. The findings of this study improve our understanding about mechanisms of resolution of inflammation and underscore that therapeutic targeting of resolution represents a promising approach to treat inflammatory disorders.

Taking account of the HMGU mission:
The present work sheds light into mechanisms that promote effective resolution of inflammatory responses by modulating efferocytosis-dependent macrophage reprograming. Importantly, the findings of this work may apply to chronic inflammatory diseases, in which resolution of inflammation fails, such as cardiometabolic diseases. In other words, better understanding of resolution of inflammation may enable its therapeutic utilization in cardiometabolic disease in the future.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:
Dr. Ünal Coskun, IPI/PLID