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The role of the pro-angiogenic protein EMMPRIN in the pathogenesis of psoriatic arthritis

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Angiogenesis is an essential component in the pathophysiology of psoriatic arthritis (PsA). Extracellular matrix metalloproteinase inducer (EMMPRIN) or cluster of differentiation 147 (CD147) is a multifunctional protein that enhances angiogenesis by inducing VEGF and MMPs. Using ELISA, we assessed the concentrations of angiogenic factors (EMMPRIN, VEGF, MMP-9, MMP-7, MMP-3, MMP-2, MMP-14) in serum of 56 PsA patients with active disease, 41 PsA patients in remission, 33 patients with active rheumatoid arthritis (RA) and 33 healthy controls. PsA patients demonstrated significantly elevated levels of serum EMMPRIN, MMP-7, MMP-14 compared to RA patients ($p<0.001$, $p<0.01$ $p<0.01$ respectively) and to controls ($p<0.0001$ $p<0.01$, $p<0.01$ respectively). The levels of VEGF ($p<0.05$), MMP-14 ($p<0.05$), MMP-2 ($p<0.0001$), TIMP-2 ($p<0.001$), OPG ($p<0.001$) and RANKL ($p<0.001$) were higher in PsA patients with active disease compared to patients in remission. Serum concentrations of MMP-9 were significantly lower in RA and PsA patients vs., controls ($p<0.0001$) with no significant difference between the two disease groups. To evaluate the mediating role of EMMPRIN in fibroblast macrophage interactions and angiogenesis, we co-cultured in vitro the human fibroblast HT1080 cell line with the human monocytic like U937 or Mono Mac 6 cell lines. Secretion of EMMPRIN, VEGF and MMP-9 were synergistically enhanced in the co-culture ($p<0.01$ for all three proteins relative to single cultures), and addition of the blocking anti-EMMPRIN antibody reduced VEGF (1.7-folds, $p<0.001$) and MMP-9 levels (1.4-folds, $p<0.001$) in the co-culture. Higher numbers of closed lumens were generated when the endothelial cell-line EaHy926 was incubated with supernatants derived from the co-cultures relative to each single culture ($p<0.05$) whereas, when EMMPRIN was blocked by the antibody, this number significantly decreased ($p<0.05$). EaHy926 cells incubated with the co-culture supernatants were more rapidly migrated to close a scratch, compared to cells where EMMPRIN was specifically blocked by antibody ($p<0.05$). Our results implicate EMMPRIN as an important mediator of angiogenesis promoting fibroblast monocytes interactions, suggesting it has a central role in the pathophysiology of PsA.

Recent Publications

1. Feld J, Nissan S, Eder L, Rahat M A, Elias E, Rimar D, Laor A, Bitterman H and Zisman D (2018) Increased prevalence of metabolic syndrome and adipocytokine levels in a psoriatic arthritis cohort. Journal of Clinical Rheumatology 24(6):302-307.
2. Simanovich E, Brod V, Rahat M M, and Rahat M A (2018) Function of miR-146a-5p in tumor cells as a regulatory switch between death and angiogenesis: macrophage therapy revisited. Frontiers in Immunology 8:1931.
3. Ben-Shaanan T L, Schiller M, Azulay-Debby H, Korin B, Boshnak N, Koren T, Krot M, Shakya J, Rahat M A, Hakim F and Rolls A (2018) Modulation of anti-tumor immunity by the brain's reward system. Nature Communications 9(1):2723.
4. Walter M, Simanovich E, Brod V, Lahat N, Bitterman H and Rahat M A (2016) An epitope-specific novel anti-EMMPRIN polyclonal antibody inhibits tumor progression. Oncoimmunology 5(2):e1078056.
5. Simanovich E, Brod V, Rahat MM, Drazdov E, Shakya J, Walter M, and Rahat M A (2016) Inhibition of tumor growth and metastasis by EMMPRIN multiple antigenic peptide (MAP) vaccination is mediated by immune modulation. Oncoimmunology 6(1):e1261778.

Biography

Michal A Rahat studied the interactions between macrophages and other cell types (tumor cells, fibroblasts and endothelial cells), their regulation by the extracellular matrix metalloproteinase inducer (EMMPRIN/CD147) and micro RNAs and their effect on macrophage function and involvement in processes such as inflammation, antigen presentation, angiogenesis, tissue repair and invasiveness/metastasis, in the context of solid tumors or inflammatory diseases. Recently, she has developed two vaccination approaches, using an antibody or an active peptide vaccination against a novel epitope in EMMPRIN and she now investigates the efficacy of these methods in inhibiting angiogenesis of autoimmune diseases or cancerous diseases in animal models. She currently serves as an Assistant Professor at the Faculty of Medicine, Technion-Israel Institute of Technology and as the Director of the Research Labs and the Head of the Immunotherapy Lab at the Carmel Medical Center.

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