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Dissection of the mechanisms regulating the CXCL12/HMGB1 heterocomplex-mediated chemotaxis in cancer cells, and in monocytes from Rheumatoid Arthritis Patients

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Chemokine synergism induced by the formation of heterocomplexes is a key aspect in the regulation of the chemokine activity. CXCL12, a chemokine involved in homeostasis and pathologies, can form a complex with the alarmin HMGB1, thus enhancing the recruitment of monocytes to inflammatory sites via CXCR4, the CXCL12 selective receptor. It has been described that the CXCL12/HMGB1 heterocomplex is able to potentiate CXCR4 intracellular signaling, including ERK1/2 activation, calcium release, and chemotaxis both *in vitro* and *in vivo*. However, key open questions remain to be addressed in order to better dissect the mechanisms sustaining the synergy induced by the CXCL12/HMGB1 heterocomplex, as well as its activity in cancers and inflammatory disease, in which CXCL12 and HMGB1 have been shown to be involved.

In the first part of the thesis work, we dissected the cytoskeleton rearrangements, chemotaxis, and CXCR4 trafficking induced by the CXCL12/HMGB1 heterocomplex in HeLa cells, a cancer epithelial cell line. Of note, cells stimulated with the heterocomplex showed a synergistic activity on actin polymerization, with formation of stress fibers, accompanied by an enhanced chemotaxis, and CXCR4 recycling to the cell surface. These effects were dependent on the activity of β-arrestins, proteins essential in GPCR trafficking and signaling.

In the second part of the work, we focused on the study of the CXCL12/HMGB1 heterocomplex activity in monocytes from patients with Rheumatoid Arthritis (RA) with different disease score. Interestingly, monocytes from patients in active disease exhibited an enhanced heterocomplex-mediated chemotaxis compare to monocytes from patients in clinical remission or healthy donors. This response was dependent on the COX2/PGE2 and JAK/STAT pathways, and the thioredoxin system, which counteracting the oxidative stress of the inflammatory environment, preserved reduced-HMGB1, the redox form of the protein that specifically binds to CXCL12.

In conclusions, we have revealed new insight on the intracellular mechanisms and mediators of the microenvironment important in sustaining the CXCL12/HMGB1 heterocomplex activity, providing important basis for the design of future studies in the context of cancer and inflammatory diseases.

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