Press Release

A molecule originally identified in the brain revealed as a potential accomplice to metastasis

Scientists at the IFOM-IEO Campus in Milan have recently uncovered a novel role for the neural adhesion molecule L1 in the regulation of the immune system. The discovery, published in the Journal of Experimental Medicine, paves the way for new therapies to treat autoimmune diseases, as well as metastatic cancers, such as colon cancer, melanoma and ovarian carcinoma.

The cells in our body interact with one another and with the extracellular matrix through special molecules called adhesion molecules. These interactions ensure that our body's tissues are compact and impermeable. They also play a fundamental role in the immune response and the development of many diseases, including neoplastic and metastatic diseases. In fact, when cancer cells become metastatic they lose the interactions that normally keep cells in their correct place, enabling them to migrate to new sites.

A particular adhesion molecule, L1, was, until now, well known as an important player in brain development: mutations in L1 cause a complex neurological syndrome called CRASH (Corpus callosum agenesis, Retardation, Adducted thumbs, Spastic paraplegia, Hydrocephalus). Now, in a study conducted at the IFOM-IEO Campus of Milan by Ugo Cavallaro (Director of the *Cell adhesion and signalling in tumour progression and angiogenesis* Programme at the IFOM [The FIRC Institute of Molecular Oncology] Foundation), in collaboration with Maria Rescigno, (Director of the *Immunobiology of Dendritic Cells and Immunotherapy* Programme at the Department of Experimental Oncology at the European Institute of Oncology), L1 was shown to play a key role also in the immune system. This research, published in The Journal of Experimental Medicine, offers interesting therapeutic perspectives for the treatment of both tumours and immunological disorders.

Using an *in vitro* and *in vivo* experimental approach, Cavallaro and colleagues demonstrated, for the first time, a role for the L1 neural adhesion molecule in the cascade of events that trigger the immune response: L1 is expressed on the surface of dendritic cells, i.e. "sentinel" cells that transport antigens from peripheral tissues to the lymph nodes, thereby triggering lymphocyte activation and the immune response. To perform this function, dendritic cells need to enter and exit the circulatory system (blood and lymphatic vessels). It is at this point that L1 intervenes by regulating the movement of dendritic cells across vessel walls. The researchers also showed that endothelial cells (which coat vessels) produce L1 following an inflammatory stimulus. The association between L1 on dendritic cells and L1 on endothelial cells allows these two cell types to interact and results in the "transmigration" of dendritic cells across vessel walls.

In addition to deepening our understanding of how our immune system works, this discovery opens the door to interesting therapeutic approaches for diverse diseases: «in the case of an "excessive" immune response, as occurs in autoimmune diseases - explains Cavallaro – it would be possible to prevent the interaction between dendritic cells and the vessel wall by neutralizing L1, e.g. with a

specific antibody. For patients with the CRASH syndrome, our findings provide a possible explanation for the frequently occurring infections seen in these patients. A neurological deficit is generally considered to be the underlying cause of these infections. However, our study points to a more obvious cause: a dysfunction of L1 in dendritic cells. If this were the case, it would be easier to treat these patients».

The research holds promise also for the identification of new pharmacological targets for anti-cancer therapies: «some types of cancers, such as colon cancer, melanoma and ovarian carcinoma – explains Cavallaro – express high levels of L1 that correlate with the invasive and metastatic potential of the tumour. Since tumour cells employ mechanisms very similar to those adopted by immunological cells to enter blood vessels and migrate, inactivation of L1 could represent a valid anti-metastasis strategy».

«The presence of L1 – adds Maria Rescigno – might also explain how cancer cells escape recognition by the immune system, a phenomenon common to many cancers known as "immunoevasion". Indeed, the aberrant expression of L1 in cancer cells could induce the migration of dendritic cells to draining lymph nodes in a partially activated state. This could trigger the development of tolerogenic T cells, which can inhibit the immune response against the tumour».

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