Press release
Immunity: here is the motor that moves the body's defences

Eps8 is called the key component of the motor that ensures that dendritic cells, a specialised patrol of the immune system, are activated in moments of danger and run to sound the alarm and activate the body's cellular defence teams. Without this protein dendritic cells, which monitor organs and tissues for viruses, bacteria parasites and also altered cells, including tumour cells, are still able to sense danger signals, but like amputees, they remain almost immobile and cannot effectively reach the command centres where they should sound the alarm. The disastrous result of their poor ability to move is failure to activate the immune response. The discovery, made by a team of researchers at the IFOM and the IEO in Milan directed by Giorgio Scita and Maria Rescigno, working in collaboration with the University of Milan, is published in the latest issue of the scientific journal *Immunity*.

Intercept the enemy, identify it and sound the alarm: this is essentially the role of dendritic cells, one of the most important **radar systems** that the **immune system** has at its disposal for developing strong and efficacious defences against possible insults that could compromise health from the outside or from within.

To achieve this they must travel through organs and tissues, to peripheral districts such as the skin or the intestine, where they register the danger signals, to the lymph nodes, veritable immunological command centres.

What is the motor that drives this machine, whose function is so vital for the body? It has long been known that the **basic component of the propulsion mechanism on which the migratory capacity of dendritic cells is based** is a protein that is fundamental for all types of cellular movement, **actin**.
Alone, however, **it is not sufficient** and the study conducted by **Giorgio Scita**, researcher at IFOM (Istituto FIRC di Oncologia Molecolare) and Associate Professor of General Pathology in the Department of Medicine, Surgery and Dentistry at the University of Milan, and by **Maria Rescigno**, researcher working at the IEO (Istituto Europeo di Oncologia Molecolare), now identify a **new component that is essential for the movement of dendritic cells.**
It is the Eps8 protein: its fine **tuning of the dynamic behaviour of actin** is indispensible for these cells to move and to travel to trigger the immune response.

«Once dendritic cells have identified their target – explains Maria Rescigno, an immunology expert who coordinates the research program entitled "Immunobiology of dendritic cells and immunotherapy" – they engulf it and then load some of its highly characteristic molecular features, its so-called antigens, onto their own surface. After having practically eaten the enemy – the scientist continues – dendritic cells undertake a tortuous journey through organs and tissues. They reach the lymph nodes and **present the antigen, in this way passing the information about the threat to other elements of the immune system.** In this way the T- and B-lymphocytes, real patrols specialised in counter-attacking, are instructed to recognise the enemy and activated so that the body can raise its defences against it.

Therefore, **movement is fundamental to defence** and acquiring the capacity to move through tissues represents a crucial step in dendritic cell maturation.
«**Movement** is a **key event in many normal and pathological cellular processes**, such as those that take place **during embryonic development** or **the dissemination of tumour metastases**» affirms Giorgio Scita, who has studied the molecular phenomena linked to cellular migration for many years and coordinates the IFOM research program entitled "Membrane and actin dynamics in the control of migratory and invasive strategies". «And it is certainly important – continues the Scientist – also **in the functioning of the immune system**. In particular, in performing the tasks assigned to the dendritic cells, which are practically obligated to move in order to trigger the immune response.

It was known that these cells have an extraordinary capacity to adapt in an extremely flexible manner to the various environmental conditions that they encounter during their journey to the lymph nodes. In fact, along the way they pass through microenvironments (defined by the various tissues in the body) that differ greatly in their chemical and physical characteristics, and degree of rigidity.
It was also known that this flexibility is based on the use of different migration strategies, but the characteristics of the motor that drives this machine and that, in the final analysis, permits the immune system to better monitor and defend the body, remained unclear.

«For this reason we have concentrated our research on cellular elements that can influence the basic components of this motor, actin – explains Scita – and in particular on Eps8, a protein that embraces the end of the chain formed by actin, regulating the functions».

In cells, **the blocks of actin assemble and disassemble** in an oriented way in a characteristic and fundamental structure, the **actin cytoskeleton.** Despite what the name suggests, this **structure is anything but static** and its **continuous remodelling** generates the **force that allows the cell to move:** it is because of this fact that **cellular protrusions can** form that, **analogous to arms, legs or tentacles, can** push against the three-dimensional matrix that serves as the substrate for the cells of the various organs and tissues; they cling to its fibres and permit the cell to drag itself with a motion reminiscent of crawling.

Also the dendritic cells move in this way on their way to the lymph nodes, after having received a danger signal. The researchers Emanuela Frittoli at IFOM and Gianluca Matteoli at the IEO, who together have done most of the experiments, have now provided greater molecular definition to this picture, demonstrating how, in order for all this to occur you need not only actin, but also Eps8.
Without Eps8 it is as if **the cell has "flaccid legs"**: they try to take a step but lose their support and become **incapable of moving effectively**. This is how the researchers saw them, nearly immobilised even though they were still able to present antigen, after they had disrupted the gene encoding Eps8 in the genome and performed **sophisticated 2- and 3-D cellular motility assays.**

Implications and prospective

This discovery, which sheds light on the **molecular mechanisms behind the behaviour of these cells and on their role in the immune system**, is very important from a variety of points of view.
It could contribute to **a better understanding of the body's response to infections** by bacteria or viruses and could have considerable **impact** also **in the study and treatment of tumours.**
In fact, immune mechanisms are among the control systems that the body normally activates to combat malignant transformation. However, **cancer cells** develop diverse **strategies to hide from the policing** performed by cells of the **immune system**. «In this context, it has emerged that some tumours escape immune surveillance by inhibiting, through a mechanism that is not yet clear, the very processes by which dendritic cells migrate» explains Scita.
The Scientist, who is currently involved in organising the International "Actin-based Motility" convention on Lake Maggiore this autumn where the most recent progress in the field of biological processes that control pathologies associated with defects of cellular motility will be addressed, concludes that: «Based on our results, it will be interesting to **evaluate how tumour development and aggressiveness are affected by different levels of Eps8 function in these cells** and, in the future, knowing the molecular determinants that allow dendritic cells to migrate could provide the background for targeted interventions to stop tumours or block the diffusion of metastases».

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