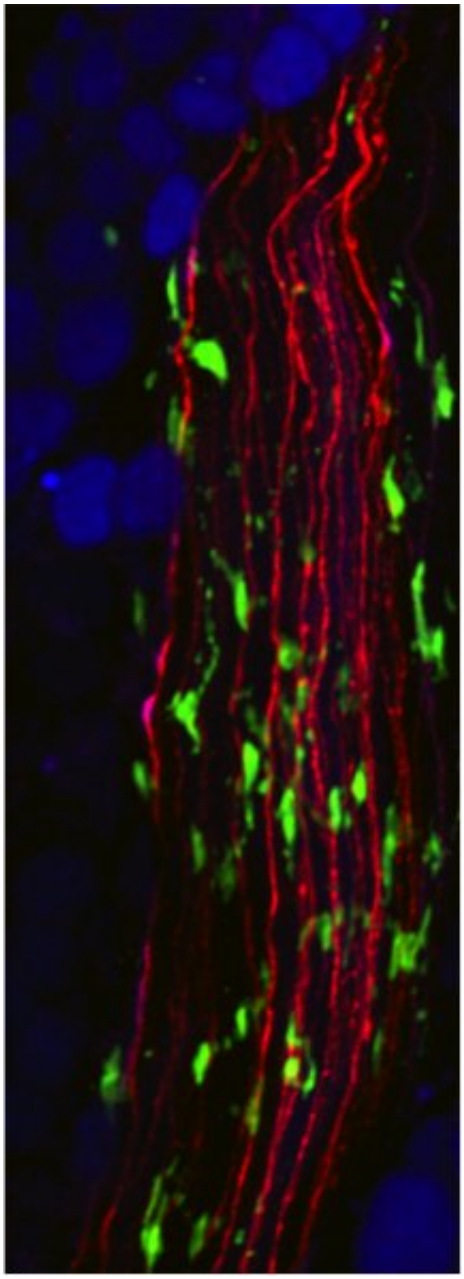
Novel immune cells control neurons responsible for fat breakdown

October 9 2017



Microscopic image of macrophages (green) associated with neurons (red) in the adipose tissue (blue). Credit: Roksana Pirzgalska, IGC

The biological causes underlying obesity have been under intense scrutiny, with studies suggesting a link between the nervous and the immune systems. Now, in a breakthrough study to be published in *Nature Medicine* on 9 October, a research team led by Ana Domingos, from Instituto Gulbenkian de Ciência (IGC; Portugal), discovered an unforeseen population of immune cells associated with neurons that play a direct role in obesity.

These immune cells are macrophages, a type of white blood cells responsible for inflammatory responses in the body. Previous studies had alluded to a role for macrophages in adipose tissue inflammation that occurs in obesity, but the mechanism of action linking these cells to neurons and fat breakdown was unclear. Now, Domingos' team showed that specialized macrophages are in direct contact with neurons and affect neuronal activation that is critical for fat mass reduction. The team had previously discovered that adipose tissue is innervated by a set of sympathetic neurons that release norepinephrine, a neurotransmitter that induces fat breakdown. Now, they show that these sympathetic neurons are in contact with a particular type of macrophage that they coined sympathetic neuron-associated macrophages (SAMs). The researchers found that SAMs clear out norepinephrine and that obese mice had many more of these cells attached to neurons than lean mice. This means that SAMs contribute to obesity by decreasing norepinephrine content in fat, thus preventing subsequent fat reduction.

By conducting genetic studies in mice, the research team was able to pinpoint the molecular mechanism underlying SAM-mediated destruction of norepinephrine. The import mechanism of this

neurotransmitter involves the transporter for norepinephrine (the protein Slc6a2) that is present in SAMs but not in other immune cells. Furthermore, they showed that blocking the import mechanism of norepinephrine by SAMs boosts fat breakdown, energy dissipation and weight loss. They further confirmed that SAMs and the associated molecular machinery for norepinephrine clearing also exist in humans, through analysis of human nervous system samples. "The role of norepinephrine transporter in SAMs offers a targeted approach that may overcome the noxious off-target effects of several known drugs that block this molecular target," says Ana Domingos. These results set the stage for the development of new anti-obesity therapies.

Obesity is a serious health condition that affects about 13 percent of the world's adult population, according to an estimate from 2014 of the World Health Organization.

More information: Sympathetic neuron-associated macrophages contribute to obesity by importing and metabolizing norepinephrine, *Nature Medicine* (2017). nature.com/articles/doi:10.1038/nm.4422

Provided by Instituto Gulbenkian de Ciencia