Heparan sulphate; inspiration for new leishmaniasis drugs

Leishmaniasis is a group of tropical parasitic diseases caused by infection with the protozoan parasite *Leishmania* and is endemic in 98 countries, with approximately 2 million new cases annually. Infection occurs when someone is bitten by an infected female sandfly. About 200 million people in Southern Europe, South and Central America, Asia and Africa live in areas where the disease is common. About 20 different strains of *Leishmania* parasites cause three main types of leishmaniasis: visceral (also known as kalar-azar) cutaneous and mucocutaneous. The latter two cause open sores on the skin and mucosal tissues, respectively, of infected people. The unsightly sores are not life threatening nor contagious, but stigmatism and prejudice from other people often leads to isolation of the infected individual, substantially impacting on their quality of life. In contrast, visceral leishmaniasis affects many different tissues of the body and can be fatal without treatment. With resistant strains emerging to the few drugs available, more detailed information about mechanisms of infection is required to fuel new approaches to therapeutics.

The role of carbohydrates in *Leishmania* infection remains relatively unexplored. To gain entry into the cells of an infected person, *Leishmania* parasites use a naturally occurring carbohydrate called heparan sulphate, which is found on the surface of mammalian cells. Inside the cell, the parasites escape destruction by the immune system and multiply in numbers. Understanding this process may provide information that is useful for the development of new drugs to combat disease.

Heparan sulphate is a carbohydrate chain made up of the sugars, N-acetylglucosamine and glucoronic acid. Specific enzymes link these sugars together to form an alternate repeating pattern. During construction, the carbohydrate chain is decorated with sulphur groups that produce a detailed 3-dimensional scaffold along with other modifications to produce a completed heparan sulphate chain. The modified structure is complimentary for the binding of different proteins and other molecules. Throughout their life cycle, heparan sulphate chains can undergo further changes. Some of the sulphates along the carbohydrate can be removed (by sulfatases) and the chain can be cut into smaller pieces (by heparanase-1). All these processes contribute to the ever-changing structure and binding properties of heparan sulphates. *Leishmania* proteins have been identified that bind heparan sulphates from different stages of the parasite’s development, suggesting that heparan sulphate has a close relationship with the parasite. However, the detailed structure of the heparan sulphate chains involved in this has not yet been uncovered. Studying heparan sulphate structures that interact with *Leishmania* parasites would enhance our understanding of the role they play in leishmaniasis and could fuel much needed new drug development for this class of neglected tropical diseases.

Marissa Maciej-Hulme
Radboudumc, Geert Grooteplein 10, Nijmegen 6525 GA, The Netherlands
School of Life Sciences, Keele University, Newcastle-under-Lyme, Staffordshire, United Kingdom

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Maciej-Hulme ML, Skidmore MA, Price HP
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