Local macrophage proliferation may play key role in atherosclerosis

Science

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By Will Boggs, MD

NEW YORK (Reuters Health) - Local macrophage proliferation appears to play a more important role than macrophage accumulation in the development of atherosclerosis, according to results in a murine model.

"Our studies were performed using murine models of atherosclerosis, powerful tools that allow us to gain novel mechanistic insight into how disease develops," Dr. Clinton S. Robbins from University of Toronto, Toronto, Ontario, Canada told Reuters Health.

"Importantly, we and others have also observed macrophage proliferation in human atherosclerotic plaques. The contribution of lesional macrophage proliferation to clinical disease, however, is not known."

Macrophages accumulate progressively in the expanding arterial wall during atherogenesis, but the mechanism of macrophage accumulation remains unclear.

Dr. Robbins and colleagues investigated the mechanism of accumulation of lesional macrophages in murine models of atherosclerosis.

In murine atherosclerotic lesions, macrophages turned over rapidly, after four weeks, and replenishment of these macrophages depended predominantly on local macrophage proliferation rather than monocyte influx.

"Moving forward, it will be important to evaluate the importance of local macrophage proliferation in human atherosclerosis and to determine how interfering with monocyte recruitment and macrophage proliferation at various stages of atherosclerosis affects plaque progression," the researchers concluded in an August 11 Nature Medicine online report.

"Our current work aims to address this important issue," Dr. Robbins said. "Specifically, we are investigating the prevalence of macrophage proliferation in human disease and

the relationship between macrophage proliferation and plaque vulnerability. Once we understand the role of macrophage proliferation in human atherosclerosis, we can explore possible approaches to target the process therapeutically."

"A long term goal of our work is to determine the efficacy of inhibiting macrophage proliferation in treating atherosclerotic disease," Dr. Robbins said. "In proof-of-concept studies, we have shown that treatment with the anti-proliferative agent 5-FU inhibits macrophage proliferation, decreases macrophage burden in plaques, and reduces atherosclerosis severity. A challenge going forward will be to identify anti-proliferative strategies that are well tolerated, possibly for long periods of time."

Dr. Charles D. Mills from BioMedical Consultants, Marine, Minnesota has published work on macrophages and disease. He told Reuters Health, "There are two basic types of macrophages, M1 (killer) and M2 (repair). I discovered and named these two types of macrophages, which do opposite things. I was somewhat surprised that the authors didn't briefly cover M1/M2, because it appears that atherosclerosis is mainly caused by M1 attacking the vessels. And, these are end cells, not the type that would be proliferating (because they're making nitric oxide that is toxic to macrophages also)."

As for this study, Dr. Mills said, "It is important to determine if the labeling, etc., allows one to determine how much of macrophage accumulation can be directly attributed to local proliferation. If it's 1%, who cares. If it's greater than about 25%, then it would be much more important to the atherosclerotic process. I'm not sure BuDr labeling and the other techniques they use allow one to quantitate."

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