# Lympho-Accumulation Found to Drive Early MF

BY BETSY BATES

LAS VEGAS — Early-stage mycosis fungoides appears to be a lympho-accumulative disorder, driven by defects in apoptosis mechanisms designed to regulate T-cell populations in the skin, according to Dr. Gary Wood.

Cell cycle defects that lead to the classic "unchecked growth" that characterizes lymphoproliferative diseases do occur in mycosis fungoides, but likely not until its later stages, Dr. Wood, who is chairman of dermatology at the University of Wisconsin, Madison, said during a dermatology seminar that was sponsored by Skin Disease Education Foundation.

In the beginning, mycosis fungoides demonstrate a low rate of apoptosis, with "cells not growing particularly quickly, but also not dying—like guests that you invite that don't go home," he commented.

Many additional clues point to early mycosis fungoides as a lympho-accumulative, rather than a lympho-proliferative, disorder, he said, including:

▶ An indolent clinical course.

▶ Development of patches, not tumor masses.

▶ Low proliferative rate and mitotic counts.

▶ Relative resistance to chemotherapy, because mycosis fungoides cells are "quite similar to normal T cells. Anything that will kill them will kill the rest of the patient."

▶ Poor growth in vitro.

Research of late has buoyed the theory of lympho-accumulation.

One or more death receptor defects have been identified in the majority of patients with cutaneous T-cell lymphoma, including defects in FAS; TNFR (R1, R2, or the antiapoptotic TRAF1 receptor); or TRAIL (DR4, DR5, DcR1, or DcR2).

Dr. Wood's team and others have found further defects in the death receptor antagonist cFLIP, which is a key player in the death receptor pathway, he noted.

He and his colleagues found low FAS expression in 30 of the 31 patients with cutaneous T-cell lymphoma and in 5 of the 6 patients with large plaque parapsoriasis, a precursor of mycosis fungoides or Sézary syndrome (J. Invest. Dermatol. 2008 Oct. 16 [Epub doi:10.1038/jid.2008.309]).

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No such abnormality was seen in the 15 patients with chronic dermatoses, he noted at the meeting.

A more targeted look identified four cutaneous T-cell lymphoma cell lines (MyLa, HH, SZ4, and SeAx) in which resistance to apoptosis correlated with levels of FAS transcripts and proteins.

Taking it one step further, Dr. Woods and his associates found that, when they triggered FAS upregulation by transfecting genes with a wild-type FAS construct, apoptosis was restored, including spontaneous FAS pathway apoptosis, in which FAS ligands, in essence, self-destruct.

"You can see a big uptake in the amount of killing," he pointed out, demonstrating the effect in each of the four tested cell lines using real time polymerase chain reaction (RT/PCR) technology.

While Dr. Wood's team has focused on FAS transfection to prime FAS and cutaneous T-cell lymphoma cells to self-destruct or to become targets of tumor-infiltrating lymphocytes, there are other ways to upregulate FAS as well.

These include interleukin-2 and bryostatin; interferon-α and -γ; and even epigallocatechin gallate (EGCG), which is the polyphenol antioxidant in green tea, he said.

"In the future, these may be useful therapeutic targets," Dr. Wood said.

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