Lymphangioliomyomatosis

To the Editors:

We read with great interest the systematic review by JOHNSON [1], regarding lymphangioliomyomatosis (LAM), which concluded that the key to the development of new treatment strategies is the understanding of the cell-type of origin and the signalling methods used to target LAM cells.

Tuberous sclerosis complex-related tumours, such as LAM, exhibit uncontrolled activation of the protein mammalian target of rapamycin (mTOR). Much hope lies in the clinical use of rapamycin as a regulator of the mTOR. Indeed, recent data in animal models and *in vivo* primary cultures of human LAM cells indicate that rapamycin does prevent cell proliferation [2–4]. However, its effect on LAM cell migration is minor [3]. More specifically, LAM cell migration, which correlates with disease severity, is regulated by the TSC2 gene product, tuberlin, through the activation of RhoA GTPase activity [3]. This implies that a combination of rapamycin and a RhoA modulator should be used in order to restrict the disease progression. Additionally, rapamycin was not found to be effective when administered before the onset of the disease, and evidence of drug resistance was found after prolonged therapy in a mouse model [4]. This also implies that rapamycin may not be the panacea for LAM, given the fact that alternative therapies have to be found.

Furthermore, the oestrogen receptors are expressed aberrantly in the lungs of LAM patients [5]. A hypothesis regarding the reason for the finding that hormonal therapy with tamoxifen or progesterone appears to have mixed success is the fact that both drugs, especially tamoxifen, act as oestrogen agonists [6]. Moreover, tamoxifen-resistant LAM cells may occur. mTOR is activated as a result of growth factor signalling through phosphatidylinositol 3-kinase and the protein kinase AKT. In breast cancer cells with aberrant AKT activity, inhibition of mTOR by rapamycin restores tamoxifen response [7]. In human ovarian and breast cancer cells, combined treatment with mTOR inhibitor and tamoxifen *in vitro* exerts additive antitumoural effects [8]. According to the above, a combination of rapamycin and tamoxifen should enhance the results of the treatment. Additionally, in *in vitro* models of breast cancer, dual inhibition of mTOR and oestrogen receptor signalling was found to induce cell death [9].

Another issue, not as significant as the above but still important, is the fact that hormonal therapy may be implicated in the occurrence of chylothorax, since it has been speculated that steroids may increase fluid accumulation and prevent the transport of fluid out of the pleural space [10].

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