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Sylviane Muller
University of Strasbourg, France

Autophagy pathway as a target of therapeutic P140 peptide used in lupus

P140 is a 21-mer peptide (sequence 131-151, phosphorylated at position 140) that is derived from the spliceosomal protein U1-70K. In a multicenter, randomized, placebo-controlled phase IIb study, P140/Lupuzor™ had no adverse safety signals and met its primary efficacy end points in lupus patients. These results confirm data generated in MRL/lpr lupus-prone mice in which the preclinical studies were performed. We found previously that P140 reduces autophagic flux in MRL/lpr B cells and that macroautophagy (the best characterized type of autophagy) is abnormally enhanced in T-lymphocytes from lupus mice and patients. More recently, we discovered that in MRL/lpr mice, P140 more precisely targets a selective form of autophagy, called chaperone-mediated autophagy. We deciphered the successive steps of P140 action leading in fine to a decay of endogenous antigen processing and loading to MHCII molecules and as a consequence, to a lower activation of auto-reactive T cells. Here, the mechanism of action of P140 was further studied in the peripheral cells from normal and lupus individuals. As in MRL/lpr mice, P140 enters human B cells via a clathrin-dependent endo-lysosomal pathway and induces a decrease of MHCII cell surface expression. It affected autophagy processes in human B cells but did not induce apoptosis of B cells from healthy or lupus patients. These findings and others provide strong arguments to conclude that the mechanism of action of P140 peptide is similar in MRL/lpr mice and lupus patients. These results shed light on mechanisms by which P140/Lupuzor modulates lupus disease in humans affected by this disorder.

Biography

Sylviane Muller has received her Doctoral degrees in Molecular Biology (1978) and Science (1984) from the University of Strasbourg, France. She has worked as a Post-doctoral Fellow at the Max-Planck Institute for Immunobiology in Freiburg, Germany. She is currently a Distinguished class Research Director at the CNRS and Professor at the Institute of Advanced Studies of the Strasbourg University (Chair Therapeutic Immunology). She is a Deputy Director of the Molecular and Cellular Biology Institute, Director of the CNRS Unit Immunopathology and Therapeutic Chemistry and Head of the Drug Discovery Center for Cancer and Inflammation. Medal is awarded 'Laboratory of Excellence'. Her research interests focus on molecular and cellular events involved in autoimmunity, especially in the lupus disease. She has discovered the P140/Lupuzor peptide that is currently evaluated in a phase III clinical trial for lupus. She is the co-author of over 345 publications, Co-Inventor of ~30 patents and Co-Founder of NeoMPS (1986) and ImmuPharma (2002) companies. She has received the CNRS Silver Medal (2009) and the CNRS Innovation Award (2015). Her research interests include molecular and cellular events involved in autoimmunity, especially in the lupus disease.

S.Muller@ibmc-cnrs.unistra.fr