Impact of Toll-like Receptor 4 (TLR4) chemical modulation by small-molecular antagonists in rare inflammatory-fibrotic diseases

Alice Italia [a], Ana Rita Franco[a], Mohamed Monsoor Shaik [a], Alessio Romerio[a], Sara Lovisa [b], Francesco Peri [a], Barbara Costa[a]

[a] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Piazza della Scienza (MI); [b] BLDG E, Humanitas University Campus, Pieve Emanuele (MI)

We present here preliminary data on a study on the possible impact of chemical modulation of TLR4 activity on fibrosis progression. Our labs developed several synthetic molecules that showed biological activity in inhibiting TRL4 activation by LPS in a dose-dependent way in both human and murine cells. Our in vitro experiments with purified receptors suggested that the antagonistic action is due to the interaction of these compounds with MD-2 and CD14 co-receptors (1).

Fibrosis is an outcome of the repair response to tissue damage caused by inflammation. When the fibrotic process is excessive or dysregulated it leads to a pathological condition that can affect different organs and functions. Here, is now clear that inflammation, which however is not the only trigger, plays a key role in the critical cellular process of fibroblasts activation that leads to fibrosis upset (2).

The recent discovery of a complex crosstalk between fibrosis progression and inflammatory pathways suggests the central role of TRL4 and its potential as new drug target(3). Here we report an in vitro screening on cellular models of fibrosis of a variety of synthetic TLR4 antagonists to identify new potential drugs targeting fibrotic diseases.

Thus, the aim is to identify new or old compounds acting on TR4 to block or prevent the fibrosis development. Principal target disses are Idiopathic Pulmonary Fibrosis (IPF) and Morphea which are rare fibrotic pathologies where a pivotal role of TLR4-mediated inflammation has been observed (4) (5).

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