P008 Interactions of taxoids with human MD-2

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Endotoxin receptor TLR4 senses the presence of LPS through binding to the TLR4-accessory protein MD-2. Murine but not human macrophages are in addition to LPS activated also by an antitumor agent taxol, which activates them through the MD-2/TLR4 complex, binding to the same site as LPS.
We show that taxol and taxotere, a less hydrophobic analogue of taxol, bind to the human MD-2, similar as to the murine MD-2. Binding site of taxol on human MD-2 overlaps with the binding site of LPS, which results in the ability of taxol to inhibit the LPS signaling on cell line expressing human MD-2. Taxotere is able to bind to both human and murine MD-2, does not cause activation of either, but inhibits the LPS signaling. Near UV circular dichroism spectra display differences in the chemical environment of both taxoids in the presence of human MD-2, while the secondary structure of MD-2 does not change appreciably upon binding. Molecular docking calculations of taxoid binding to MD-2 suggest the orientation of bound compounds in the hydrophobic binding pocket of MD-2. Understanding of the effect of structural differences between different taxoids will contribute to the understanding of signal transduction activation process and identification of the structural differences of MD-2 between different species.