INFECTIOUS DISEASES (BACTERIAL, FUNGAL, VIRAL, PARASITIC, INFESTATIONS)

SIRT3-INDUCED MACROPHAGE POLARIZATION THROUGH AUTOPHAGY IN PROMOTING MYCOBACTERIUM LEPRAE LATENT INFECTION

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Background: The formation of Mycobacterial granuloma is a typical process of antagonism between the pathogen and the host, and M2 macrophages differentiation is closely related to this course. Sirt3 is a type III protein deacetylase that shuttles between the cytoplasm and the mitochondria.

Objective: We intend to analyze the differentiation characteristics of sirt3-deficient macrophages in Mycobacterial granuloma formations.

Materials and Methods: Sirt3+/- or Sirt3-/- mouse bone marrow cells were cultured in MG-CSF (5 ng/ml) for 5 days to become M0 macrophage. IFN-γ (5 ng/ml) or IL-4 (5 ng/ml) stimulated at the corresponding time points. Western Blot detects LC-3 and p62 expression. LC-3 antibody labels LC-3 protein (green) and lysotracker labeled lysosomes (red) were also applied in fluorescence confocal microscopy to detect autophagic flow.

Results: The autophagy level of M1 macrophages was high with activated LC-3 and degraded of autophagic flow protein p62, while the expression of LC-3 in M2 macrophages was weak and degradation of p62 was rare. M0-type macrophages have LC-3 and p62 levels intermediate to M1/M2. M1 macrophages had high levels of autophagy and LC-3 formed more small-vesicle structure; LC-3 expression in M2 macrophages was weaker, with fewer vesicles. Sirt3 deficiency was found to cause a significant reduc5on of M2 macrophages. Macrophages with Sirt3 deficiency showed enhanced LC3 protein expression and vesicle structure. Sirt3 defect also contributed to autophagy enhancement and induction of M1 macrophages. The analysis of clinical leprosy samples showed that Sirt3 expression was gradually up regulated in the pathogenesis of M. leprae infection.

Conclusions: Our data demonstrate that Sirt3 can inhibit the differentiation and function of M1 and promote that of M2 during macrophage differentiation. It is suggested that Sirt3 induced changing of autophagy level plays an important role in the process of macrophage differentiation.