Backgound: Interleukin (IL)-12 induced T helper (Th) 1 polarization is critical for adequate cell-mediated immune responses against intracellular pathogens such as M. tuberculosis. To gain insights into Th1 type immunity I performed a genome wide analysis for IL-12 target genes. The results unequivocally identified proprotein convertases (PC) furin as a novel IL-12/Stat4 target gene. Furin has been previously linked to the pathogenesis of several diseases including metastatic cancers, cystic fibrosis and infectious diseases. Consequently, furin inhibitors have been proposed as possible therapies for such diseases. I have explored furin's physiological role in T cells using a T cell-specific furin knockout. The striking finding is that conditional deletion of furin in T cells results in loss of peripheral tolerance and systemic autoimmune disease. Objective: To evaluate the role of furin and as a regulator of immune responses; specific aims: 1. Furin's molecular mechanisms of action in T cells, 2. The role for furin in diseases of broken peripheral tolerance, 3. Furin as a regulator of innate immunity. Significance: Studying furin in T cells will help to explain the pathogenesis impaired peripheral tolerance observed in diseases like IBD and celiac disease, and understand the regulation of Th1 type immune responses that are critical in combating intracellular pathogens, such as M. tuberculosis. On the other hand, furin plays also an important role in the activation of pathogens (e.g. HIVgp160, B. Anthracii toxins) and upregulates metastatic activity of cancers and pathogenesis of cystic fibrosis. This research will tackle the cell-type specific function and regulation of proprotease convertase activity by identifying novel furin targets and regulators of its activity. This will
enable creating more specific, cell-type specific means for furin regulation; this will be instrumental in avoiding unwarranted side effects of general furin inhibitors in clinic.

Field of Science

/medical and health sciences/health sciences/infectious diseases

/medical and health sciences/clinical medicine/pneumology/tuberculosis

/natural sciences/biological sciences/genetics and heredity/genome

/medical and health sciences/clinical medicine/oncology/cancer

Programme(s)

FP7-PEOPLE - Specific programme "People" implementing the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007 to 2013)

Topic(s)

PEOPLE-2007-4-3.IRG - Marie Curie Action: "International Reintegration Grants"

Call for proposal

FP7-PEOPLE-IRG-2008

See other projects for this call

Funding Scheme

MC-IRG - International Re-integration Grants (IRG)

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