ANALYSIS OF REGENERATIVE POTENTIAL AND HOMEOSTASIS IN CACHECTIC MUSCLES: THE EFFECTS OF PHYSICAL ACTIVITY

Emanuele Berardi, Paola Aulino, Veronica Cardillo, Mario Molinaro, Sergio Adamo and Dario Coletti

Dept. Histology and Medical Embryology, Sapienza University of Rome and Interuniversity Institute of Myology

Cachexia, a muscle wasting syndrome associated to many chronic diseases, is a bad prognostic factor, interferes with therapy and worsens quality of life. With the aim to investigate the mechanisms underlying the loss of muscle homeostasis and to test countermeasures against cachexia, we investigated the effects of physical activity on mice bearing a colon carcinoma (C26). We find that while muscle of C26-bearing mice show increased muscle fiber damage, wheel running does not exacerbate damage in the majority of the muscles. Exercise has beneficial effects in cachectic mice including rescued muscle homeostasis and increased life span. Satellite cells activation in cachexia fails to maintain muscle homeostasis, possibly due to disregulation of Pax7 expression, rescued to control level by exercise. In addition, cytokines hamper muscle regeneration by activating non apoptotic caspase pathways in a population of PW1 Interstitial Cells (PICs), a phenomenon which ultimately results in loss of myogenic potential. PICs express the stem cell markers Sca-1, CD34 and PW1, can be rescued to myofiber formation by gene delivery (dominant negative form of PW1 or Hsp70 overexpression), pharmacological (caspase inhibitors) or hormonal (i.m. injection of the myogenic factor Arg^8-Vasopressin) approaches: these are all aimed at reducing caspase activation, highlighting caspase role in myogenic differentiation. Exercise increases the circulating levels of Vasopressin, suggesting it as a possible mediator of the beneficial effects of exercise on cachexia. All together our data highlight the importance of physical activity for an integrated approach aimed against cancer cachexia.