Al collegio docenti del Dottorato in Medicina Molecolare

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Ciclo XXXVI° Tutor: Prof.ssa Antonella Naldini

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Introduction

Dendritic cells (DCs) are the most potent antigen presenting cells and they are required to adapt to low oxygen tensions, through the activation of several mechanisms including autophagy, since they patrol hypoxic microenvironments, such as the tumour microenvironment (TME). Malignant melanoma cells are characterized by migratory and invasive capabilities, in which Carbonic Anhydrases are strictly involved, and by an aberrant reactivation of the embryonic developmental pathways, e.g. Hedgehog (Hh) pathway.

Methods

Human monocyte-derived DCs were isolated from buffy coats, treated with pharmacological autophagy inhibitors and siRNAs targeting SQSTM1/p62 and exposed to normoxia (20% O2) or hypoxia (2% O2); DC viability was assessed by JC-1 assay; autophagic flux was evaluated by Lysotracker confocal analysis and autophagic marker expression (Western Blot); glycolytic enzymes and inflammatory cytokines expression was assessed by qRT-PCR.
Melanoma Cell lines (SK-MEL-28 and A375) were treated with siRNAs targeting Hh pathway transducers and CAXII, exposed to 20% and 2% O2, and Wound healing assay, Zymography, modified boyden chamber, Western Blot and qRT-PCR were performed.

Results

Our results showed that hypoxia-induced autophagy in DCs is mediated by PI3Ks. Furthermore, the inhibition of the autophagic mediator/adaptor SQSTM1/p62, with either pharmacological inhibitor or siRNA, resulted in the impairment of glycolytic, survival and inflammatory pathways. Moreover, we demonstrated that CAXII and the Hh pathway are relevant in melanoma migration and invasion.

Publications (Full papers)

Monaci, S., Coppola, F., Rossi, D., Giuntini, G., Filippi, I., Marotta, G., Sozzani, S., Carraro, F. and Naldini, A. (2022). Hypoxia Induces Autophagy in Human Dendritic Cells: Involvement of Class III PI3K/Vps34. Cells, 11(10), 1695. I.F. 7,66.
Giuntini, G.; Coppola, F.; Falsini, A.; Filippi, I.; Monaci, S.; Naldini, A.; Carraro, F. Role of the Hedgehog Pathway and CAXII in Controlling Melanoma Cell Migration and Invasion in Hypoxia. Cancers 2022, 14, 4776. https://doi.org/10.3390/cancers14194776 I.F. 6,57

Conferences

Coppola F., Monaci S., Rossi D., Giuntini G., Filippi I., Marotta G., Sozzani S., Carraro F. and Naldini A. Hypoxia induces autophagy in human monocyte-derived dendritic cells: involvement of Class III PI3K/VPS34. SIICA 2022, XIII national congress, Naples, 23/05-26/05 2022.
Coppola F., Monaci S., Falsini A., Aldinucci C., Rossi D., Filippi I., Sozzani S., Carraro F. and Naldini A. Hypoxia triggers autophagy in human monocyte-derived dendritic cells. HypoxEu live 2022, Dublin, 11/09-14/09 2022.
Falsini A., Giuntini G., Coppola F., Monaci S., Aldinucci C., Naldini A. and Carraro F. Inhibition of CAXII impaired melanoma cell migration and invasion under hypoxia. HypoxEu live 2022, Dublin, 11/09-14/09 2022.

Seminars Attended

15/12/21: Precision Oncology in breast cancer: from biology to clinical application. Cro Aviano.
09/12/21: Second HypoxEU meeting: An international forum on oxygenation and biology. HypoxEU.
27/01/22: Chromatin Immunoprecipitation (ChIP) Workshop, Proteintech.
07/02/22 (15.00 – 17.15); 14/02/22(10.00 – 12.15); 21/02/22 (10.00 – 12.15):3Days for 3Rs,IPAM.

24/02/22: ELISA Workshop; Proteintech.
15/03/22: Third HypoxEu meeting: An international forum on oxygenation and biology. HypoxEU
29/03/22: The consequences of Sex Bias in Preclinical Research, Charles River.