

The interplay of oxygen, diet and microbiota in inflammation and cancer: lessons from fruit flies

S-04.5-2

C. Pitsouli¹

¹University of Cyprus, Nicosia, Cyprus

Diet and microbiota impinge on inflammatory disease and cancer, and oxygen availability plays a key role in angiogenesis and tumorigenesis. To uncover the basic mechanisms contributing to inflammation and cancer in vivo, we are using the fruit fly, *Drosophila melanogaster*, as a powerful genetic model. Focusing on the adult fly intestine, which is structurally, molecularly and cellularly similar with the human gut, we have addressed the role of oxygenation, diet and microbiota in intestinal homeostasis, infection-induced inflammation and tumorigenesis. We have shown that the fly gut is oxygenated by a complex vascular network, the tracheae, which expands extensively upon infection-induced inflammation and in tumors. This neoangiogenesis-like phenotype depends on the conserved FGFR/FGF/Hif-1 α pathway and promotes inflammation and cancer. In addition, oxygen is necessary for intestinal stem cell (ISC) mitosis during regeneration and tumor growth, and neither can proceed in hypoxic conditions (*Published in: Tamamouna V et al. (2021) Nature Cell Biology 23(5): 497-510*). Furthermore, we have shown that ISCs depend on the absorption of the essential vitamin B7 (or biotin), and the recycling of cholesterol: when these nutrients are not available, ISC mitosis is abolished and cancer is reduced. Interestingly, we have found that silencing of the biotin internalization receptor Smvt or the cholesterol recycling receptor Npc2c causes microbial dysbiosis. This altered microbiota composition impinges on dietary nutrient availability and affects animal physiology (*Published in: Neophytou C & Pitsouli C (2022) Cell Reports 38(10): 110505; Neophytou C et al. (2023) Metabolites 13(10) 1084*). In conclusion, we have shown that oxygen, biotin, cholesterol, and microbiota control ISC regeneration and cancer in flies. Expanding these studies in mammals may lead to the development of chemicals targeting intestinal disease and cancer.