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Sommario/riassunto

"If one asks a cancer scientist a seemingly naive question such as what are the hallmarks of cancer cells, he-she will probably cite at first somatic mutations and genomic rearrangement, leading to excessive proliferation, resistance to apoptosis, and dissemination potential (Hanahan and Weinberg, 2011). Intriguingly, all of these hallmarks are physiological properties of B- and T-lymphocytes, selected by evolution because they ensure an efficient immune response against pathogens. So, it is a fascinating paradox to observe that lymphoma remains a relatively rare cancer as compared to epithelial cancers. Hence, understanding the tumor suppressor mechanisms that mitigate lymphomagenesis or eradicate lymphoma cells at preclinical stages appears an extraordinary challenge. After a short overview of the current models used to analyze lymphomagenesis, we will highlight that the frontier between reactive lymphoproliferation and overt lymphoma is not always clear. Then, we will present how the classification of lymphomas based on the concept of cell of origin might reveal important phenotypical properties of lymphoma subtypes. Finally, we propose an overview of the main hallmarks of lymphomas and discuss their contribution in the most frequent subtypes of lymphomas. How to study lymphomagenesis As in other scientific fields, the nature of our knowledge of lymphomagenesis is tightly linked to the tools used to produce this knowledge. Hence, it seems interesting to start this review with a methodological perspective, providing a brief overview of the different scientific approaches which have brought major contributions to our understanding of lymphomagenesis. Epidemiology was the first approach which shed light on the mechanisms of lymphomagenesis, by deriving statistical correlations from direct observation of cohorts of patients. First, epidemiology has established the link between lymphoma incidence and aging. The incidence of most lymphomas follows an exponential growth after the fifth decade as observed for most cancers, suggesting that common processes are shared with solid tumors (Sarkozy et al., 2015; Rozhok and DeGregori, 2016). In the case of Hodgkin lymphomas, the bimodal distribution of incidence suggests that specific mechanisms are occurring in young patients, which have not been fully elucidated to date. Second, epidemiology has also proven a counter-intuitive association of lymphomas with immunosuppression, either inherited (common variable immunodepression for example) or acquired after HIV infection, or immunosuppressive drugs (van Leeuwen et al., 2009; Kaplan, 2012). This association revealed the role of the immune system in repressing the growth of transformed lymphocytes, either by active eradication of tumor cells or by exerting a competition for resources . Third, the analysis of the geographic distribution of lymphoma subtypes also shows striking differences,

such as the higher incidence of T-cell lymphoma in Asia as compared to Western countries (Perry et al., 2016). These differences suggest two non-mutually exclusive hypotheses, related to environmental or genetic differences. The fourth major insight from epidemiological studies was to shed light on the role of pathogens such as Helicobacter pylori, HCV, EBV or HTLV1 in specific subtypes of lymphoma (Lecuit et al., 2004; Suarez et al., 2006; Couronne et al., 2018), which has been then confirmed experimentally. Besides pathogens, epidemiological studies have also demonstrated the role of environmental exposures such as herbicides in lymphomagenesis, which might have important consequences for health policies (Weisenburger, 2021). More recently, molecular epidemiology based on genome wide association studies have demonstrated the association of host genetic polymorphisms with the risk of specific lymphoma subtypes (Cerhan et al., 2014), highlighting unsuspected pathways which can then be experimentally explored"--