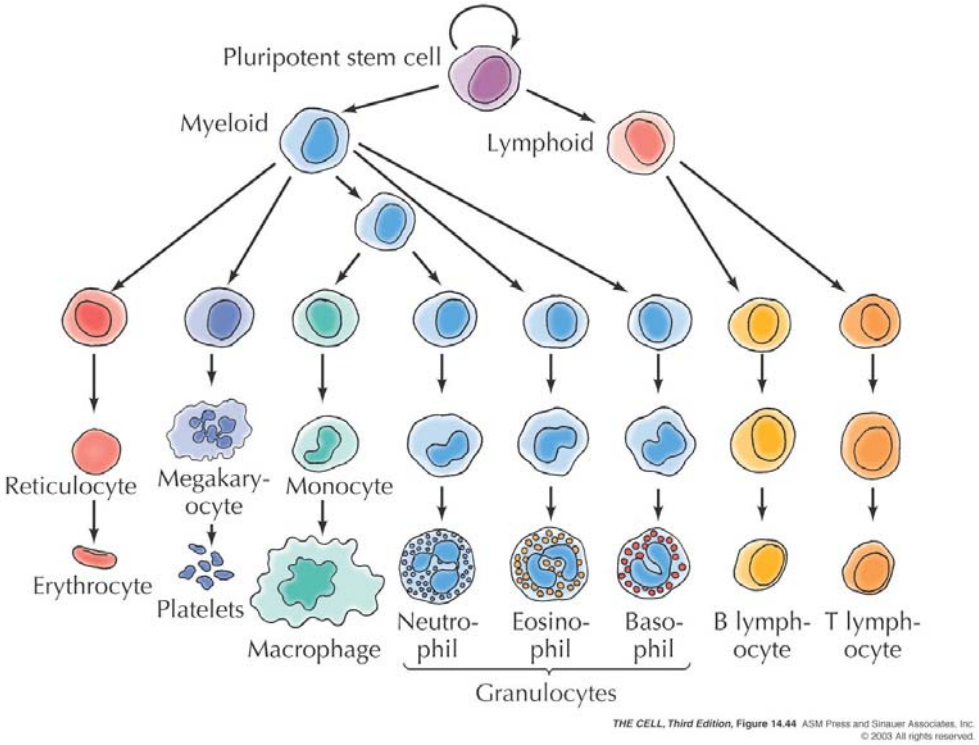
Parte III: Manipulação da informação

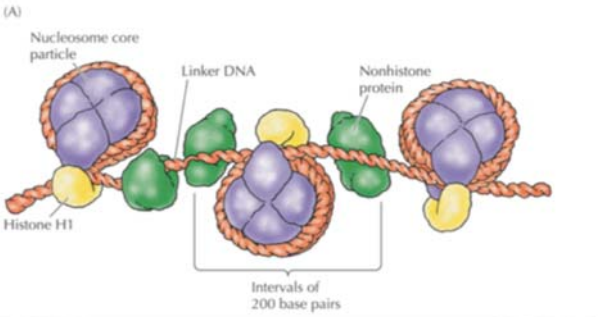
"Transcritómica"

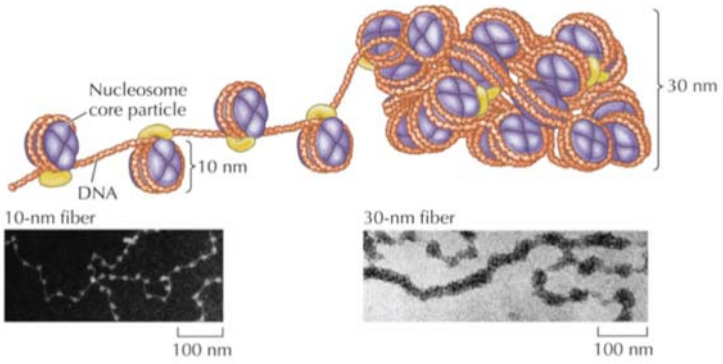
A diferenciação celular assenta em processos irreversíveis de modificação da expressão génica



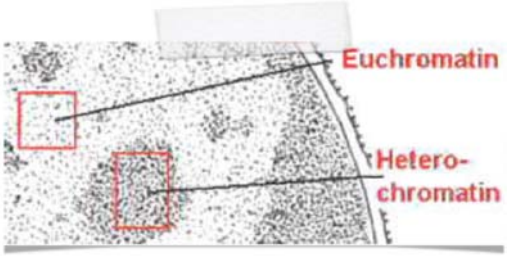
THE CELL, Third Edition, Figure 14.44 ASM Press and Sinauer Associates, Inc.

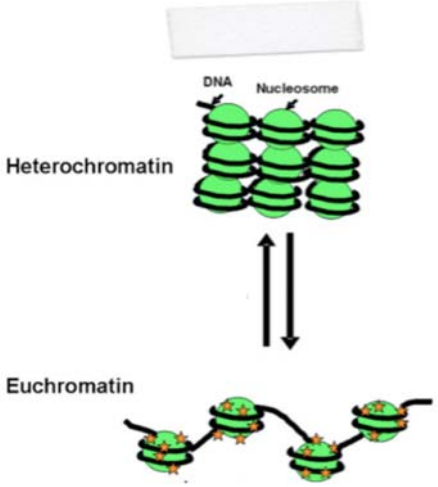
O DNA nas células: nucleossomas e cromatina

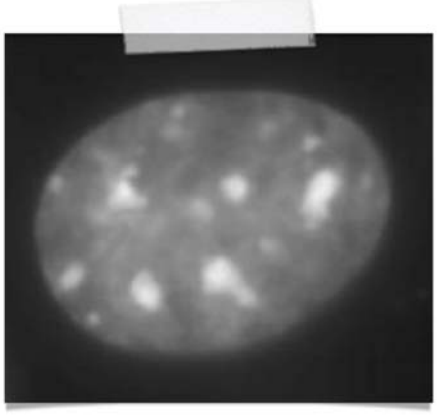




Heterocromatina e eucromatina

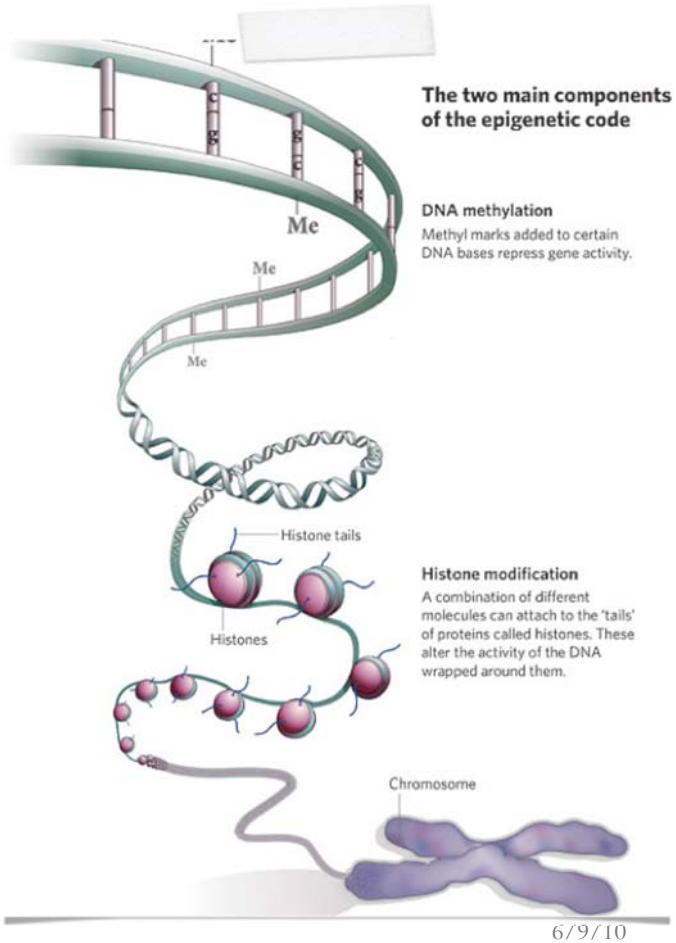




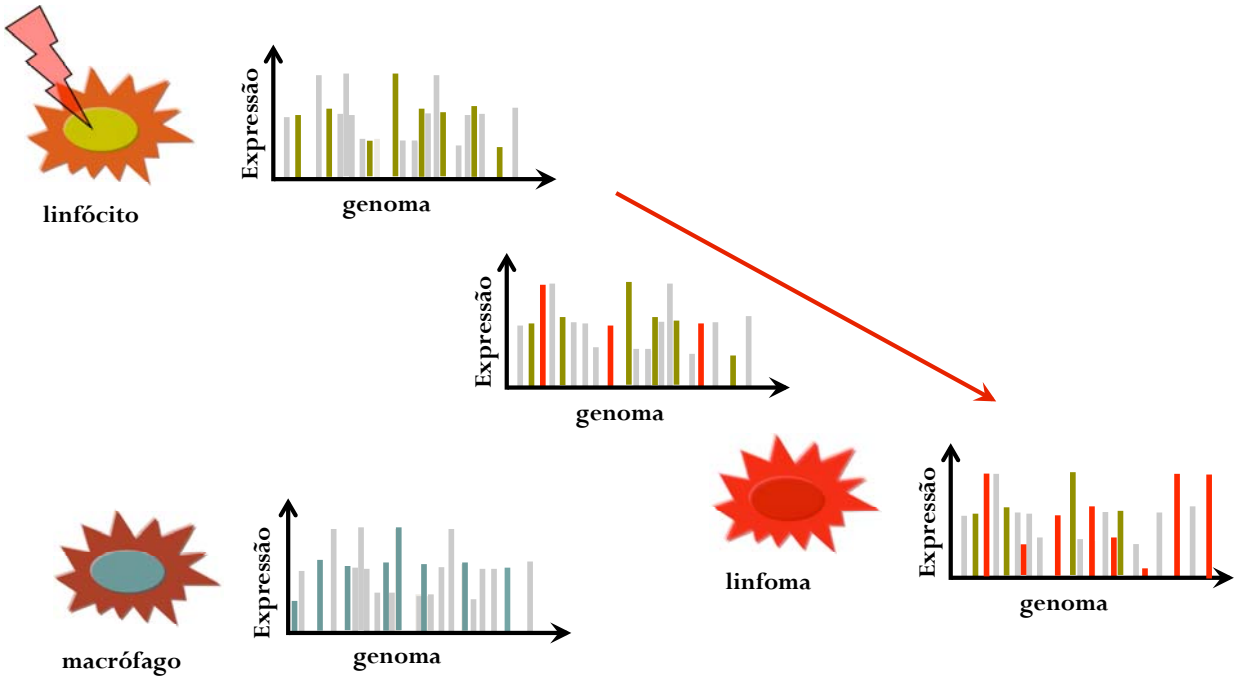


Modificações epigenéticas e condensação da cromatina

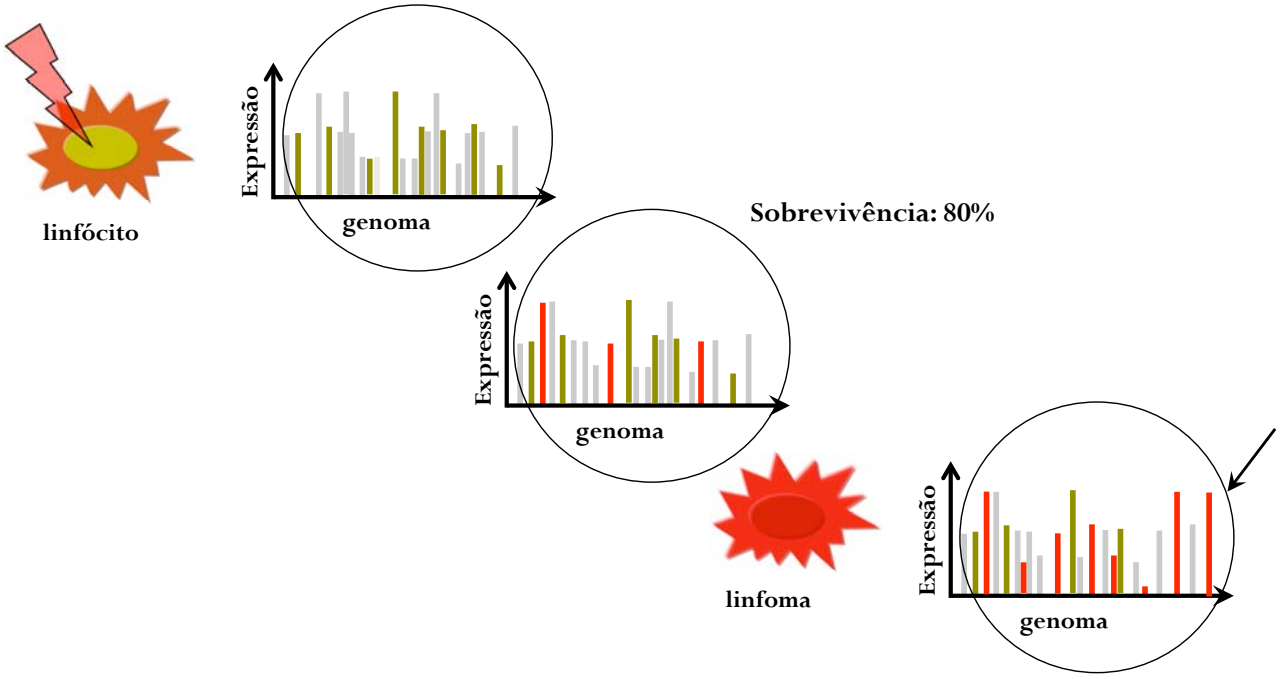
- Metilação do DNA
- Modificação das histonas



O estado patológico como uma perturbação do perfil de expressão génica normal

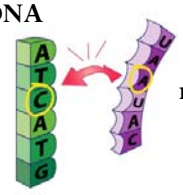


Tecnologia dos microarrays: análise sistemática dos perfis de expressão génica

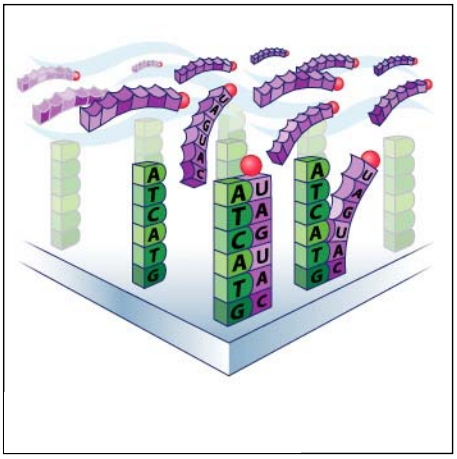


Microarrays de DNA: princípios técnicos

Sonda de DNA

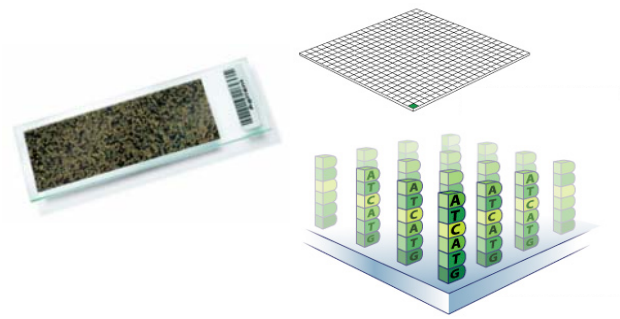


mRNA



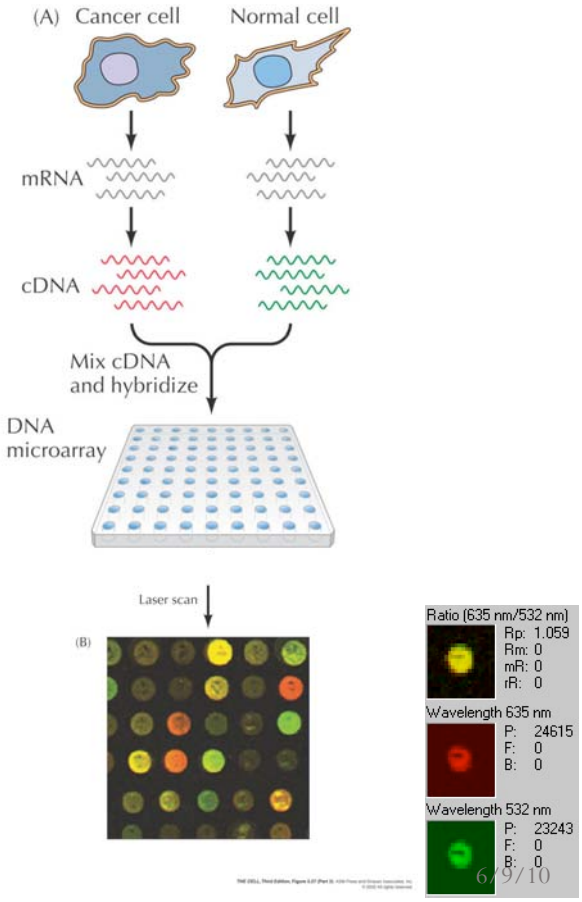
Hibridação da matriz com a amostra e detecção quantitativa das posições que adquirem fluorescência

O *microarray*: matriz de sondas de DNA



> Perfil de expressão génica do tecido

cDNA microarray

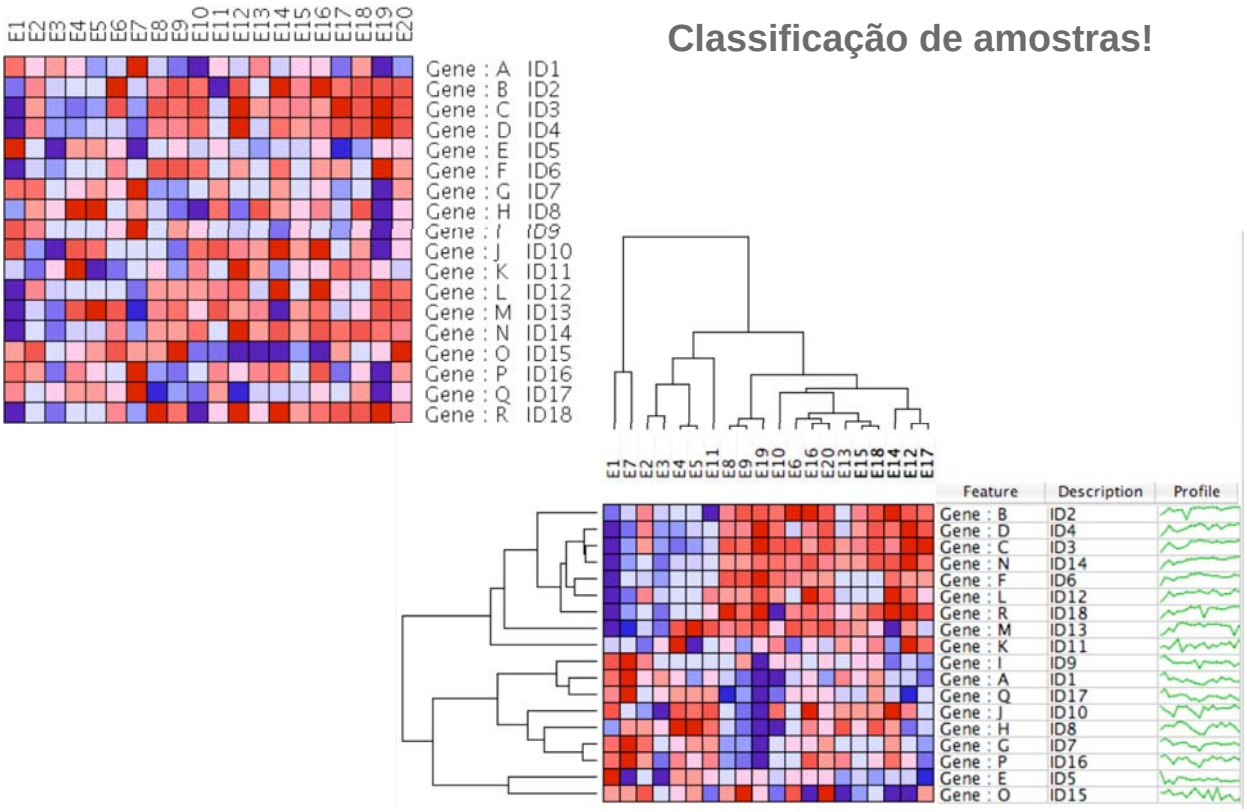


Uma lista de genes...

Gene	Amostra 1	Amostra 2	Amostra 3	Amostra 4	Amostra 5	Amostra 6
A	1506	950	89	0	847	902
B	4537	1242	345	1245	342	121
C	853	674	4342	5746	45373	5722
D	21465	25245	4577	22356	2536	5383

...

Classificação de amostras!



articles

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

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[*] These authors contributed equally to this work

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma, is clinically heterogeneous: 40% of patients respond well to current therapy and have prolonged survival, whereas the remainder succumb to the disease. We proposed that this variability in natural history reflects unrecognized molecular heterogeneity in the tumours. Using DNA microarrays, we have conducted a systematic characterization of gene expression in B-cell malignancies. Here we show that there is diversity in gene expression among the tumours of DLBCL patients, apparently reflecting the variation in tumour proliferation rate, host response and differentiation state of the tumour. We identified two molecularly distinct forms of DLBCL which had gene expression patterns indicative of different stages of B-cell differentiation. One type expressed genes characteristic of germinal centre B cells ('germinal centre B-like DLBCL'); the second type expressed genes normally induced during *in vitro* activation of peripheral blood B cells ('activated B-like DLBCL'). Patients with germinal centre B-like DLBCL had a significantly better overall survival than those with activated B-like DLBCL. The molecular classification of tumours on the basis of gene expression can thus identify previously undetected and clinically significant subtypes of cancer.

Despite the variety of clinical, morphological and molecular parameters used to classify human malignancies today, patients receiving the same diagnosis can have markedly different clinical courses and treatment responses. The history of cancer diagnosis has been punctuated by reassortments and subdivisions of diagnostic categories. There is little doubt that our current taxonomy of cancer still lumps together molecularly distinct diseases with distinct clinical phenotypes. Molecular heterogeneity within individual cancer diagnostic categories is already evident in the variable presence of chromosomal translocations, deletions of tumour suppressor genes and numerical chromosomal abnormalities. The classification of human cancer is likely to become increasingly more informative and clinically useful as more detailed molecular analyses of the tumours are conducted.

The classification of human lymphomas has steadily evolved since their initial recognition by Thomas Hodgkin in 1832 (ref. 1). Beginning with the distinction of Hodgkin's disease from other malignant and non-malignant conditions[2,3], a variety of lymphoma classifications have been advanced on the basis of both morphologic and molecular parameters[4]. The most recent classification scheme, the Revised European–American Lymphoma (REAL) classification, was introduced to categorize distinct clinical–pathological entities[5]. However, within this classification system, various morphologic subtypes were unified into groups despite the suspicion that they "include more than one disease entity"[5].

Diffuse large B-cell lymphoma (DLBCL) is one disease in which attempts to define subgroups on the basis of morphology have largely failed owing to diagnostic discrepancies arising from inter- and intra-observer irreproducibility[5,6]. Diffuse large B-cell lymphoma is an aggressive malignancy of mature B lymphocytes, with an annual incidence of over 25,000 cases, accounting for roughly 40% of cases of non-Hodgkin's lymphoma. Patients with DLBCL have highly variable clinical courses: although most patients respond initially to chemotherapy, fewer than half of the patients achieve a durable remission[6,7]. Although a combination of clinical parameters is currently used to assess a patient's risk profile, these prognostic variables are considered to be proxies for the underlying cellular and molecular variation within DLBCL[8].

An important component of the biology of a malignant cell is inherited from its non-transformed cellular progenitor. Each of the currently recognized categories of B-cell malignancy has been tentatively traced to a particular stage of B-cell differentiation, although the extent to which these malignancies maintain the molecular and physiological properties of normal B-cell subsets is not clear. The rearranged immunoglobulin genes in DLBCL and most other non-Hodgkin's lymphomas bear mutations that are characteristic of somatic hypermutation, an antibody-diversification

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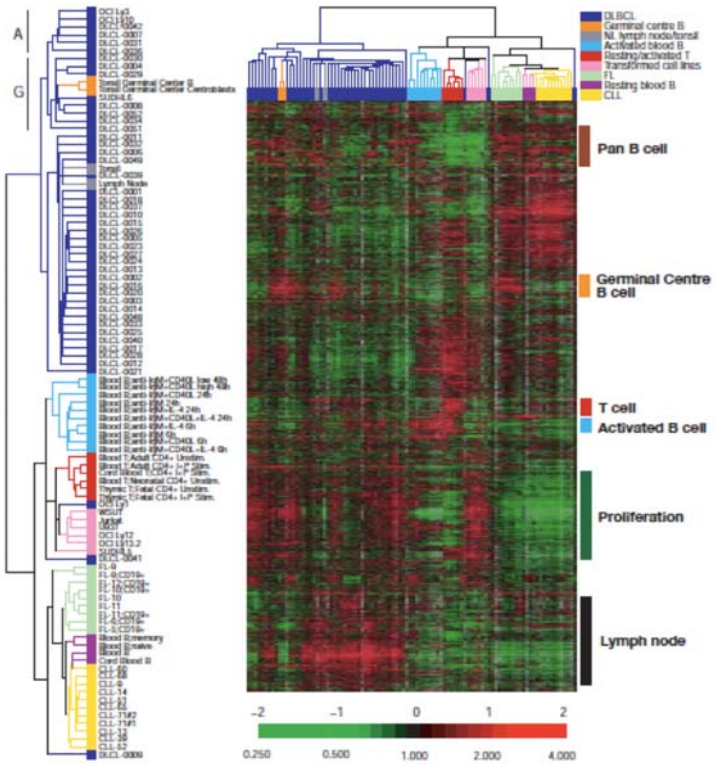
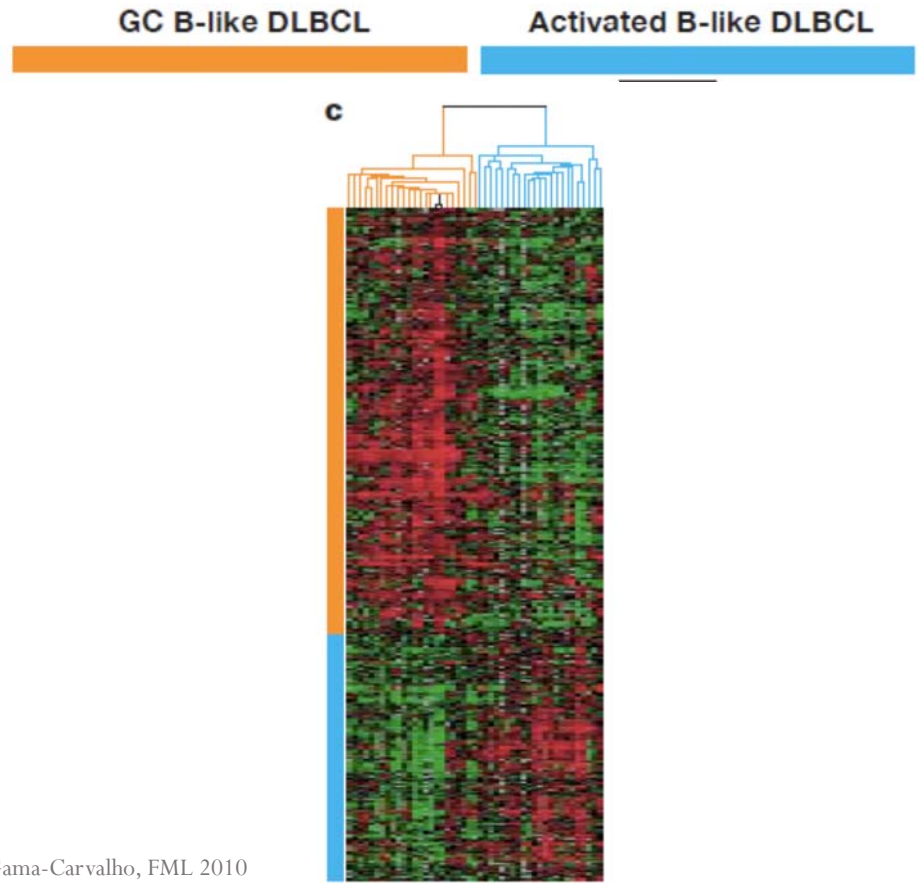
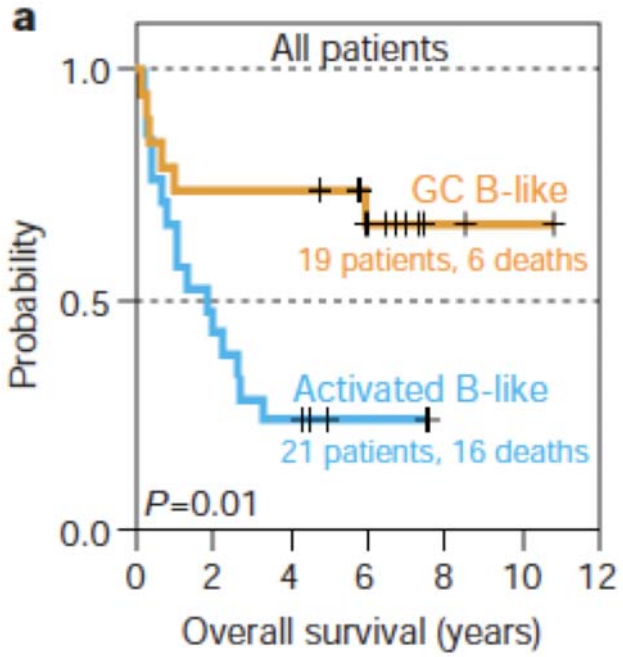
Classificação de amostras





Correlação com prognóstico



É possível fazer uma classificação molecular dos tumores e correlacionar com prognóstico.

E agora?