**Introduction**

After the identification of genetic elements in DNA it became apparent that specific cell functions required sophisticated mechanism to regulate gene expression [1]. This is obtained by modifications of DNA and of histones: methyl residues can be inserted on DNA (cytidine) or on histones (lysine or arginine), while acetyl groups on histones are added or removed to turn genes on or off. The epigenetic machinery is very complex consisting of different protein complexes responsible for the different steps required: by applying a simplification that is certainly inaccurate but useful in practical terms, proteins involved in epigenetic regulation can be divided into writers, erasers and readers. When it was found that these mechanisms may also be responsible for the malignant behaviour of transformed cells [2,3] researchers started to look for specific inhibitors that could be used in the "epigenetic treatment" of patients [4].

Some drugs have long been in clinical use under a different label: this applies to Valproic acid and to anti metabolites such as Cytarabine (Cytosine arabinoside), 5-aza-cytidine, and Decitabine. Cytarabine was used according to different protocols: when given in low, repeated doses it did not result in relevant anti proliferative effect and it was able to induce sporadic but consistent cases of differentiation of leukemic cells [5]. One of the advantages of these regimens was their very limited toxic side effects which allowed prolonged and well tolerated treatment even in elderly patients [6]. By today standards these should be considered in every respect "epigenetic" treatments. On the other hand the term "epigenetic treatment" could be used for any therapy that leads to reprogramming of gene expression. All-trans retinoic acid is an exceptional example of how malignant cells can be redirected toward physiological development through pharmacological manipulation of gene expression [7]. In a similar way estrogens and anti-estrogens regulate gene expression through epigenetic control [8,9] and should therefore be included in this definition.

Concerning histone acetylation-deacetylation several molecules acting on these mechanisms are now in clinical use: the first was Valproic acid, while Belinostat, Panobinostat and Vorinostat (SAHA) were later added to this list. Today a number of molecules acting on similar or on different targets have been registered for clinical use, especially in haematological malignancies [10,11], or are in different phases of clinical evaluation [12]. With reference to solid tumours we recently reviewed studies reporting on their epigenetic treatment [13].

Traditionally the biological characterization of malignant cells is more accurate in haematology and this may at least in part explain why epigenetic treatment is in a more advanced phase for haematological malignancies [14]. Progress however is also being made in solid tumours: several histological types have been carefully analysed and today a sort of "epigenetic signature" can even be used to identify carcinomas of unknown origin [15]. Brain tumours are among the histological types that have been studied in detail [16] and several potential epigenetic targets have been identified [17,18]. The identification of isocitrate dehydrogenase (IDH) mutations as a prognostic element [19-21] is of particular interest. Mutated IDH can produce R (-)-2-hydroxyglutarate which is under many aspects an "on co metabolite" [22]. IDH role and the relevance of its mutations have been well described [23] and since this enzyme and its products play a role in the regulation of cell metabolism it appears that epigenetic control and energetic metabolism are strictly related [24-28].

**Conclusion**

The use of molecules that interfere with the epigenetic regulation of gene expression is a promising strategy especially in tumour types that do not respond to traditional anticancer agents. In order to accelerate drug development we need to identify those tumours that have a better probability of responding. The crossroad between epigenetics and cellular energetic metabolism is a particularly stimulating field of research that may bring excellent results in the future if adequately exploited.

**References**


