Chirality helps light to strike cancer

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Introduction

Every morning, as soon as we open our eyes and we check our appearance in the mirror, we meet chirality. An unusual word, perhaps too much. A vital concept, as its importance. From greek *kheir*, hand. The first example of chirality. However, even if one hand represents the mirror image of the other, they are not superimposable. Hands are chiral. We are chiral. Public authorities would not be delighted in knowing that face reconstruction, having only one half of it, is not possible.

Lord Kelvin was the first who introduced the terms chiral and chirality: "I call any geometrical figure ... chiral, ... it has chirality, if its image in a plane mirror, ..., cannot be brought to coincide with itself" [1]. This states for a geometric definition. When applied to molecules, the term chirality, is decidedly fuzzy. Molecules are not geometrical objects, and chirality at molecular scale depends entirely on the context of the query. Chemically, Lord Kelvin renewed the Pasteur's dissimmetry concept, who recognized that the two enantiomers (pair of molecules, chemically identical, not mirror-superimposable) of tartaric acid were capable to polarize light differently (right vs. left) as a consequence of the asymmetric spatial grouping of the atoms. He said, "Optical activity is the signature of Life" [2].

Chirality belongs to our daily lives, even without being aware of it. DNA helix, where all our genetic past and future is stored, is an asymmetric (chiral) molecule. Olfactory receptors, thanks to the presence of chiral groups, discriminate fragrances. 50% of the drugs are chiral: just one enantiomer is "active", while the effect of the "not active" one is not always known, sometimes deleterious. The physiological recognition of molecular asymmetry is adapted to develop nature-inspired sensing devices.

Chirality features us, belongs us, and anthropologically excites the scientific community [3]. If Pasteur defined the optical activity as Life's signature, homochirality, and its evolutionary origin, deals with its fingerprint (of the Life). The intriguing homochirality of life, with its mystery, stimulates long-standing efforts to understand its origin.

Leaving the anthropological sphere, procedures whom rationally allow to develop chiral molecules are not so far. Knowledge of the physiological recognition of molecular asymmetry coupled to the suitability to create *ad hoc* building blocks and/or aggregates, chiral, has allowed the growth of PhotoDynamic Therapy (PDT), to cure carcinogenic tissues [4]. It needs essentially on two components: PhotoSensitizer (PS) and photons. Chemistry and light! PS (organic molecule) is excited with light (visible) and can be promoted to an excited singlet state ($S_0 \rightarrow S_n$). Then, electron passes to the quantum mechanics-forbidden triplet state by means of intersystem crossing ($S_n \rightarrow T_1$) and transfers energy to ground state triplet oxygen ($T_1 \rightarrow T'_0$) to yield singlet oxygen ($T'_0 \rightarrow S'_1$), Fig 1.

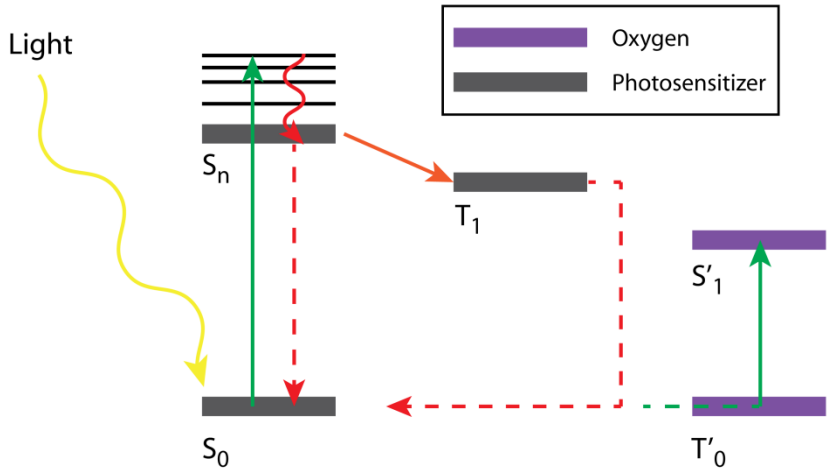

Figure 1: Energy level pathways for a photosensitizer in the absorption process and following generation of singlet oxygen.

The generated species rapidly attacks any organic compounds it encounters (i.e cancer cells) being highly cytotoxic. Commonly utilized PSs (porphyrins, chlorophylls) are chromophores capable to guarantee a satisfactory light absorption and generation of reactive oxygen species. However, these antennas should be specifically localized in a region to ensure maximum process and destruction of target.

What does chirality matter? The knowledge of the mechanisms of molecular stereorecognition allows the development of molecules that selectively recognize particular regions, such as cell membranes. Fascinating properties of chirality, coupled to effective light-matter interaction, could represent an improvement in treating cancer, alternatively to the more destructive approaches (radio/chemotherapy).

Kill cancer

The effectiveness of the PDT is strongly dependent on the PS biorecognition. Depending on the localization site, it is possible to design molecules with moieties that are specific to a precise interaction, involving effect of charge, hydrophobicity, as well as the chirality. Its information, codified in the molecular structure, plays a fundamental role in the membrane organization through recognition processes. Mitocondria, endoplasmatic reticulum, lysosomes, and cellular membranes, represent the localization where isomers of a bioactive molecules can sensitizing malignant cells to ionizing radiation [5]. Chirality of the biomembranes components plays a crucial role in the recognition, providing the distinction of enantiomers, as reported for peptides, bilirubin and steroidal derivatives stereoisomers [6]. Recently, the use of a chiral-functionalized chlorophyll-a derivative, compared to the same compound substituted by a non-chiral functionality, showed an increased PDT efficacy towards tumor lung cancer in mice [7].

However, chiral recognition phenomena is crucial in the development of PS scenario; chirality can be transferred from periphery to molecule core or manifested as a consequence of PSs aggregation. Considering

porphyrins as model, their aggregation may lead to the arrangement of different chiral-resulting aggregates or, oppositely, to a chirality suppression (present at monomeric level) [8]. Aggregates formation allows to tune light absorption. It is possible to modulate the maximum absorption wavelength and the extinction coefficient (greater amounts of reactive oxygen species generated). Still, aggregation can lead to an enhancement of the "membranophilic" feature of PSs, allowing a better recognition and cell/tissue retention.

Taking advantage of the outstanding light-absorbing properties of porphyrins, the hydrophobic feature of steroids and the amphiphilicity due to sugar (even their homochirality), is possible to create innovative PSs. The steroidal substituents, due to the composition of the media (solvent-promoted), lead the aggregation phenomena of porphyrin-based platforms while, the presence of sugar moieties improves transport into neoplastic tissue enhancing the affinity to the cell surface. Porphyrins and porphyrin-like compounds with sugar moieties should not only have a good aqueous solubility but should also exhibit membrane interaction. Subsequent to aggregation process, chirality owed to the stereogroups is successfully transferred to supramolecular structures, obtaining an high degree of asimmetry (Pasteur's dissimmetry). Finally, these chiral suprastructures will be highly recognized by the target tumoral cells, and a low energetic radiation (600/700 nm) will promote the chain-reaction which leads to necrosis or apoptosis activation, Fig 2.

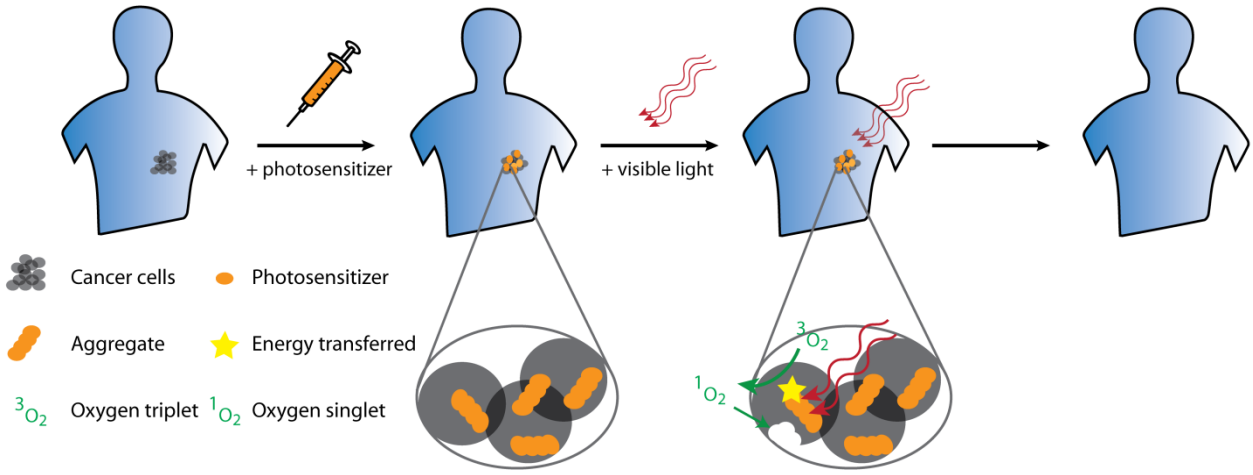

Figure 2: Photodynamic therapy sequence.

Outlook

PDT-era began with pioneering work of Thomas Dougherty and his group in the seventies. Currently, is becoming a tangible treatment to destroy malignant and pre-malignant cells. The combination of light and a organic molecule, instead of aggressive treatment represented by radio/chemotherapy, could be an important treatment of the future. The capability to apply weak energetic radiation produces a net reduction of organism damages. Considerable efforts are being undertaken to improve the selectivity of photosensitizing agents. By knowing the molecularly stereorecognition present in most of biochemical processes, the rational

modular design of chirality, could represent the *leitmotiv* in maximizing the interaction of the PS with target. Despite of its great appealing and potentiality in tumor destruction, PDT still has some issues. *In vivo* stability of the PSs, toxicity of the breakdown products, healthy cells photodamaging and dark toxicity represent predominant drawbacks. The fully comprehension of the biochemical recognition at cellular scale and the *ad hoc* modulation of chirality, the use/develop of diverse PSs, coupled to chemical conjugation of proteins, sugars, antibodies, and hormones, represent powerful tools to make PDT really effective in destroying cancer and other diseases.

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