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Network pharmacology and drug repurposing pave the way for precision oncology

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Abstract

Genomic profiling has shown that not all cancer patients who share similar macro- and microscopical features harbour the same underlying molecular mechanism. This suggests the urge for matching patients to mechanism-based cancer therapies, independent of their primary tumour location and histology [1]. Currently, precision oncology trials provide personalised treatments based on the druggable variants found in a patient genetic makeup. Typically, those trials target single genetic variants [2, 3] or provide combination therapies targeting single, mechanistically unrelated proteins which has been proven to be ineffective and or insufficient [4, 5]. In parallel these variants are allocated to so-called canonical signalling pathways, e.g., KEGG pathways, Wiki Pathways. However, these are rather curated mind maps only combining similar signalling proteins or messengers. They do not represent true cellular signalling entities. Alternatively, signalling modules can be constructed in an unbiased manner from the interactome using validated seed proteins, also termed cancer driver genes, resulting in fragments and often mixtures of the above curated pathways [6]. These modules likely represent the true cancer mechanism and concerted network modulation with multiple mechanistically related drugs all acting on the same module i.e., network pharmacology, promise to be much more effective than targeting single unrelated variants [7]. As complex tumours will require multiple drugs targeting several modules [8], we start with low complexity tumours with a low mutational burden, e.g., thyroid cancer and diffuse intrinsic pontine gliomas (DIPG) [9]. Here, we (i) construct de-novo disease modules to identify drug targets and repurposable drugs, (ii) apply diagnostic assays to detect the patient specific perturbed modules and (iii) decide on the therapeutic strategy to correct the modules using network pharmacology. Repurposable drugs are ranked based on clinical feasibility and other parameters. This allows a fundamentally new approach to cancer therapy often using low-side effect drugs acting in concert to improve patient survival and quality of life by implementing biology-informed drug interventions.

Keywords

Network pharmacology, Precision oncology, Module construction, Drug repurposing, Thyroid cancer, DIPG

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