**Discovery of selectively cytotoxic inorganic nanomaterial using machine learning reinforced genetic algorithm on normal and cancerous cell lines**

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The characteristic properties of metal and metal oxide nanoparticles (NPs) such as surface properties, shape diversity, surface charge, dissolution rate, and controlled release of metal ion contribute to their toxicity and researchers are investigating these features as well as biochemical properties of cell such as type of cell, composition and permeability of cell membrane, metabolic activity, protein expression, and antioxidant defense mechanism to assess the cytotoxic activity of NPs on different normal and cancerous cell lines [1-2].

While nanoparticles are potential anti-cancer agents, they lack selectivity and mainly used for drug delivery. Additional functionalities for these NPs are often introduced through chemical modifications. Nevertheless, such modifications can significantly increase the complexity of the system, making clinical application more difficult, and can also result in unpredictable changes in behavior within living organisms that may alter the therapeutic effects of the delivered drug molecules [3].

For many years, assessment of toxicity and selectivity of nanomaterials have been conducted in vitro and in vivo models. However, the process is complex, time consuming and expensive due to heterogeneity of nanomaterials. Furthermore, the lack of a standard protocol for comparing toxicity results makes it difficult to draw definitive conclusions [4].

In this study, for the first time, an advanced and fully automated computational screening platform to identify selectively cytotoxic inorganic nanomaterials was developed. To demonstrate the effectiveness of this approach, a light gradient boosting machine (LGBM) learning regressor model was used to quantitatively predict the cytotoxicity of nanomaterials with a high degree of predictive accuracy (Q2 = 0.795). In order to efficiently evaluate a vast number of candidate nanomaterials and determine the most effective and selective options, LGBM learning regressor model is integrated with a genetic algorithm (GA), which emulates the natural process of evolution. Using ML reinforced GA, selectively cytotoxic inorganic NMs were identified, and Ag NP (with main parameters; concentration = 64 μg/ml, reaction time = 24 hrs, hydrodynamic diameter = 203.85nm and zeta potential = -7.28 mV) showed the highest selectivity with 56.96% toxicity on cancerous HepG2 cell line and 14.82% toxicity on hepatocytes.

Our approach not only enables the identification of highly selective cytotoxic nanomaterials based on relatively non-selective examples, but also has the potential to be extended to a significantly larger chemical space of nanomaterials and living entities, for which viability can be defined.

**Reference**

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