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Evaluation of Mechanism of Action, Metabolic Stability, and in vivo Efficacy of the Anti-cancer Compound Combretastatin A4 & Two Novel Structurally Simplified Analogues

Daniel Tarade
University of Windsor, tarade@uwindsor.ca

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Cancer has been a global concern for a long time. The Canadian Cancer society estimates that two in five Canadians will be diagnosed with cancer within their lifetimes. With such dire statistics, it is obvious that more research needs to be conducted towards finding effective and selective cancer treatments. One of the most interesting anti-cancer drugs discovered within the past several decades is the natural compound combretastatin A4 (CA4), which was isolated from the South African tree *Combretum Caffrum*. CA4 has been evaluated as an anti-cancer agent through phase II/III clinical trials and has been shown to be an effective addition to traditional chemotherapeutic regiments. However, CA4 has been largely ineffective as a monotherapy because of its short half-life in the human body and conformational instability. Therefore, there has been a need for new analogues or 'versions' of CA4, which may be more effective at treating cancer in humans. Our research collaborators at McMaster University have recently synthesized two structurally simplified analogues of CA4. Preliminary results suggest that these analogues are effective at causing various cancer cell types to commit suicide (apoptosis). Researchers have not only explored new analogues of CA4 but have also explored what how CA4 functions to kill cancer cells. It has been found that CA4 disrupts microtubule (a major protein component of cellular skeleton) assembly, which prevents the completion of cell division (mitosis). However, it is not fully known which cellular pathways are activated following mitotic arrest and, overall, what is required for cell death. Research has shown that mitochondrial collapse occurs following CA4 treatment – hypothesized to be an indirect target – and that various pro-apoptotic factors and apoptotic proteins are released and activated, such as apoptosis inducing factor (AIF), cytochrome c, and caspases. However, knockdown and pharmacological inhibition studies have failed to identify any of these proteins as being critical for CA4 induced cytotoxicity. These evidences suggest that CA4 targets additional cellular processes, which may be crucial for CA4-induced cytotoxicity. My research aims to create a chronology of cellular events that occur following cancer cell treatment with either combretastatin A4 or two novel analogues as a means of not only determining if the novel analogues are more effective that CA4 but also uncovering the causal connection between mitotic arrest, mitochondrial collapse, and eventual cell death. To determine if the novel analogues of CA4 are more or less effective than CA4, various cellular assays using various human cancer cell lines will be employed. These assays can be used to determine the percentage of cell suicide, cellular viability, and mitochondrial integrity at various time points as well as detect if mitotic arrest has been triggered. The chronology of cellular events will look at mitotic arrest, mitochondrial collapse, and cell death at the 3, 6, 12, and 24 hour time point to try and determine if there is a causal connection between the various cellular events. I have found that for CA4, cell cycle arrest occurs as early as 3 hours post treatment in human leukemia cells. Then, only at the twelve hour time point, is mitochondrial collapse detected. Lastly, cell suicide is first detected at the 24 hour time point. The data collected fits the predominant hypothesis about CA4’s method of action; namely that microtubules are directly targeted, resulting in mitotic arrest, which leads to downstream mitochondrial collapse and cell death. A similar chronology of events was detected for one of the novel analogues of CA4. However, for the second analogue, significant mitochondrial collapse and cell death was witnessed without being preceded by massive mitotic arrest. This evidence suggests that perhaps CA4 can directly target the mitochondria, as an analogue retains the ability to collapse mitochondria without being able to potently impede mitosis.