Expansion of cell death models to understand the balance between necrosis and apoptosis.

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***Short Abstract* — Dysregulated programmed cell death is a hallmark of cancer present in most cancer types. To date, most cell-death related work has focused on understanding and inducing apoptosis execution. Recently, necrosis has been characterized as a second major form of programmed cell death that has been recognized as a regulated pathway (rather than a random event) that presents a novel target for cancer treatment. The present work will use computational and theoretical modeling approaches to complement experimental work. This modeling approach is required due to the complexity in signaling pathway crosstalk between apoptosis and necrosis, the complexity of protein-protein interactions associated with unexpected outcomes, and non-linear effects that arise from simple perturbations, all of which cannot be rationalized with simple analysis methods. Motivated by recent observations that dysregulated necrosis in Myelodysplastic Syndrome (MDS), an aggressive pre-leukemic condition, is driven by necrosis, we use experimental data to motivate, construct, calibrate, and probe plausible mechanistic hypotheses about the regulation and commitment of cell death to either necrosis or apoptosis. We will show how we use PySB, our Python-based modeling platform, to (1) generate models of programmed cell death that provide systems-level mechanisms to rationalize experimental observations, and (2) use these models to develop predictive hypotheses of signaling pathway decision processes under different cellular conditions or drug perturbations. The discoveries from this work will have immediate impact in experimental design to probe and treat MDS as well as other similar cue-response signaling systems in molecular cancer cell biology.**

***Keywords* — apoptosis, necrosis, rules-based modeling, model programs, executable models, PySB.**

I. Purpose

About 50% of cancer phenotypes exhibit inhibition of programmed cell death in tumorigenic cells. [1,2] Some novel anticancer drugs aim to induce apoptosis as a PCD-driven method of cancer treatment.[3] However, programmed necrosis, another potent form of PCD has only recently been recognized as a potential therapeutic target.[4] Cells that undergo necrosis explode, leaving behind cellular detritus. This leads to an immune response and associated inflammation, further exacerbating tissue damage. Excessive bone marrow progenitor cell death is a prominent feature of Myelodisplastic Syndrome (MDS) and leads to bone marrow failure, a major morbidity of the disease. Current medical therapies have successful response rates of less than 20% in one year and over 30% of patients diagnosed with MDS will progress to acute leukemia.[5] Multiple studies of MDS have demonstrated excessive bone marrow cell death but these studies do not distinguish between apoptotic and necrotic death.[6] Data from our collaborators has demonstrated that excessive bone marrow cell death is driven by necrosis. Consequently necrosis inhibition through targeted drugs poses a novel and promising, yet unexplored, therapy for MDS. A characteristic feature of necrosis execution is Rip kinase activity. Although the mechanistic aspects of necrosis signaling pathways are not well understood, important protein-protein interactions have been identified and the overlap between apoptosis and necrosis has been established[7].

II. Approach

The current modeling work is being carried out with the PySB modeling framework being co-developed in my laboratory.[8] Briefly, PySB allows the composition, integration, and exploration of mathematical models using a programming framework rather than listing long complex mathematical equations. The mathematical representation is generated automatically by the program leaving the user to spend more time on the biology and less time in technical details. One of the key advantages of our novel programmatic approach to modeling is that biological models can be expressed as native computer code that can be revised, expanded, and shared in a modular format as done in software programs. This enables us to compartmentalize and explore individual parts of the model as needed. Our lab is committed to model reuse and transparency. Our models and programs are available online for the modeling community through the Git/GitHub version and sharing control system (https://github.com/clopezx/anrm).

. For the present work, we are composing the apoptosis-necrosis reaction model (ANRM) as a modular program that can be executed to generate a mathematical model representation (in this case ODEs). We will show the development of a *Necrosis Receptor Layer*, which involves TNF ligand and receptor, and FAS ligand and receptor and the interactions between these molecules that lead to FADD and TRADD adaptor protein assembly and a complex similar to the death inducing signaling complex (DISC) in apoptosis termed Complex I. Both modules share some interactions with the activation of Caspase 8 in the execution of either necrosis or apoptosis execution. We will also show how we deal with the crosstalk aspects between necrosis and apoptosis and how the model can respond to different cues with one or another cell death outcome. Preliminary results for model calibration to data will be discussed.

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