Editorial

It has been a great pleasure to commission the reviews published in this edition of *The Open Cell Signaling Journal* by experts from their respective fields. Reviews have become an important part of the publishing landscape, and in the field of apoptosis research with over 160 thousand papers referenced in PubMed in the past ten years, are almost essential. The six reviews included in this edition of *The Open Cell Signaling Journal* are an attempt to make sense of areas of this vast literature. I hope you will find them interesting and at the same time, that they provide new insights by looking at the process of cell death from a signaling perspective.

The review by **Cristina Muñoz Pinedo** and **Alfredo Caro Maldonado** discusses the role of cellular starvation in a cell's apoptotic response. It is clear that cells die without food. If a cell commits suicide when it is infected with a virus this will prevent viral replication and spread and thereby protect the organism. The benefits of cells dying in a genetically programmed manner in response to lack of nutrients are however not as intuitively obvious. This review outlines a convincing argument that cells do respond to starvation by apoptosis and explores the implications of it. The fact that tumor cells have a special metabolism that makes them more susceptible than normal cells to lack of glucose and glutamine has reignited interest in this particular area of research and provides an exciting new area to target in cancer therapy which is also discussed in this review.

The hope that specific activation of apoptosis pathways in tumor cells will provide an effective treatment for cancer has been one of the engines behind the massive experimental efforts to understand apoptosis. But apoptosis plays an important role during normal development and was first recognized by Karl Vogt in the mid 1800s when he was studying the development of the midwife toad tadpole. The preponderance of reviews on the role of apoptosis in cancer in the literature is balanced in these reviews with articles on morphogen regulation of developmental cell death and cytokine dependant survival. **Mark Ditzel** discusses the role of the morphogens of the Hedgehog family in the classical example of apoptosis required for limb development. Strikingly, Sonic Hedgehog appears to be able to play both a pro-and anti-apoptotic role in this one scenario. **Anissa Jabbour** and **Paul Ekert** describe how signaling from cytokines, such as GM-CSF and IL-3, that are important for the expansion of some hemopoietic lineages in response to infection, help these cells to survive. As befits a review in a Journal such as TOCELLSJ that is dedicated to cell signaling, their work describes how signaling from these cytokine receptors regulates the cell death machinery at the molecular level. In particular, it provides a detailed analysis of the role of both pro-apoptotic and anti-apoptotic Bcl-2 family members in this process.

Despite intense study, the precise manner in which pro- and anti-apoptotic Bcl-2 proteins regulate cell survival remains unknown. **Grant Dewson** has made several important contributions to our understanding of how the pro-apoptotic family members are able to kill cells and gives a clear and elegant summary of the field. A number of compounds that activate the Bcl-2 blockable or intrinsic cell death pathway by mimicking the pro-apoptotic compounds are currently performing well in clinical trials and a better understanding of how the natural molecules kill will enable the development of better drugs [1].

The so-called extrinsic cell death pathway is the other major apoptotic pathway that has attracted a lot of pharmaceutical interest. Work dating back over 140 years led to the hope that a molecule induced by LPS, that turned out to be Tumor Necrosis Factor (TNF), would be a potent tumor specific killer, as its name suggests [2]. Unfortunately, TNF is extremely toxic and at the moment can only be used to treat tumors in bodily extremities where the systemic toxicity can be prevented. Thus, when the related ligand TRAIL was found to be a potent killer of tumor cells without systemic toxicity in 1999, hopes were high that this would be a new wonder drug. Unfortunately, clinical trials with TRAIL or TRAIL agonists have not lived up to the initial hopes but more than 10 years on from the original discoveries, there is still much to learn about this signaling system. The key signaling pathways for both TRAIL and TNF are expertly dealt with in the review by **Henning Walczak** and **Chahrazade Kantari**.

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The extracellular cell death signaling pathway review dovetails nicely with the final review from **Ian Gentle** and **Ueli Nachbur** that looks at the interaction of cell death signaling and the viral response. TNF and other cytokines in the same family play critical roles in the body's response to viral pathogens. As a consequence, viruses have evolved proteins that counter-attack this pathway at almost every step [3]. This review gives an excellent flavor of the battle and also deals with the Bcl-2 pathway and the role of the default necroptosis pathway.

Taken together these reviews give a signaling perspective on apoptosis from experts in each of the areas. I hope they will provide a valuable foothold on and prospect over the intimidating mountains of literature in these fascinating areas and encourage the reader to investigate further. Finally, I would like to acknowledge that some of the contents in the reviews from Jabbour, Dewson and Gentle were first published in the Australian Biochemist, and thank Rebecca Lew, the Editor of that magazine, for her help in editing these reviews.

REFERENCE

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